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Recent advances in attempts to improve medication adherence – from basic research to clinical practice, volume II

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Published in
Frontiers in Pharmacology

ISSN 1664-8714
ISBN 978-2-8325-5755-6
DOI 10.3389/978-2-8325-5755-6

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Recent advances in attempts to improve medication adherence – from basic research to clinical practice, volume II

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Citation

Kardas, P., Agh, T., Potočnjak, I., Ghiciuc, C. M., Herdeiro, M. T., eds. (2024). *Recent advances in attempts to improve medication adherence – from basic research to clinical practice, volume II*. Lausanne: Frontiers Media SA.
doi: 10.3389/978-2-8325-5755-6

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frontiers | Frontiers in Pharmacology

TYPE Editorial
PUBLISHED 25 November 2024
DOI 10.3389/fphar.2024.1521468

OPEN ACCESS

EDITED AND REVIEWED BY
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RECEIVED 01 November 2024
ACCEPTED 08 November 2024
PUBLISHED 25 November 2024

CITATION
Kardas P, Potočnjak I, Ghiciuc CM, Herdeiro MT and Agh T (2024) Editorial: Recent advances in attempts to improve medication adherence – from basic research to clinical practice, volume II.
Front. Pharmacol. 15:1521468.
doi: 10.3389/fphar.2024.1521468

Editorial: Recent advances in attempts to improve medication adherence – from basic research to clinical practice, volume II

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KEYWORDS

healthcare systems, medication adherence, chronic disease management, digital health technologies, intervention strategies, non-communicable diseases, patient edcuation, polypharmacy

Editorial on the Research Topic
Recent advances in attempts to improve medication adherence – from basic research to clinical practice, volume II

This second volume of the Research Topic, "Recent advances in attempts to improve medication adherence–from basic research to clinical practice," builds on the previous work of Volume I (Kardas et al., 2023), spotlighting significant new developments in this critical field. Despite decades of focused research, achieving optimal adherence to evidence-based, long-term therapies remains a substantial challenge with direct implications for individual health, public health outcomes, and the sustainability of healthcare systems (Sabaté, 2003). Volume II presents novel insights and innovations aimed at improving adherence from both research and clinical perspectives.

The complexity of non-adherence is influenced by many factors, including the aging global population, the rise of non-communicable diseases, and the prevalence of multimorbidity and polypharmacy (World Health Organization, 2015). Events like the COVID-19 pandemic have further exacerbated these challenges. However, it is increasingly recognized that medication adherence is not solely the patient's responsibility. It is shaped by a variety of non-patient-related factors and serves as an important indicator of the quality of care. Therefore, rather than assigning blame, all stakeholders must collaborate to create environments that support adherence and enable patients to successfully follow their therapeutic regimens. A recent pan-European survey on medication adherence management emphasized the importance of addressing adherence barriers at multiple levels. It highlighted the need for collaboration among healthcare professionals and

advocated for promoting and utilizing digital technologies within clinical practice to improve medication adherence (Kamusheva et al., 2024; Hafez et al., 2024).

To improve adherence, interventions that are proven effective and cost-effective are urgently needed (Ágh et al., 2022). Resources must be used wisely, and this requires rigorous research to support the design, implementation, and benchmarking of interventions. This Research Topic aimed to highlight recent advances in this area by presenting a wide range of studies, from basic theoretical questions to the real-world implementation of interventions, with a focus spanning from individual patients to system-wide approaches.

The theoretical background helps standardize methodologies and benchmark the results of both scientific research and clinical practice. For several years, the ABC consensus terminology and taxonomy set key standards for basic concepts in the field of medication adherence (Vrijens et al., 2012). However, until now, no similar 'gold standard' existed for various interventions and technological solutions in this area. The European Network to Advance Best practices and technoLogy on medication adherencE (ENABLE) COST Action (van Boven et al., 2021) has filled this gap, establishing a cohesive set of consensus terms and definitions. These terms include 'medication adherence technology,' 'medication adherence enhancing intervention,' 'best practice,' and 'reimbursement,' all of which can help promote consistency in research and clinical practice (Kardas et al.).

To further support benchmarking of national approaches to medication adherence management, ENABLE created a list of key indicators related to medication adherence (IRMAs). The list includes 26 items, covering country characteristics, social/economic factors, therapy- and patient-related factors, condition-related factors, and healthcare system-related factors. An expert survey built a unique database of these indicators for 39 European countries and Israel, providing a solid foundation for tailored interventions aimed at improving adherence and informing health policy development (Ágh et al.).

Medication adherence is most often associated with chronic conditions, but it is equally important in infection treatment, particularly for long-term infections. It is therefore noteworthy that a new instrument was developed to assess medication adherence among tuberculosis (TB) patients in Indonesia (Rianto et al.). The structured questionnaire, validated through rigorous testing, measures socio-economic, healthcare team, and condition-related factors, offering a valuable tool for targeted interventions in TB care.

Available evidence proves that medication adherence in mental conditions is particularly low. A systematic review of current literature put more light over this topic, looking for sociodemographic and clinical predictors of adherence to pharmacological treatment in patients diagnosed with a depressive disorder (Del Pino-Sedeño et al.). Meta-analysis of 39 included studies identified age and ethnicity as key predictors of adherence.

Another group of drugs with particularly low adherence rates is statins, partly due to the asymptomatic nature of hyperlipidaemia, and treatment typically requiring long-term commitment. The recent COVID-19 pandemic created particularly difficult conditions for execution of such therapy. An analysis of nationwide Polish real-word data on prescribing and dispensing allowed for detailed insight into execution of that treatment under unfavourable conditions (Kardas et al.). Although access to statins was maintained, nearly half of the patients remained non-adherent, and approximately 1/7 of prescribed statin doses were never dispensed. These results underscore the need for targeted interventions to improve medication adherence to this drug class of high public health importance.

Even life-threatening conditions like cancer are not immune to the issue of non-adherence. A study from Romania assessed adherence in breast cancer patients receiving oral anti-cancer drugs, finding non-adherence rates between 12.8% and 14.7%, depending on the drug type (Turcu-Stiolica et al.). This highlights the critical need for targeted interventions in cancer treatment.

Identifying non-adherence in patients with cognitive impairments is challenging. Therefore, an important question is whether simple questionnaire tools can be effectively used in this context. A study assessing the diagnostic validity of two self-reported adherence tools - the Morisky Green test and Batalla test - found that these questionnaires effectively identified non-adherence in patients with mild cognitive impairment and dementia, with high specificity but moderate sensitivity (Barnestein-Fonseca et al.). Given their ease of use in clinical practice, the study supports the integration of self-reported methods into routine adherence assessments for cognitively impaired patients, highlighting their practicality.

Achieving adequate adherence is essential for good clinical outcomes. A longitudinal study in children and adolescents with asthma showed that adherence to inhaled corticosteroids, along with correct inhalation technique, was associated with better clinical outcomes such as symptom control, exacerbations, and health-related quality of life (Lizano-Barrantes et al.). However, a third of the participants had suboptimal inhalation technique, pointing to the need for improved patient education. Unfortunately, healthcare professionals often lack sufficient knowledge of proper inhaler techniques and may be inadequately prepared to teach these skills to patients (Maepa et al., 2019).

Under the light of this, somewhat surprising results were provided by a study (Achterbosch et al.), which assessed the effect of shared decision-making (SDM) on medication adherence in patients with chronic obstructive pulmonary disease (COPD) and asthma. Despite a sound theoretical background supporting the use of SDM, this study found no significant association between SDM and adherence. Therefore, there is a room for further investigation into the mechanisms linking SDM and adherence, as SDM alone may not directly influence patients' adherence to inhalation medications.

On the other hand, in a study examining adherence in patients with severe mental disorders, a psychosocial group intervention focusing on lifestyle behaviours led to a significant improvement in treatment adherence (Sampogna et al.). Interestingly, participants who engaged in moderate physical activity showed better adherence. The study highlights the potential of lifestyle-based group interventions to enhance adherence in mental health settings, suggesting that this approach could be easily integrated into routine clinical practice.

Many interventions targeting adherence are - for various reasons - only short term. This makes the study (Bandiera et al.),

which explored the impact of a 6- *versus* 12-month pharmacist-led medication adherence program in patients with diabetic kidney disease, particularly valuable. The findings revealed that patients in the 12-month group had better adherence to antidiabetics and antihypertensive medications compared to those in the 6-month group, indicating that longer intervention durations can lead to sustained improvements in adherence, with potential long-term benefits.

Obvious limitations of such long-term adherence programs are their costs and scarcity of human resources. Novel digital technologies may help to partially address these issue. One example is a study (Larsen et al.) that explored the potential of a mobile app to enhance adherence to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) among antidepressant users. Results showed a noticeable improvement in adherence, with a significant reduction in non-adherence scores following app use. Interestingly, while half of the participants found the app useful, it was not preferred over traditional sources of information.

However, not every simple intervention proves effective. A study evaluating the impact of pocket cards containing key medication information, distributed after a school-based education program, found no significant benefit from the cards. Although the cards did not improve adherence, the structured education program remained valuable, and other tools should be explored to enhance medication knowledge retention (Sakai et al.).

Optimisation of the drug therapy is one of the initial steps toward improving adherence. A study (Jošt et al.) evaluated the effectiveness of pharmacist-led medication reconciliation at the hospital discharge over patient safety and healthcare utilization. Results indicated that medication reconciliation reduced the likelihood of a clinically important medication error by 20-fold. These findings underscore the importance of medication reconciliation as a key measure for patient safety.

The growing need for clinical pharmacy services (CPS) is further underscored by aging populations and the subsequent rise of polypharmacy. Unfortunately, a review of CPS development in Central and Eastern Europe reveals underutilization of pharmacists' potential to manage medication-related problems (Urbańczyk et al.). Therefore, the authors call for wider adoption of CPS to meet global healthcare challenges effectively.

As polypharmacy becomes an increasingly prevalent problem, negatively affecting medication adherence, effective solutions are more than needed. However, there is only limited information available on their performance in real life settings. This created the background of a cross-sectional study which benchmarked existing polypharmacy management programs in elderly across Europe (Kardas et al.). Findings from over 900 healthcare professionals allowed to assess their effectiveness, applicability, scalability and cost-effectiveness, as well as to create a benchmarking application enabling comparisons across national and European contexts to aid clinicians and policymakers.

An educational intervention aimed at healthcare professionals in primary care demonstrated the effectiveness of training on inhalation technique, as reported in a recent cluster randomized trial (Vázquez-González et al.). The study found that healthcare professionals who received training showed significant improvements in their knowledge and skills regarding inhalation techniques, which are essential for patient adherence and effective asthma management. This highlights the critical role of provider education in achieving optimal patient outcomes and the potential for integrating such interventions into routine clinical practice.

Another study (Bell et al.), adopting a public health perspective to medication adherence, was conducted in Ireland on secondary prevention after stroke. The study revealed ongoing failures to meet adherence targets post-discharge, despite the known importance of medication in recovery. Semi-structured interviews and focus group with healthcare professionals explored the challenges faced by healthcare professionals in community multidisciplinary teams, focusing on continuity of care and its impact on medication adherence. The value of this approach is that it revealed gaps in care organization and communication post-hospitalization.

In conclusion, Volume II of "Recent advances in attempts to improve medication adherence–from basic research to clinical practice" emphasizes the multifaceted nature of adherence challenges. Solutions must go beyond individual efforts and involve a system-level approach that addresses the unique needs of patients. This volume offers promising directions for improving adherence and underscores the importance of collaborative, resource-efficient strategies.

Author contributions

PK: Writing–original draft, Writing–review and editing, Conceptualization. IP: Writing–original draft, Writing–review and editing. CG: Writing–original draft, Writing–review and editing. MH: Writing–original draft, Writing–review and editing. TA: Conceptualization, Writing–original draft, Writing–review and editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

The Research Topic editors would like to express their gratitude to all contributing authors and peer reviewers who made this Research Topic possible.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that Generative AI was used in the creation of this manuscript. Generative AI was used for the purpose of linguistic corrections.

Publisher's note

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frontiers | Frontiers in Pharmacology

TYPE Policy and Practice Reviews
PUBLISHED 02 August 2023
DOI 10.3389/fphar.2023.1244151

OPEN ACCESS

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RECEIVED 21 June 2023
ACCEPTED 17 July 2023
PUBLISHED 02 August 2023

CITATION
Urbańczyk K, Guntschnig S, Antoniadis V, Falamic S, Kovacevic T, Kurczewska-Michalak M, Miljković B, Olearova A, Sviestina I, Szucs A, Tachkov K, Tiszai Z, Volmer D, Wiela-Hojeńska A, Fialova D, Vlcek J, Stuhec M, Hogg A, Scott M, Stewart D, Mair A, Ravera S, Lery F-X and Kardas P (2023), Recommendations for wider adoption of clinical pharmacy in Central and Eastern Europe in order to optimise pharmacotherapy and improve patient outcomes.
Front. Pharmacol. 14:1244151.
doi: 10.3389/fphar.2023.1244151

Recommendations for wider adoption of clinical pharmacy in Central and Eastern Europe in order to optimise pharmacotherapy and improve patient outcomes

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Clinical pharmacy as an area of practice, education and research started developing around the 1960s when pharmacists across the globe gradually identified the need to focus more on ensuring the appropriate use of medicines to improve patient outcomes rather than being engaged in manufacturing and supply. Since that time numerous studies have shown the positive impact of clinical pharmacy services (CPS). The need for wider adoption of

CPS worldwide becomes urgent, as the global population ages, and the prevalence of polypharmacy as well as shortage of healthcare professionals is rising. At the same time, there is great pressure to provide both high-quality and cost-effective health services. All these challenges urgently require the adoption of a new paradigm of healthcare system architecture. One of the most appropriate answers to these challenges is to increase the utilization of the potential of highly educated and skilled professionals widely available in these countries, i.e., pharmacists, who are well positioned to prevent and manage drug-related problems together with ensuring safe and effective use of medications with further care relating to medication adherence. Unfortunately, CPS are still underdeveloped and underutilized in some parts of Europe, namely, in most of the Central and Eastern European (CEE) countries. This paper reviews current situation of CPS development in CEE countries and the prospects for the future of CPS in that region.

KEYWORDS

clinical pharmacy, cost-effective treatment, medication errors, drug utilization, drug safety, medication adherence, health policy, polypharmacy

1 Introduction

The most recent definition formulated by the European Society of Clinical Pharmacy (ESCP) states: "Clinical pharmacy aims to optimize the utilization of medicines through practice and research in order to achieve person-centred and public health goals" (Dreischulte et al., 2022). This area of practice, education and research started developing around the 1960s when pharmacists across the globe gradually identified the need to focus more on ensuring the appropriate use of medicines to improve patient outcomes rather than being engaged solely in manufacturing and supply (Carter, 2016). Since that time numerous studies have shown the positive impact of clinical pharmacy services (CPS). CPS has been demonstrated to be economically beneficial in multiple evaluations throughout the years (Byrne and Dalton, 2017), including American College of Clinical Pharmacy summaries from 1996 onwards (Schumock et al., 1996; 2003; Perez et al., 2008; Touchette et al., 2014). An intensified involvement of the clinical pharmacist in all stages of the patient journey named "integrated medicines management" or "seamless care" has been demonstrated beneficial for both patients and healthcare systems due to reduced average length of stay in hospitals, reduced number of and longer time to readmissions, number of outpatients visits, medication burden and healthcare costs (Spehar et al., 2005; Scullin et al., 2007). The implementation of clinical pharmacy services leads to optimized drug utilization and improved drug safety (McMullin et al., 1999; Anderson and Schumock, 2009; Simoens et al., 2011; Reardon et al., 2015; Rychlickova et al., 2016). CPS stimulate appropriate prescribing, promote the use of drugs with a higher Medicines Appropriateness Index (MAI) and a lower Medicines Administration Error rate (Hanlon and Schmader, 2013; Scott et al., 2015). Pharmacist-led chronic disease management leads to higher patient satisfaction and improves patient adherence (Schulz et al., 2019; McCarthy and Thomas Bateman, 2022). Clinical pharmacists educate patients and enhance patient health literacy, which contributes to a reduction of adverse drug reactions (ADRs) (Spehar et al., 2005; Simoens et al., 2011). Medicines reviews and patient education before hospital discharge improves outpatient drug safety by reducing potential adverse effects, drug-drug interactions and inappropriate overuse of medication. Clinical pharmacy practices ensure safe prescribing with numerous scientifically validated tools (Curtin et al., 2019), particularly important for populations at higher risks of adverse drug outcomes, e.g., for older patients, paediatric population, and patients with renal and hepatic failure. Finally, CPS are also perfectly well placed to address current global challenges, such as the World Health Organisation (WHO) Global action plan on antimicrobial resistance (WHO, 2015). Pharmacist-led Antimicrobial Stewardship programs have proved successful in reducing antibiotic consumption and overall hospital expenditures, ensuring prudent use of antimicrobial agents (Brink et al., 2016). Another important target for CPS is Medication without Harm, the third global patient safety challenge launched in 2017 by the WHO (WHO, 2017). It aimed to reduce the level of severe avoidable harm related to medication by 50% over 5 years globally. Assuming that medication errors, drug-drug interactions are avoidable and can be significantly reduced or indeed prevented by improving the system and practice of medication use, the use of CPS seems to be a natural solution. Additionally, integrated medicines management models of providing CPS also correspond with another key action area—transition of care.

Moreover, the need for wider adoption of CPS worldwide becomes urgent, as the global population ages. Ageing leads to a rising prevalence of chronic diseases, and related multimorbidity, which further increases the need for medicine use and often leads to polypharmacy (Kardas et al., 2013). Thus, due to the an increasing proportion of older, the prevalence of polypharmacy is rising. In 2015, approximately 5% of the population in OECD countries was aged 80 years and above, This percentage is expected to double by 2050 (OECD, 2021). Of note is that multimorbidity increases markedly with age—a Scottish study reported that multimorbidity was prevalent in as many as 81.5% of individuals aged 85 years and over, with a mean of 3.02 comorbidities (Mair et al., 2017). This increasing number of comorbidities is associated with frequent polypharmacy not only due to the need to treat simultaneously various different conditions but also because current treatment guidelines are based mostly on "non-geriatric evidence." This complicates the optimal selection of multidrug regimens particularly in very old and frail patients. In relation to the economic impact, it is estimated that mismanaged polypharmacy contributes to 4% of the world's total avoidable costs due to sub-optimal medicine use, with a

total of US$18 billion, representing 0.3% of total global health expenditure, that could be avoided by appropriate polypharmacy management (Mair et al., 2017). Apart from that, increasing complexity of treatment simply requires team efforts to improve patient outcomes. Collaborative care models including pharmacist were already shown to be beneficial in different settings of care (Grimes et al., 2014; Hahn et al., 2018; Lee et al., 2019).

Another key component related to polypharmacy is non-adherence to prescribed medication. Non-adherence may either be intentional or non-intentional. Both of these cases become more prevalent with higher number of drugs being prescribed and it has been demonstrated that there is a correlation between non-adherence and the number of medicines being taken (Kardas et al., 2013). Research suggests that between 50% and 80% of patients with chronic health conditions may be non-adherent. Non-adherence has been estimated to be responsible for 48% of asthma deaths, an 80% increased risk of death in diabetes and a 3.8-fold increased risk of death following a heart attack (Mair et al., 2017).

All these challenges urgently require adoption of a new paradigm of healthcare system architecture. Clinical pharmacy offers an effective answer to many of these challenges, as illustrated by case examples in the United States, Canada and Australia, countries that already allowed clinically trained pharmacists to work effectively with other healthcare professionals in direct patient care, in various aspects of medicine management and in different settings of care. In Europe, the United Kingdom serves as another good practice example of a healthcare system integrating CPS in both inpatient and outpatient settings of care.

Scotland has developed one of the few well-organized polypharmacy management programs in Europe (Stewart et al., 2017). NHS Scotland Polypharmacy Guidance offers probably the most comprehensive guidance on a patient-centred approach to ensure safe and appropriate use of medicines in patients using polypharmacy (Scottish Government Polypharmacy Model of Care Group, 2018). In 2012, a 7-step person centred approach was introduced to consider appropriate polypharmacy in the context of multimorbidity. Initially, polypharmacy reviews were incentivized by enhanced service payments to general practitioners and later by inclusion in their Quality Outcome Framework (QOF) targets. Since 2013, with the policy driver of the Governments "Prescription For Excellence" additional funding has enabled pharmacists to work alongside general practitioners to support appropriate polypharmacy management (Mair et al., 2019). Through its work, in 2015, Scotland led and EU project called SIMPATHY engaging with 10 partners across 8 EU countries to determine how the management of polypharmacy could be achieved across the EU by 2030. This work came up with six key recommendations: use a systems approach that has multidisciplinary clinical and policy leadership; nurture a culture that encourages and prioritizes the safety and quality of prescribing; ensure that patients are integral to the decisions made about their medicines and are empowered and supported to do so; use data to drive change and measure outcomes; adopt an evidence-based approach with a bias toward action; utilize, develop, and share tools to support implementation (Mair and Fernandez-Llimos, 2017).

In Northern Ireland, integrated medicines management (IMM) program including both hospital and community sectors has been also set up. It involves a number of activities performed by clinical pharmacists: medication reconciliation in conjunction with patient monitoring, patient counselling, discharge prescription preparation and collaboration at the community–hospital interface. IMM resulted in significant improvements in the quality and safety of medicines yielding both patients' health gains and substantial savings for the healthcare system (Scott et al., 2015). This concept was further adopted in some other European countries including Republic of Ireland, Norway and Sweden (Gillespie et al., 2009; Hellström et al., 2011; Galvin et al., 2013; Lea et al., 2020).

Europe-wide, the Council of Europe has defined through the work of its European Directorate for the Quality of Medicines & Healthcare (EDQM) a legal framework for its 39 European member states for the promotion and implementation of the concept of pharmaceutical care and related services in health systems at a national level. This framework is provided by Resolution CM/Res(2020)3 on the implementation of pharmaceutical care for the benefit of patients and health services, adopted in 2020 (Committee of Ministers Resolution, 2020). Among other things, the Resolution covers aspects of healthcare workforce and education, advocating for strengthening the role of suitably qualified pharmacists for performing pharmaceutical care and clinical pharmacy services (Committee of Ministers Resolution, 2020). Countries where CPS were introduced are currently reaping various benefits, with optimized drug utilization, enhanced drug safety and medication adherence, among the others, leading to better sustainability of their healthcare systems (Gillespie et al., 2009; Hellström et al., 2011; Galvin et al., 2013; Schulz et al., 2019; Lea et al., 2020; McCarthy and Thomas Bateman, 2022).

Unfortunately, CPS are still underdeveloped and underutilized in some parts of Europe, namely, in most of the Central and Eastern European (CEE) countries. Therefore, this review describes the current situation of CPS development in CEE countries and the prospects for the future of CPS in that region. The CEE countries are defined most often as EU member states which were part of the former Eastern bloc. However, the scope of this paper covers also some other countries belonging regionally to Central and East European region, i.e., Austria, one entity of Bosnia and Herzegovina (Republic of Srpska—RS), Bulgaria, Czech Republic, Croatia, Estonia, Greece, Hungary, Latvia, Poland, Serbia, Slovenia and Slovakia. For ease of reading, they will be collectively called CEE countries in the rest of the text. Data presented in this paper were obtained thanks to the expertise of representatives from listed countries and a review of available national data related to the topic (literature, legislation, statistics, etc.), valid as per January 2023. Moreover, the goal was to emphasise the need for wider adoption of CPS in CEE countries and formulate relevant recommendations and call for action.

2 Current scenario of clinical pharmacy in CEE countries

2.1 Specificity of CEE countries

Along with many historical reasons, a need to change the paradigm of the healthcare system, stimulate acceptance of the new roles of pharmacists, and for the implementation of the new

TABLE 1 Basic characteristics of analysed countries.

Country	Approximate population size (mln)[a]	Share of population over 65 (%) in 2019[b]	Share of population over 65 (%) prognosed for 2050[b]	GDP *per capita* USD PPP[c]	Healthcare expenditure *per capita* USD PPP[d]
1. Austria	8.9	19	28	59,976	5,705
2. Entity of Bosnia and Herzegovina—Republic of Srpska	1.1	N/A	N/A	6,699	1,477
3. Bulgaria	6.9	N/A	N/A	26,793	2,123
4. Croatia	3.9	N/A	N/A	34,023	2,079
5. Czechia	10.5	20	30	44,802	3,805
6. Estonia	1.3	20	28	43,494	2,507
7. Greece	10.6	22	35	31,177	2,319
8. Hungary	9.7	19	27	36,687	2,170
9. Latvia	1.9	20	32	35,150	2,074
10. Poland	38.2	18	30	37,771	2,289
11. Serbia	6.7	N/A	N/A	21,588	1,686
12. Slovakia	5.4	16	29	31,320	2,189
13. Slovenia	2.1	20	31	43,970	3,737

GDP, gross domestic product; PPP, purchase power parity.
[a]Population size for 1, 3, 4, 5, 6, 7, 8, 9,10, 12, 13 (OECED, 2023c), for 2 (Institute of Statistics Republic of Srpska, 2023a), for 6 (Study programme on clinical, 1960).
[b]Share of population over 65 for 1, 5, 6, 7, 8, 9, 10, 12, 13 (OECD, 2021).
[c]GDP, *per capita* for all, except 2 (OECED, 2023a), for 2 (Institute of Statistics Republic of Srpska, 2023b).
[d]Healthcare expenditure for 1, 6, 7, 8, 9,10, 12, 13 (OECD, 2021), for 3, 4, 5 (OECED, 2023b), for 2 (WHO, 2022), for 11 (WHO, 2018).

services before the investment can be recouped may be identified as the most important barriers of adoption and development of clinical pharmacy in CEE countries. Consequently, the current level of development and use of CPS in most of the CEE countries is still low.

Table 1 presents the basic characteristics of analyzed CEE countries taking into account their population size, share of population over 65 years with predicted changes, gross domestic product (GDP) *per capita* and healthcare expenditure. According to OECD data from 2021 regarding healthcare expenditure *per capita*, all excluding Austria, were below the European average. Moreover, Estonia, Latvia, Poland and Slovakia experienced marginal increase in number of physicians and nurses per 1,000 population over past 20 years. As underlined in OECD report: "Overall, countries with higher health spending and higher numbers of health workers and other resources have better health outcomes, quality and access to care." This links with fact that projected share of population over 65 years will be gradually increasing in all regions in the coming years (OECD, 2021). With increasing age, multimorbidity, polypharmacy and health services utilization becomes more prevalent. A recent analysis of a large European cohort found polypharmacy to be present in 32.1% of citizens aged over 65 years, on average, with Czech Republic with 39.9% being the highest across the studied countries (Midão et al., 2018). Prevalence of polypharmacy, calculated dispensing of five or more drugs for the whole Polish population, ranged in 2019 from 21.8% for January-June, to 22.4% for July-December. However, among those aged 65+, the relevant numbers were 62.3%, and 62.9%, respectively (Kardas et al., 2021). Research from Slovakia showed that among 459 nursing homes residents over 65 years, polypharmacy (use of ≥ 5 drugs by patient daily) was present in 83% of all patients (Jankyova et al., 2020). According to data from Slovenia, 10% of the Slovenian population was treated with at least five medications concomitantly and 4% with over ten medications (Stuhec, 2021).

Nevertheless, CEE countries adopted to a lesser extent some of the tools designed to recognize potentially inappropriate prescribing like EU (7)-PIM list as reported by Fialová et al. (2019).

Similarly, the problem of medication non-adherence seems to be particularly pronounced in CEE countries: in a multinational study as many as 57.6% of Polish patients studied and 70.3% of Hungarian ones reported non-adherence to chronic therapy, whereas corresponding values for West European countries ranged from 24.1% for the Netherlands to 41.5% for England (Morrison et al., 2015).

All these new targets for healthcare systems need to be interpreted in the context of an increasing shortage of healthcare professionals in many European countries, not only in the CEE ones. These deficits are particularly problematic among nurses andphysicians, and the prospects for the future are even more concerning (OECD, 2021).

As illustrated above, there are many reasons to conclude that CEE countries urgently need to adopt new solutions aiding the provision of better healthcare for their citizens. One of the most appropriate answers to these challenges is to increase the utilization of the potential of highly educated and skilled professionals widely available in these countries, i.e., pharmacists, who can be engaged in direct patient care under the auspices of clinical pharmacy to provide better and faster access to healthcare.

2.2 Best practice examples among CEE countries

Although the majority of CEE countries are still lacking sufficient clinical pharmacist development, the Czech Republic and Slovenia can serve as best practice examples with their successful implementation of reimbursed CPS.

2.2.1 Czech Republic

In the Czech Republic (CZ) postgraduate training in clinical pharmacy started back in 1981, with a long tradition of pregraduate education (since 1970's). Speciality training in CP was always considered a core for the clinical growth of pharmacists into independent clinical experts skilled in individualization and optimization of drug schemes in high-risk patients and/or high-risk clinical situations.

At the beginning of specialty training in CZ, the first tutors were trained at departments of clinical pharmacology or abroad-in the United States, United Kingdom and other countries. Later, some tutors were employed in various clinical medical wards and some in hospital pharmacies with limited capacity to provide CPS in clinical wards. In 2005, under the Institute for Postgraduate Education in Healthcare in Prague, Department of Clinical Pharmacy, the first team of advanced clinical pharmacy tutors was established and each of the tutors was responsible for the development of a specific CP subarea (e.g., CP in palliative care, cardiology, oncology and hemato-oncology, geriatrics, pediatrics, etc.). Despite good quality specialty training and skilled supervisors, the lack of paid positions greatly limited further development of CPS. Moreover, hospital pharmacies employing the majority of graduates and specialists in clinical pharmacy engaged them mainly in duties within the pharmacy departments with limited access to clinical wards. Currently, specialty training in clinical pharmacy lasts 5 years and includes clinical rotations of CP trainees among various clinical inpatient and outpatient departments/healthcare facilities to enable the growth of CP specialists in all general aspects of CPS in various patient populations (Institute for Postgraduate Education in Healthcare, 2022) Higher level certified courses (above this general training) are planned, particularly for some specific areas of CP (e.g., CP in intensive care units, psychiatric departments and therapeutic drug monitoring for high-risk patient groups). Currently, not only the Institute for Postgraduate Education in Prague, but also the University Educational Centre in Clinical Pharmacy at the Faculty of Pharmacy, Charles University help with postgraduate education in clinical pharmacy. Specialty training is fully led on accredited CP workplaces (Faculty of Pharmacy in Hradec Kralove, 2023; Institute for Postgraduate Education in Healthcare, 2022).

According to "Concepts of Clinical Pharmacy field" (summarizing history, major guidelines and position of clinical pharmacy field) issued by both Czech professional clinical pharmacy societies—Section of Clinical Pharmacy of the Czech Pharmaceutical Society (Vlček et al., 2016) and Czech Professional Society of Clinical Pharmacy (Gregorová et al., 2014), stage 3 of medication reviews (comprehensive clinical medication reviews) can be independently provided by and remunerated (in inpatient and outpatient care) only for specialists in clinical pharmacy.

It is important to emphasize that after decades of intensive educational effort, the path to fully established and reimbursed clinical pharmacy services led mainly through legislative and accreditation changes.

With the commencement of healthcare facilities in CZ in 2009, hospitals were searching for clinical pharmacists (an obligatory legislative condition to ensure medication safety in all healthcare facilities) and some of these hospitals allowed clinical pharmacists to establish Departments of Clinical Pharmacy, independent of hospital pharmacies, functioning only as clinical workplaces and employing full-time specialists in clinical pharmacy. The first of such workplaces were founded in Hospital Na Bulovce and Hospital Na Homolce in Prague, the Czech Republic (Gregorová et al., 2014). In 2011, legislation defined special care by clinical pharmacists, called "clinical-pharmaceutical care (Czech Republic Parliament, 2011), which was a chievement in developing the whole effort of clinical pharmacy and remuneration of CPS in CZ.

This "special care by clinical pharmacists" helped to distinguish between the activities of specialists in clinical pharmacy from dispensing and consultation services in pharmacies and led to the extremely rapid development of further legislation, reimbursement schemes and new positions of clinical pharmacists as full-time experts in clinical pharmacy - specialists in acute care (since 2012) and ambulatory care (since 2021) (Ministry of Health of Czech Republic, 2012). An important point for establishing "clinical-pharmaceutical care" was an understanding that the key functions of clinical pharmacists are clinical, provided in or for clinical departments (not in and for pharmacies) and need a similar legislative framework as other clinical professions. In 2012, a decree ensured the availability of clinical pharmacists in inpatient wards (every hospital was obliged to use a minimum of 1 clinical pharmacist per 200 beds) (Ministry of Health of Czech Republic, 2012) and in 2015 reimbursed performance for the clinical pharmacy profession was approved by insurance agencies, first for acute care and then in 2020 for ambulatory care. Residential places (paid from funds of the Ministry of Health) are now also being discussed for clinical pharmacists.

All these changes led to a substantial increase is the number of specialists in clinical pharmacy in CZ (by 2022, 170 pharmacists graduated in specialty of clinical pharmacy and 150 are undersigned for the specialty training). Czech clinical pharmacists currently can be employed outside pharmacies in independent working positions (in acute and ambulatory care, and new positions are now established also in home care, long-term care facilities, hospices, etc.). Full-time clinical pharmacy positions enable clinical pharmacists in CZ to devote their professional time only and fully to comprehensive clinical medication reviews. They are involved also in other inpatient and outpatient activities ensuring medication safety and appropriate medication use (works on clinical guidelines, internal directives, appropriate medication use procedures, adherence support, etc.) (Gregorová et al., 2014; Vlček et al., 2016; Gregorová and Langmaierová, 2022).

In conclusion, after decades of unsuccessful "bottom-up efforts" only, contending with numerous barriers to the development of clinical pharmacy services in CZ (1975–2010), an important legislative change enabled change and thus turned the whole situation into the high demand for acute and primary care

clinical pharmacists and fast development of CPS within the healthcare system.

Concerning a rapidly ageing population, CZ postgraduate education includes also the course for pharmacists in "Pharmaceutical care for geriatric patients," focusing on the training of pharmacists firstly in simple medication reviews in older patients and preparing specialists for such signal reviews (providing in the future first medication checks, e.g., in social homes, nursing home facilities, etc.). These professionals will help to prioritize difficult cases of older patients for interventions of clinical pharmacists and to resolve simple medication-related problems with specific use of knowledge of geriatrics. This novel-certified course, focusing mainly on complex older adults with polypharmacy, is under the responsibility of clinical pharmacy education as well (Gregorová and Langmaierová, 2022).

In addition to advanced undergraduate, specialty and postgraduate (PhD) education, CP development in CZ has secured several important professional and legislative bodies, namely, the Czech Professional Society of Clinical Pharmacy and Section of Clinical Pharmacy of the Czech Pharmaceutical Society, Accreditation Committee of the Clinical Pharmacy of the Ministry of Health, and also Association of Clinical Pharmacy Workplaces (newly established in January 2022). CP in CZ has developed as a full educational, practical and scientific field (Gregorová et al., 2014; Vlček et al., 2016; Gregorová and Langmaierová, 2022).

2.2.2 Slovenia

Slovenia developed advanced clinical pharmacy practice over the last 10 years, primarily due to highly-skilled and enthusiastic clinical pharmacists, support from the national insurance company and the Ministry of Health, as well as the shortage of clinical pharmacologists, geriatricians and other specialists (Slovenian Pharmacy Act, 2016; Stuhec et al., 2019; Stuhec, 2021; Stuhec and Tement, 2021). There is only one pharmacy school in Slovenia (Faculty of Pharmacy Ljubljana, University of Ljubljana) which provides undergraduate and postgraduate education. Specialization in clinical pharmacy is available and lasts 3 years. Clinical pharmacists are included within the two different Slovenian associations: The section of Clinical Pharmacists (organized as one of the sections of the Slovenian Pharmaceutical Society) and the Section of Hospitals Pharmacists (organized as one of the sections of the Slovenian Chamber of Pharmacy).

Three advanced and fully reimbursed clinical pharmacy services have been developed in Slovenia recently: clinical pharmacist consultant in all primary care settings from 2018, a seamless care system in all Slovenian hospitals from 2023 and a clinical pharmacist as a mandatory team member in the psychogeriatric team in all psychiatric hospitals from 2020 (Slovenian Pharmacy Act, 2016; Rules on the provision of pharmacy services by hospital pharmacies, 2022; Stuhec, 2021). All services require clinical pharmacy specialists and health institutions are paid extra for these services (e.g., hospitals and primary care settings). Clinical pharmacy is included and well-defined in Slovenia in the new Slovenian Pharmacy Act (valid from 2017). According to this Act, clinical pharmacy is an integral part of hospital pharmacy and pharmacists must be included in all medication-related processes and healthcare teams on the hospital ward. Each Slovenian hospital must provide clinical pharmacy services to its patients and hospital managers are responsible in ensuring the correct staffing level. In addition, a medication review service and many important clinical pharmacy services are defined and included in this Act (e.g., medication review, hospital clinical pharmaceutical services and seamless care) (Slovenian Pharmacy Act, 2016). The Slovenian Ministry of Health also developed an essential legislation document—Rules on the provision of pharmacy services by hospital pharmacies, where it is specified that only clinical pharmacists specialists (specialization is necessary) can work as clinical pharmacists independently in the hospital wards with beginning of year 2023 (Rules on the provision of pharmacy services by hospital pharmacies, 2022). Clinical pharmacists must be included in the team, have full access to patients and all datasets, and provide medication reviews where they decide. All seamless care processes have been defined inside this Sub Act (e.g., best possible medication history, medication reconciliation at admission, medication reconciliation at discharge, personal medication card before discharge and home dispensing).

A clinical pharmacy service cannot be developed without successful reimbursement models. In this context, all three models described have been reimbursed and some others are underway (e.g., outpatient clinics for patients with mental disorders in psychiatric hospitals). Clinical pharmacy ambulatory settings in all psychiatric hospitals (outpatients only for patients with mental disorders) have also been positively evaluated by the Slovenian Ministry of Health (evaluation committee) and proposed for national reimbursement in 2024. All psychiatrists in Slovenia will have an opportunity to refer patients with mental disorders to these settings in psychiatric hospitals, where clinical pharmacists specialists with experiences in mental disorders pharmacotherapy (minimum 3 years) will provide a medication review (Slovenian Ministry of Health, 2022). In 2023, discussions are taking place about pharmacist dependent prescriber in primary care settings (similar to the US model of collaborative practice agreement).

The Slovenian experience shows that clinical pharmacists must be actively included in reimbursement negotiations, health politics, health policy development, health insurance and the Ministry of Health (Stuhec, 2021).

2.3 Lack of CPS in most CEE countries

The Czech Republic and Slovenia have been able to fully implement and reimburse some CPS over recent years. Unfortunately, this is not the case for most of the other CEE countries and some other parts of Europe. The most recent situation of clinical pharmacy profession in 11 countries with a short description and summary of data are presented in Table 2.

2.3.1 Austria

Undergraduate CP lectures in Austria are available at the Universities of Innsbruck, Graz, Vienna and Salzburg. Currently, only basic elements of clinical pharmacy are scheduled in their curricula (Karl-Franzens-Universität Graz, 2018; Universität Wien, 2019; Paracelsus Medizinische Privatuniversität, 2020; Leopold-Franzens-Universität Innsbruck, 2021). The Austrian Chamber of Pharmacists offers a postgraduate weekend seminar focusing on basic medication analysis and clinical pharmacy service provision in

TABLE 2 Summary of data about details of CPS in CEE countries (data valid as per January 2023).

Country	Professional education in clinical pharmacy included in		Hospital-based clinical pharmacy services	Outpatient clinical pharmacy services*	National association(s) of clinical pharmacy	Specialization, duration of the training
	Undergraduate training	Postgraduate training				
Austria	No	Yes	Yes Reimbursed	N/A	N/A	N/A
Entity of Bosnia and Herzegovina - Republic of Srpska	Yes, but optional	Yes, 3 years	Available in two hospitals Reimbursed	Available in selected places, Not reimbursed	N/A	Yes, 3 years
Bulgaria	Yes	Yes	Yes Not reimbursed	N/A	N/A	Yes, 3 years
Croatia	Yes	Yes	N/A	N/A	Section for clinical pharmacy under Croatian pharmaceutical society as well as the committee for clinical pharmacy under Croatian pharmaceutical chamber	Yes
Czechia	Yes	Yes	Yes Reimbursed	Yes Reimbursed	Section of Clinical Pharmacy of the Czech Pharmaceutical Society and Czech Professional Society of Clinical Pharmacy	Yes, 5 years
Estonia	Yes	Yes	N/A	N/A	Not available, existing within Estonian Society of Hospital Pharmacists	N/A
Greece	No	Yes	N/A	N/A	N/A	N/A
Hungary	Yes	Yes	Yes Not reimbursed	N/A	Hungarian Society of Hospital Pharmacist	Yes 3 years
					Hungarian Chamber of Pharmacists (hospital and clinical pharmacy section)	
					National Healthcare Service Centre (Hospital and clinical pharmacy section)	
Latvia	Yes	Yes, 2.5 years	Available in 5 hospitals Not reimbursed	N/A	Section at the Pharmacists' Society of Latvia	Yes, 2.5 years
Poland	Yes	Yes	Yes, only in a few hospitals Not reimbursed	N/A	Yes, Polish Society of Clinical Pharmacy	Yes, 3 years
Serbia	Yes	No	Yes, only in a few hospitals Not reimbursed	Yes, only in a few hospitals Not reimbursed	The Section of Hospital pharmacists and Section of Pharmaceutical Care within the Pharmaceutical Association of Serbia	Yes, 3 years
Slovakia	Yes	Yes	Available Reimbursement for TDM laboratory items only	Available on demand. Not reimbursement	Section of Clinical Pharmacy, Slovak Pharmaceutical Association	Yes, 3 years
Slovenia	Yes	Yes	Yes Reimbursed	Yes Reimbursed	The Section of Clinical Pharmacists, which is organised as one of the sections of the Slovenian Pharmaceutical Society	Yes 3 years

N/A, not available; *includes services provided in general practice, outpatient clinics.

community settings (Medikationsanalyse Basiskurs, 2023). The University of Vienna offers a postgraduate certificate course in clinical pharmacy which lasts one semester part-time (Klinische Pharmazie, 2012). There is currently no Master's degree in clinical pharmacy offered at Austrian higher schools. However, it is planned to be implemented in autumn 2023. Only 42 of all 266 hospitals in

Austria have a pharmacy department and even less offer the provision of clinical pharmacy services (Österreichische Apothekerkammer, 2020).

It is stated in the Austrian regulations for pharmacy services that "patient-oriented services (clinical pharmacy)" should be provided by the hospital pharmacy (RIS, 2022). Nevertheless, the provision of clinical pharmacy services is not included in the Austrian pharmacy profession act (RIS - Apothekengesetz - Bundesrecht konsolidiert, 2022). In the Austrian health structure plan (ÖSG) it is stated that "the availability of a sufficient number of pharmacists to provide clinical pharmaceutical services (including structured medication management, reduction of polypharmacy) must be ensured" (Bundes-Zielsteuerungskommission, 2017). However, there is no defined number as to how many clinical pharmacists per patient can be considered "sufficient." Since January 2020 clinical pharmacy services can be registered in Austrian hospitals in the insurance reimbursement catalogues, although currently they are not directly remunerated and data is collected for informational reasons and for consideration of potential reimbursement implementation in the future. They must be requested by a physician or otherwise justified using standard operating procedures which are not readily available at this point and have to be implemented by each hospital individually (Müller, 2012). No national association of clinical pharmacy has been established. Austria has two associations of hospital pharmacists. In one of them membership is dependent on additional membership with the Austrian association of employed pharmacists (AAHP, 2023; VAAOE, 2023).

2.3.2 Entity of Bosnia and Hercegovina—Republic of Srpska

In the Republic of Srpska, clinical pharmacy education has been included in undergraduate studies as an optional course. Starting from 2023/2024 academic year, CP will become an obligatory course and will include practical education at the hospital in addition to theoretical education at the university. A postgraduate course in clinical pharmacy was first introduced in the academic year 2021/2022, as a 3 years long specialization which led to the achievement of the title of a clinical pharmacist. Postgraduate studies at the Faculty of Medicine leading to a PhD degree are available for pharmacist with an option to choose a thesis topic from the field of clinical pharmacy.

Hospital-based CPS are implemented only in 2 out of 10 hospitals in the Republic of Srpska while outpatient clinical pharmacy services have not been developed yet. Clinical pharmacy is not included in the legislation, but there is official reimbursement for hospital-based CPS by the national health insurance fund (each written consultation of a clinical pharmacist is paid 20 euros). Standards for providing CPS are still not yet developed. There is no national association of clinical pharmacy in the Republic of Srpska due to a small number of practising clinical pharmacists. However, it is worth noting that, they all cooperate and exchange knowledge and experience on daily basis.

2.3.3 Bulgaria

The legislative analysis showed that clinical pharmacy and clinical pharmacists are mentioned only in 2 documents: Ordinance 28 for the structure, order, and organization of work in the pharmacies (2008) and Good Pharmaceutical Practice in Bulgaria (2020). At least one Master of Pharmacy with a postgraduate degree in Clinical Pharmacy or an undergraduate specialization in Clinical Pharmacy should work in hospitals with more than 400 beds for active treatment or with at least 10 clinics/wards with beds, as well as in medical establishments that perform activities in medical oncology and/or clinical haematology. Clinical pharmacists should follow the principles of clinical pharmacy and be active participants in the treatment process.

The legislation in the country gives some basic rules as no specific clinical pharmacy services have been implemented for any group of Bulgarian patients. Despite the slow but stable progress in legislation on Clinical pharmacy, there are no specific clinical pharmacy services for patients nor reimbursement of such services. No national association of clinical pharmacy is established so far. However, there is a national non-profit organization, representing hospital pharmacists, offering clinical pharmacy training (OHPB, 2022). The organization has adopted the European Standards of hospital pharmacy with Sections 4, 5 detailing the responsibilities of clinical pharmacists (European Society of Hospital Pharmacy, 2023).

2.3.4 Croatia

Although clinical pharmacy in Croatia has been developing since 1998, there are still no CPS included in the legislation. Clinical pharmacy education has a continuum through undergraduate and postgraduate education as well as clinical pharmacy specialization. After finishing the postgraduate degree in clinical pharmacy pharmacists can finish a full 3-year specialization in clinical pharmacy. Candidates become clinical pharmacists for primary or hospital care via two different specialization programs.

At the moment there are over 300 pharmacists with a postgraduate degree in clinical pharmacy as well as 40 specialists in the field of clinical pharmacy in Croatia. Regardless of the legislation gap CPSs and related activities are being developed by academic research and pilot projects in primary and hospital settings. In primary care, data from these activities show services having a positive impact on clinical, safety and quality of life (QoL) in anticoagulated patients through a randomized trial (Falamić et al., 2018; 2019; 2021). Other pilot projects providing comprehensive medication management have shown that the service is affordable and impacts positively on QoL, adverse drug reactions and healthcare utilization (Brajković et al., 2022b; 2022a; Mucalo et al., 2022). Medication reconciliation research from hospital setting shows clinical pharmacists detect medication discrepancies and prevent adverse patient outcomes at admission, as well as help reduce unintentional discrepancies associated with potential harm at discharge (Marinović et al., 2016; 2021). Clinical and hospital pharmacists in Croatia have proven that their involvement in the hospital medicines policy leads to substantial cost savings for the healthcare system (Javor et al., 2021).

The legislative gap regarding CPS is foreseen to be resolved in 2023 with the planned passing of the new Pharmacy Law. This should set up foundations for the negotiations of the CPS reimbursement. Standards of providing CPS and other activities of clinical pharmacists are yet to be developed on the national level, taking into account the practice and standards of other European countries and professional organizations.

2.3.5 Estonia

Currently clinical pharmacy is included in the pharmacy curriculum at the University of Tartu as a separate subject. During the pharmacy internship, students can learn about the work of a clinical pharmacist in a hospital setting and select research project in the field of clinical pharmacy. An international e-learning clinical pharmacy and patient consultation continuous professional development course was developed at the same university as a form of postgraduate education for pharmacists who work either at hospitals or community pharmacies. The programme is characterized by a problem-based approach and a large amount of practical training (Clinical, 2023). An international MSc e-course in clinical pharmacy is under development. The listed courses are taught and/or developed by practicing clinical pharmacists (of whom there are less than 10 in Estonia) and who have acquired their education abroad, mainly in the United Kingdom and Ireland.

CPS are not currently standardized for neither hospital nor outpatient setting. Services are not reimbursed. They are provided in the hospital setting with a focus on the selection of the most suitable evidence-based treatment regimen for the patient and the achievement of the best treatment results. Medication review has been recently described as a structured clinical pharmacy service for primary care, but its implementation and reimbursement are still under development. Legalization of the clinical pharmacist specialty as a separate independent profession has been initiated. Clinical pharmacists belong to the Estonian Society of Hospital Pharmacists.

2.3.6 Greece

Greece has three undergraduate schools of pharmacy all of which are located in large urban areas. Undergraduate studies consist of 4 years of theoretical and practical courses plus 1 year of traineeship at a hospital and a community setting. None of the three schools currently offer patient-related courses like pharmacotherapy or medicines optimization (Aristotle University of Thessaloniki, 2018). One of the three schools offers a postgraduate master's degree in Clinical Pharmacy. It provides theoretical knowledge around disease management and includes a 5-month practical training at the hospital (Master in Clinical Pharmacy, 2023). Besides management tasks like stock turnover, online medicine orders or communicating with medicine suppliers both hospital and community pharmacists' activities are limited mainly to the dispensing process (Greece Pharmacy Profession, 2023).

Pharmacists perform clinical activities in their daily practice only in a few private hospitals. The services offered mostly arise from the personal interest and engagement of the pharmacist rather than an organized framework. Community pharmacy owners belong to local pharmaceutical associations while pharmacists working in public hospitals are represented by the Panhellenic Association of Hospital Pharmacists or PEFNI (PEFNI, 1988). The former associations comprise the Panhellenic Association of Pharmacists or PFS (PFS, 2016). There is no association of clinical pharmacy at the moment in Greece. New legislation regarding secondary care has been introduced by the Greek government recently. Certain major changes have been implemented with the aim of improving the services offered by public hospitals, but pharmacists are not mentioned as providers of clinical services (Greek hospital legislation, 2023). Clinical tasks of community pharmacists are also limited and sporadic. Annual influenza vaccination has been incorporated in pharmacists' activities in the last few years and further discussions are in progress with the view of being remunerated by the state.

2.3.7 Hungary

In Hungary there are four Universities with a Faculty of Pharmacy. At each university students can learn about the concept of clinical pharmacy services. The University of Szeged has the longest history of undergraduate training for professional education in clinical pharmacy. According to the main European trends, Hungarian universities are willing to keep focusing on clinical pharmacy services. A 1-month hospital pharmacy internship is mandatory for every student before graduation. Postgraduate training is also available at all the universities, but it is not focused solely on clinical pharmacy and includes both hospital and clinical pharmacy training within 3-year study programme. After graduating in this specialization there are several 2-year sub-specialization opportunities (oncology, infectious diseases, paediatrics, medication information and counselling, parenteral medications, toxicology, clinical radiopharmacy), aimed at pharmacists working in a given area to gain relevant expertise. Postgraduate training can either be a state-run central residency training programme or self-financed, the former being the most common route.

Currently there are 501 hospital and clinical pharmacy specialists, 29 of them having additional sub-specialties. CPS are not yet reimbursed in Hungary. Good practice guidelines by the National Institute of Pharmacy and Nutrition exist but are limited to inpatient counselling by pharmacists, individual, per-patient drug dispensing (unit dose or daily dose), cytotoxic compounding, in-house parenteral infusion manufacturing (including parenteral nutrition therapy). More advanced CPS, including medication review are rare, but there are hospitals where it is achieved on specific wards. Partially as a result of the state-run central residency training programme, the number of pharmacists working in hospitals has been rapidly growing. The implementation of automated dispensing systems in Hungarian hospitals is also on the rise and there is a tendency for CPS to develop more effectively in these hospitals.

The last update of national pharmacy standards was made in 2012, but a new version is now being prepared. It is planned that it will define "clinical pharmacy services" and describe CPS processes. Three institutions are involved in matters relevant to clinical pharmacy in Hungary: Hungarian Society of Hospital Pharmacists, Hungarian Chamber of Pharmacists (section of hospital and clinical pharmacy), National Directorate General for Hospitals (Health Professional Colleges—Hospital and Clinical Pharmacy Council).

2.3.8 Latvia

Both undergraduate and postgraduate education in clinical pharmacy are provided by Riga Stradins University. Undergraduate education - an introductory course in Clinical pharmacy is also provided by the University of Latvia (obligatory course). The first clinical pharmacist started working at Childrens' Clinical University Hospital in October 2008.

Although there are many pharmacists with a Master level education in clinical pharmacy, only some of them work as clinical pharmacists. There are still very few hospital-based CPS. In total, four clinical

pharmacists are actively working in five hospitals. One of the pharmacists works in two hospitals. There are no outpatient CPS at the moment. CPS are included in legislation but there is no special reimbursement for the services. There are no standards of providing CPS at the national level. Activities depend on particular hospital needs. Clinical pharmacy section is a part of the Pharmacists' Society of Latvia.

2.3.9 Poland

The first initiatives concerning clinical pharmacy in Poland date back to 1970s. Nevertheless, pharmacist involvement in direct patient care was not adopted into practice for a long time (Bryla et al., 2020). In the last few years, an increase in the importance of the pharmacist's role and gradual development of CPS has been observed. In 2020, a national consultant for clinical pharmacy was appointed followed by subsequent appointments of regional consultants. The Pharmacy Profession Act was published the same year. It includes the definition of clinical pharmacy services.

In 2021 the Ministry of Health (MoH) released a report describing pharmaceutical care in community pharmacies (Polish Ministry of Health, 2020). Medicines review service was piloted in community pharmacies. The publication of pilot results was anticipated at the time of preparing this manuscript.

Further steps were taken to describe CPS and in 2022 another report prepared by a working group established by the MoH was released. The report describes 5 main services: medicines reconciliation, medicines review, patient education, therapeutic drug monitoring, specialized medicines service (includes high-risk oncology therapies and other specialist treatments dispensed from hospitals). The concept described in the document assumes pharmacist's involvement in all levels of care–from admission to discharge, including CPS in general practice and long-term care facilities (Polish Ministry of Health, 2022). However, currently there are no formal requirements to employ clinical pharmacists and CPS are not reimbursed. Most activities are undertaken by pharmacist working in hospital pharmacy who are motivated to devote part of their time to clinical duties. A few pieces of works have described potential roles for the pharmacist and their benefits or the pharmacist's perspective of the patient's safety, but only one reported outcomes from a clinical pharmacy service fully integrated into medical care (Urbańczyk et al., 2022).

Clinical pharmacy is included as a subject in undergraduate education. Additionally, pharmacist can complete a postgraduate specialization which lasts 3 years. Around 270 people have already graduated obtaining this title, but estimates are probably not accurate as the programme changed over years and not everyone has formally registered. In 2020 Polish Society of Clinical Pharmacy was established. The Society released the first Polish standard in clinical pharmacy (Medicines reconciliation) and more standards are currently being developed (Bryla et al., 2020; Polish Society of Clinical Pharmacy, 2021).

2.3.10 Serbia

Clinical pharmacy has been an obligatory subject during undergraduate studies at Faculty of Pharmacy University of Belgrade since October 2006 (University of Belgrade, 2023). Specialization in clinical pharmacy lasts 3 years and there are currently approximately 35 specialists (Study programme on clinical, 1960). Moreover, similar content is offered within the specialisation in pharmacotherapy (3 years' duration, approximately 25 specialists), Pharmaceutical care (18 months' duration, approximately 550 specialists) and Pharmacotherapy in pharmacy practice (18 months' duration, approximately 100 specialists). Research in clinical pharmacy in Serbia is on the rise mainly due to project tasks within the specialization thesis and collaboration with the university.

Significant progress in delivering clinical pharmacy/pharmaceutical care services by pharmacists in Serbia has been made in the past decade. Pharmacists in primary care have piloted the following pharmacist roles: diabetes counsellor, asthma consultant, antibiotic consultant, new medicines service and counsellor on the safe use of medicines during breastfeeding. However, in many community pharmacies, services are still limited to traditional pharmacy practices such as procurement of drugs, extemporaneous compounding, dispensing of prescriptions, and selling medicines. There are only 5 services recognized officially by the nomenclature of health services in primary care settings (only two related to clinical pharmacy) and approximately 30 services in secondary and tertiary health settings (only a few related to clinical pharmacy), Pharmacists are not paid based on the services provided (Rule book on the nomenclature of health, 2023a; Rule book on the nomenclature of health, 2023b).

A new document on nomenclature based on piloted services with confirmed evidence is planned to be adopted next year. Moreover, Good Pharmacy Practice paper which defines standards and guidelines enabling the provision of pharmaceutical services was published in the Official Gazette and it needs to be applied from the beginning of April 2023 (Good pharmacy practice, 2021).

2.3.11 Slovakia

There are two pharmacy schools providing pharmacy studies in Slovakia: Comenius University in Bratislava and Faculty of Pharmacy and University of Veterinary Medicine and Pharmacy in Košice. There is an obligatory course of clinical pharmacology/pharmacy and pharmacotherapy included in the undergraduate curriculum (Švec and Kuželová, 2012). Other courses available pharmacists are an obligatory one-semester courses of Social Pharmacy and Pharmacoeconomics, Pharmaceutical care and an optional course on Hospital Pharmacy. Postgraduate doctoral education is provided by Comenius University in Bratislava, Faculty of Pharmacy in the scientific programme of clinical pharmacy (Comenius University in Bratislava, 2022a; Comenius University in Bratislava, 2022b). Postgraduate specialty education in clinical pharmacy is provided by Slovak Medical University in Bratislava. Pharmacists need to complete the specialty in retail pharmacy in the first stage (3 years), thereafter they can continue studying clinical pharmacy for 2 years to become a clinical pharmacist (Minimal standard for specialty study program in clinical pharmacy, 2010).

The level of development of hospital-based and outpatient CPS is low in Slovakia. In fact, there are 116 hospitals (general and specialized), and only 16 clinical pharmacists' posts. At present, 3 clinical pharmacists work full-time in departments of clinical pharmacology, together with clinical pharmacologists with the main

interest in optimizing pharmacotherapy in hospitalized patients, therapeutic drug monitoring, identifying adverse drug reactions and interactions, administering medication via enteral feeding tube, medication risk assessment in pregnancy and lactation, patient education. Three clinical pharmacists are providing toxicological consultancy at the National Toxicological Information Centre. The others are based in hospital and community pharmacies. They are focusing on hospital/community pharmacy services and from the point of clinical pharmacy mainly in a medication information service.

CPSs are not mentioned within the Slovak legislation, but the Ministry of Health issued the document—Concept of healthcare in clinical pharmacy, which presents the standard of providing CPSs (Minimal standard for specialty study program in clinical pharmacy, 2010). CPSs are included in the catalogue of medical services, but are not reimbursed from compulsory insurance in Slovakia despite the efforts of the Section of clinical pharmacist. CP are associated in the Section of clinical pharmacy established in 1990 (Clinical Pharmacy Section, 2023).

3 Actionable recommendations

Due to underdevelopment of CPS in CEE countries we call for the undertaking of the necessary steps to allow its wide implementation. The most needed actions for the next decade are composite activities including supporting education and practice of clinical pharmacists with legislation and reimbursement of CPS. With this in place, one can expect optimized drug utilization, drug safety and medication adherence and consequently improved quality and cost-effectiveness of healthcare services in CEE countries. In light of these aims, following actionable recommendations can be set:

1. Including clinical pharmacy in the education portfolio in CEE countries both in undergraduate and postgraduate pharmaceutical education with the concomitant assurance of the possibility to perform clinical activities.
2. Enabling and supporting research in clinical pharmacy field, taking particular care of benchmarking of available interventions. Key clinical pharmacy institutions should be identified and collaborative programme needs to be developed.
3. Allowing interprofessional collaboration and adopting CPS across all healthcare settings with the aim to assure a high quality continuum of care.
4. Adopting best practices from other countries and guidance provided by relevant organisations and authorities, such as WHO or EDQM.
5. Creating national legislative framework supporting clearly defined workplaces for pharmacists and reimbursement schemes of CPS.
6. Forming national CP scientific societies to promote policy changes as a professional body. Working collaboratively with them to use their expertise and facilitate development of standards regarding clinical pharmacy profession and practice in CEE.
7. Campaigns directed to the public should be organized to promote and explain the role of clinical pharmacists in direct patient care.

4 Discussion

CEE countries have multiple challenges to face such as an ageing society with high prevalence of polypharmacy, shortage of healthcare professionals to assure continuity of care, financial constraints. At the same time, they are under great pressure to provide both high-quality and cost-effective health services. However, it does not differ from other European countries. Under such circumstances, it is reasonable to consider a wider engagement of clinical pharmacists who are well positioned to prevent and manage drug-related problems as well as ensuring safe and effective use of medications.

As described earlier, most of the CEE countries have not yet developed CPS to significant extent. Some steps have been made, but only in relation to improvements in areas of education and practice in order to implement clinical pharmacy services. In contrast, the Czech Republic and Slovenia belonging to CEE region have managed to successfully adopt solutions already existing in other countries with a long history of CPS presence. Consequently, CPS are currently available there in both hospitals and primary care. In both of these countries, the pharmacist's efforts to develop appropriate skills and raise the awareness of benefits of CPS have resulted in important changes in legislation, which has paved the way to the reimbursement of CPS. Being inspired by these success stories, the following are important points to consider in developing CPS in the other CEE countries.

4.1 Education and research

The provision of high-quality CPS requires appropriate training. Therefore, continuous improvement of education (both undergraduate and postgraduate) and gaining relevant clinical skills in practice are of utmost importance. Most CEE countries have undertaken steps to include clinical pharmacy in their educational portfolio, but a lack of opportunities to practice in inpatient and outpatient settings can be an obstacle in achieving further progress. Pharmacists should have opportunities to practice in a clinical setting under the supervision of more experienced colleagues, similarly to other professions. This was also confirmed by a recent initiative led by the European Society of Clinical Pharmacy Education Committee, which aimed to map clinical pharmacy education and practice in Europe. Results of a cross-sectional survey focused on three complementary domains of undergraduate education, postgraduate education, and practice proved that whilst almost all out of 40 studied countries provided clinical pharmacy education at the undergraduate level, the breadth and depth varied. Around two-thirds of countries provided master level clinical pharmacy programmes which were also highly variable, with similar results for continuous professional development. These results prove that there is a need for further development of clinical pharmacy education at all levels (Moura et al., 2022). In addition, all CEE countries will be in need of academic teachers who are skilled both in research and practice.

Education is inseparably connected with research. Combining practice with conducting research builds up the evidence enabling the wider promotion of CPS. Therefore, activities of this kind should be encouraged in CEE countries in order to collect data on clinical

pharmacy performance in different scenarios. Of note is the fact that comparing the data between the countries might be challenging, because of major differences in healthcare systems. However, it is entirely feasible to adapt such work to local systems. There is already an evidence base demonstrating that CPS are beneficial in multiple aspects such as optimized drug utilization and overall hospitalization costs (McMullin et al., 1999; Reardon et al., 2015; Rychlickova et al., 2016), increased drug safety (Anderson and Schumock, 2009; Simoens et al., 2011), improved medication adherence (Schulz et al., 2019; McCarthy and Thomas Bateman, 2022), reduced hospital admissions (Scullin et al., 2007; Gillespie et al., 2009), reduced length of hospital stay (Scullin et al., 2007), reduced outpatient healthcare utilization and costs (Byrne and Dalton, 2017), higher patient satisfaction (Yuliandani et al., 2022) and positive feedback from other healthcare professionals (Chevalier et al., 2016). Nevertheless, research on the theory and practice of CPS in CEE countries is still of value, as this may help to benchmark available solutions, prioritizing the best ones, and their wider implementation. Therefore, CEE should promote clinical pharmacy research based on the impact of clinical pharmacists on different outcomes (i.e., reduced average length of stay in hospitals, reduced number of and longer time to readmissions, number of outpatients visits, optimized drug utilization, improved drug safety, reduced medication burden and healthcare costs, higher patient satisfaction and improvement in patient adherence to prescribed medicines), which is often necessary for successful national reimbursement.

4.2 Interprofessional collaboration and development of core CPS

According to a number of standards, pharmacists should be members of a multidisciplinary team and use their expertise to optimize pharmacotherapy for individual patients (Bond et al., 2004; Mccusker et al., 2013; Fernandes et al., 2015). Collaborative, effective work as a team should be a starting point for other activities to ease the adoption of a new collaborative model. The duties of a clinical pharmacists can overlap with other professionals, but they complement each other. However, tasks and models of providing services together with shared responsibility need to be clearly identified. This helps to place CPS in the system.

Using experience from various countries, a number of evidence-based services could be implemented in CEE. This includes but is not limited to multidisciplinary ward rounds, medicines reconciliation, medicines review, patient education, medicines information, therapeutic drug monitoring, and pharmaceutical care plans (Bond et al., 2004; Mccusker et al., 2013; Fernandes et al., 2015). Additionally, services specific to a particular country could be adapted depending on the need. Currently, the CEE countries have managed to develop, to different extents, activities provided mainly in hospitals. However, the goal should be to cover both hospital and ambulatory care settings, including primary care and long-term care facilities as this also benefits patients and healthcare system (i.e., improved disease management and adherence) (Santschi et al., 2014). In order to assure patient-centeredness at all levels of the continuum of care, the models of "seamless care" or "integrated medicines management" should be implemented (Spehar et al., 2005; Scullin et al., 2007). Particular services can be implemented gradually, giving priority to the most strategic ones from the country's perspective. National ministries of health, insurance companies, professional bodies, academia, scientific societies and patient organizations should be engaged in the process.

4.3 Legislative frameworks

All CEE countries have demonstrated a substantial "bottom-up" approaches in developing CPS in their regions. Unfortunately, in many cases, years of efforts did not allow them to reach the level of countries recognized as models of best practice. Analyzing available data, it seems that they mainly lack appropriate legislative frameworks to support the shift from medicine supply roles to pharmacist delivered patient-centered services for the purpose of improving rational use of medications. Stakeholders need to acknowledge that national healthcare systems cannot afford not to use the full potential of pharmacists. Therefore, CPS should no longer be optional (because then in essence they would be excluded from the team and patients), but should be widely adopted similarly to other evidence-based solutions. This requires appropriate legislation and setting up of framework for new services using experience from other countries. It should also include constituting workplaces for clinical pharmacists in healthcare settings and aiming to reimburse services for wider adoption of process changes.

However, there is a real need for "top-down" activities. National policies and legislation need to support clinical pharmacy programs. Only with this support in place, will clinical pharmacists have the resources and support needed to provide high-quality, evidence-based care to patients. This also includes relevant funding for clinical pharmacy education, research, and practice, as well as changes in laws and regulations that allow clinical pharmacists to practice to the full extent of their training and expertise. In addition, residency spaces for CP should be secured and costs covered similarly to other medical professions.

As mentioned in the "Introduction" section, in March 2020 the Committee of Ministers of the Council of Europe adopted Resolution CM/Res(2020)3 on the implementation of pharmaceutical care for the benefit of patients and health services (Committee of Ministers Resolution, 2020). The Resolution and upcoming EDQM's guidelines on Medication Review provide national authorities and healthcare professionals with guidance on how to implement pharmaceutical care and clinical pharmacy services, when needed through the allocation of appropriate budgetary resources such as incentives for performing pharmacy services or workforce resources.

Governments, competent health authorities and professional bodies across Europe are encouraged to put into practice the above resolution in their countries with a view to promote patient-centered care, encourage more responsible use of medicines, contribute to rationalizing healthcare resources, and helping reduce inequalities in healthcare in Europe.

Whenever possible, cooperation should be established with other international organizations and healthcare stakeholders to develop synergies, avoid duplication of efforts, and eventually meet the common objective of achieving better, patient-centered healthcare in Europe through policy-making decisions at the governmental level.

Another important document setting the scene for CPS in CEE is Medication without Harm, the third global patient safety challenge launched in 2017 by the WHO (WHO, 2017).

4.4 Stimulating role of European, national and international associations of clinical pharmacy

Not all CEE countries have established societies representing the clinical pharmacy profession which could advocate for the development of CPS and set standards of practice. However, existing national and International pharmacy professional societies and associations can support developments of CPS in CEE countries by forming powerful coalitions, harnessing expertise, facilitating learning and providing tools. Hence, an unprecedented role can be played by European Society of Clinical Pharmacy (ESCP), which was founded in 1979 and now has members from more than 45 countries across the globe, representing all pharmacy sectors. ESCP is an organization that promotes, supports, implements and advances education, practice and research in clinical pharmacy in order to optimize outcomes for patients and society (European Society of Clinical Pharmacy, 2023a). The vision of ESCP is to play the role of an international leader in advancing quality and innovation in clinical pharmacy education, practice and research. Several years ago, ESCP launched a 'Best Practice Papers' initiative in collaboration with the International Journal of Clinical Pharmacy. These papers aim to disseminate best practices in clinical pharmacy, and to enhance the exchange of knowledge and experiences to promote innovative and sustainable clinical pharmacy service. Best practices relate to developments in practice and education, which are supported by thorough development and implementation processes along with high quality, robust and rigorous research evidence of evaluation outcomes. These outcomes may include aspects such as acceptability, adoption, appropriateness, effectiveness, cost-effectiveness, efficiency, satisfaction, sustainability, etc. With a focus on development, implementation and evaluation, there is consideration of key facilitators, barriers and how these were overcome. It is hoped that these will act as a stimulus for similar developments in other countries, including CEE. In collaboration with the European Association of Hospital Pharmacists, ESCP launched the Oath to Society in October 2021. The Oath is intended to act as a contract for excellence in providing compassionate patient care, working as part of the healthcare team, advancing the pharmacy profession, and showcasing how pharmacists work every day. It also represents the promise made to patients and the public, and healthcare professionals and acts as a compass for the highest standards of ethics, integrity, and professionalism (European Society of Clinical Pharmacy, 2023b).

4.5 Need for public campaigns to increase the awareness of clinical pharmacy in CEE countries among healthcare professionals and lay public

Public campaigns are important to promote clinical pharmacy, because they raise awareness about the role and value of clinical pharmacists in healthcare. By educating the public and healthcare professionals about the expertise and services that clinical pharmacists provide, such as medication management, campaigns can help increase the demand for these services. Additionally, public campaigns can help to dispel any misconceptions about the role of clinical pharmacists and demonstrate the valuable contributions they make to the healthcare team. This in turn can help to increase the visibility and recognition of the profession.

Author contributions

Conceptualization, PK; methodology, KU and PK; resources, KU, SG, VA, SF, TK, MK-M, BM, AO, IS, AS, KT, ZT, DV, AW-H, DF, JV, MS, AH, MSC, DS, AM, SR, F-XL, and PK; data curation, KU; writing—original draft preparation, KU and PK; writing—review and editing, SG, VA, SF, TK, MK-M, BM, AO, IS, AS, KT, ZT, DV, AW-H, DF, JV, MS, AH, MSC, DS, AM, SR, and F-XL; supervision, PK; project administration, KU. All authors contributed to the article and approved the submitted version.

Acknowledgments

We would like to acknowledge the input of other representatives from different countries who helped in gathering the data and were not directly involved in manuscript preparation.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 13 October 2023
DOI 10.3389/fphar.2023.1254291

OPEN ACCESS

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RECEIVED 06 July 2023
ACCEPTED 28 September 2023
PUBLISHED 13 October 2023

CITATION
Kardas P, Aarnio E, Agh T, van Boven JFM, Dima AL, Ghiciuc CM, Kamberi F, Petrova GI, Nabergoj Makovec U and Trečiokienė I (2023), New terminology of medication adherence enabling and supporting activities: ENABLE terminology.
Front. Pharmacol. 14:1254291.
doi: 10.3389/fphar.2023.1254291

New terminology of medication adherence enabling and supporting activities: ENABLE terminology

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Introduction: Medication non-adherence negatively affects the effectiveness of evidence-based therapies and sustainability of healthcare systems. Lack of agreed terminology of medication adherence enabling and supporting activities leads to underuse of the available tools. The ENABLE COST Action was aimed at proposing a new terminology for these activities in order to help both scientific research and its clinical application.

Methods: Initial discussions within the ENABLE Working Groups allowed for the conceptualization of four interlinked terms related to adherence, i.e., "medication adherence technology", "medication adherence enhancing intervention", "best practice" and "reimbursement". The iterative process of internal discussion was structured around two dedicated international workshops. Moreover, extensive stakeholder consultations have been organised, including an interactive online survey used to assess the level of agreement with, and the clarity of relevant terms and definitions proposed.

Results: Detailed analysis of the results of this process allowed for fine-tuning of the items, and finally, for proposing the final set of definitions. Across all the three phases of this process, the definitions were substantially modified to better reflect the concepts, simplify the language, and assure completeness and cohesiveness of terminology. Feedback obtained from the stakeholders helped this process and confirmed that the final terms and definitions were well received by the experts active in the field of medication adherence.

Discussion: Covering the gap in the existing terminology, this work proposes a cohesive set of terms and definitions applicable to medication adherence enabling and supporting activities. Promoting evidence-based approach to this field, this terminology may help research, clinical practice and policy.

KEYWORDS

medication adherence, non-adherence, interventions, technology, drugs, terminology, taxonomy, health policy

Introduction

Medication adherence is a basic precondition for full effectiveness of evidence-based therapies, and therefore, a key enabler of optimal health outcomes. Indeed, non-adherence leads to profound health and economic consequences at both individual and societal levels. Perhaps, the most important one is reduced treatment effectiveness. As expressed in the well-known quote of Dr. C. Everett Koop, a former Surgeon General of the United States, "Drugs do not work in patients who do not take them". Unfortunately, the more potent is the medication, the greater are losses suffered by the patients deviating from advised therapy, including the fatal consequence of fully preventable premature death (Neto et al., 2021; Mafruhah et al., 2023). Moreover, non-adherence increases the risk of complications associated with the underlying conditions. It also leads to impaired patient quality of life, due to both distressful symptoms as well as limitations in daily activities. Consequently, non-adherence leads to increased healthcare costs due to the need for additional appointments, tests, treatments, hospitalizations, institutionalizations, *etc.* According to a dedicated report by the Organisation for Economic Co-operation and Development (OECD), non-adherence contributes to nearly 200,000 premature deaths in Europe, and generates up to EUR 125 billion annual costs in excess healthcare services (Khan and Socha-Dietrich, 2018). Apart from that, it generates tremendous indirect costs resulting from mortality, absenteeism and the reduced productivity of employees.

Thus, addressing non-adherence is crucial not only for improving patient outcomes and quality of life but also for reducing healthcare costs, promoting better use of pharmaceuticals and fostering a sustainable healthcare system. For these reasons, the problem of non-adherence has been extensively studied for the last 50 years. Unfortunately, despite the number of scientific papers published on that subject grossly exceeding 100,000, we are still far from finding an ultimate solution (Kardas et al., 2023). In real-life settings, non-adherence to medication is still highly prevalent. The seminal World Health Organization (WHO) report, published 20 years ago, estimated that only 50% of patients with chronic diseases adhered to their medication regimens (World Health Organization, 2003). Regrettably, current statistics of non-adherence are very similar (Foley et al., 2021). High prevalence of non-adherence is still the case across a number of conditions, even in life-threatening ones, such as HIV/AIDS (Konstantinou et al., 2020).

What is worse, despite the fact that there are a lot potentially effective interventions available, they are implemented very rarely (Kardas et al., 2022). This is, at least partly, due to lack of relevant terminology, which hinders knowledge transfer between research and practice and results in underuse of available tools. A compelling example of this scenario is evident in the absence of a specific definition for adherence-targeting activities, even within well-cited systematic reviews (Nieuwlaat et al., 2014; Mbuagbaw et al., 2015; Mistry et al., 2015; Morrissey et al., 2016). A recent study, focused on identifying reimbursed medication adherence enhancing interventions across European countries, encountered a significant obstacle due to the absence of a standardized definition for such interventions. This lack of clarity not only posed challenges in identifying reimbursed adherence interventions, but also complicated determinations about which programs should be categorized as adherence-focused (Ágh et al., 2022). Undoubtedly, standardizing of what is called the best practice, interventions, and technology could provide a solution to this problem.

For more than a decade, the ABC taxonomy has stood for a consensus terminology which provides basic definitions to medication adherence area (Vrijens et al., 2012). The ABC taxonomy has been further applied in the EMERGE guidelines which set the standards for reporting scientific studies on medication adherence (De Geest et al., 2018). Unfortunately, no agreement has yet been reached on the terminology applicable to activities aimed at improving medication adherence. This is an important barrier towards fair benchmarking of current interventions, showcasing identified technologies, and stimulating their wider implementation and reimbursement in different healthcare systems. Consequently, the adoption of more effective ways of supporting medication adherence is halted or slowed down by the lack of relevant terminology. Therefore, the alignment and consensus on these terms is of key importance for the advancement of this field.

The European Network to Advance Best practices and technoLogy on medication adherencE (ENABLE) is a multinational research collaboration supported by COST Action (CA19132). It is aimed at facilitating a more rapid and efficient transformation of healthcare systems towards better adherence support. The main goal of ENABLE is to facilitate the adoption and use of medication adherence best practices and technologies by health systems across Europe. This goal is currently being pursued by fostering knowledge on medication adherence, raising awareness of adherence enhancing solutions, accelerating clinical application of novel technologies, and working collaboratively towards economically viable policy, and implementation of adherence enhancing technology across healthcare systems. (van Boven et al., 2021).

Owing to the unprecedented engagement of the stakeholders, ENABLE is well placed to tackle the problem of the lack of consensus on terminology for medication adherence supporting activities. As a unique platform for collaboration and networking of experts interested in medication adherence, currently ENABLE comprises over 200 members from 40 countries (39 European ones and Israel), of which a majority are researchers active in this field. Moreover, ENABLE engages a range of other stakeholders, including healthcare professionals, such as physicians, pharmacists, psychologists, and nurses, patient representatives and advocacy partners, regulatory bodies such as registration authorities, payers, health insurance policymakers, as well as healthcare equipment manufacturers and IT companies.

Activities of ENABLE are organised around 4 Working Groups (WGs), focused on interlinked areas, namely,: mapping best practices available in European countries (WG1 Current Practices and Unmet Needs), identifying and showcasing adherence technologies (WG2 Adherence Enhancing Technologies), identifying suitable reimbursement strategies for implementation of medication adherence

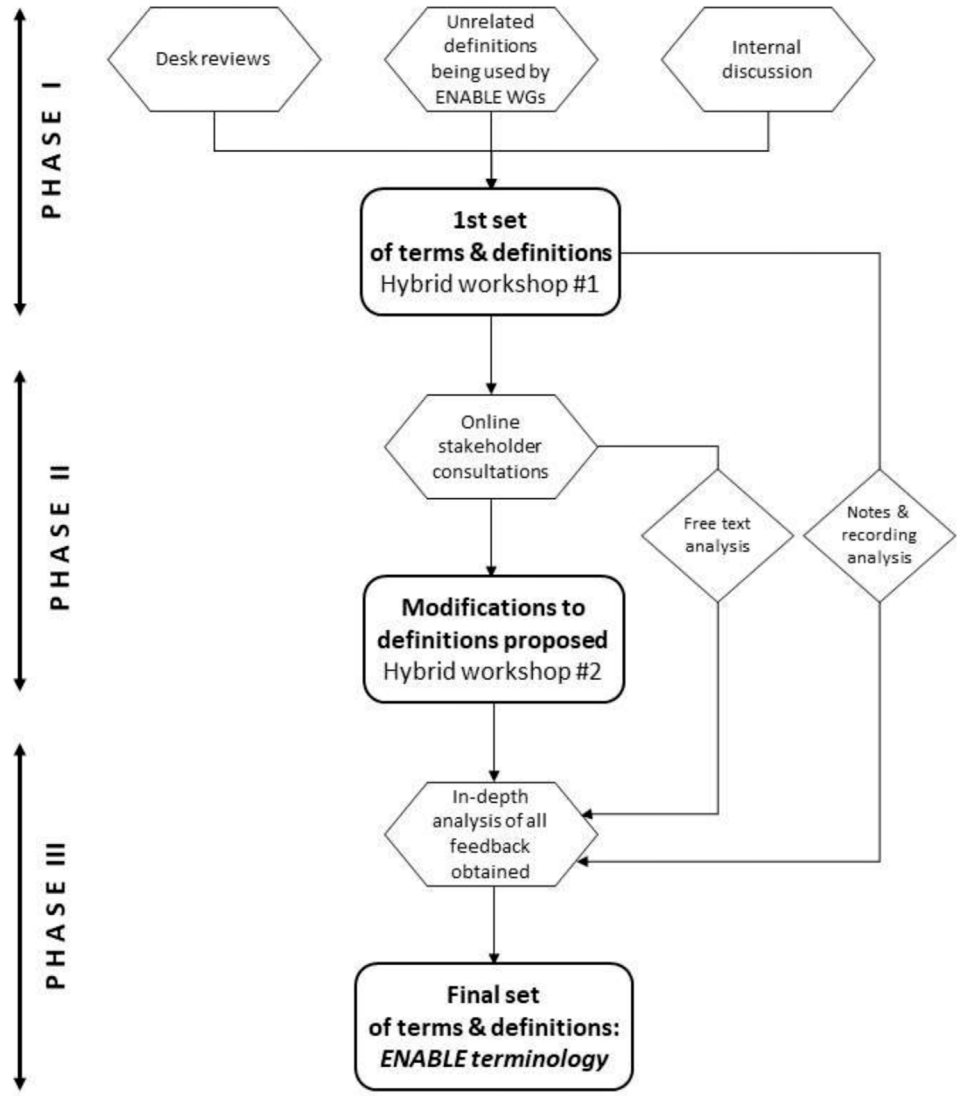

FIGURE 1
Flow chart of the methodology of the terminology agreeing process.

interventions in healthcare systems (WG3 Sustainable Implementation of Adherence Enhancing Technologies), and communication and dissemination activities (WG4 Communication and Dissemination).

Thus, the structure of the action provides a practical and goal-oriented framework to agree on consensus terminology through extensive stakeholder consultations. The context of the ENABLE network offers several opportunities, i.e., representation of numerous countries and multiple expertise backgrounds, networking funding instruments (workshops and networking activities), as well as constraints of time and resources.

In this paper, we report on the process of developing a cohesive set of relevant terminology regarding medication adherence supporting activities based on stakeholder consultation, with a view to creating a conceptual framework to coordinate ENABLE activities, and more broadly, proposing this framework for further stakeholder input, and ultimately for guiding research and practice on medication adherence.

Methods

Terms and definitions constituting terminology of medication adherence enabling and supporting activities were drafted. They were fine-tuned and agreed according to an iterative process illustrated in Figure 1. Details of the process are described below.

Phase I: problem description and first set of definitions

Internal discussion on the forum of four WGs of ENABLE was a starting point to agree on the terms and definitions of target terminology of adherence enabling and supporting activities through an iterative process. Since October 2020, each WG had developed various activities following their specific objectives and planned outputs, for which they have adopted and defined/operationalized terms relevant

for their focus. These definitions, however, were neither consulted across the WGs, nor constituted a cohesive set of terminology. Therefore, during the first year of the Action, it become apparent that, in order to maximise the impact of each output, coordinated action is necessary to align terminology and use it to describe the overall process of generating and implementing medication adherence research into routine practice sustainably and at scale.

Therefore, in early 2022, work on aligning terminology was initiated. Meetings between WGs coordinators allowed to formulate the problem of lack of adherence enabling and supporting activities terminology and set the goal of aligning definitions. This process followed up on the work related to the development of the ENABLE repository framework (Nabergoj Makovec et al., 2022), which was based on the principles of good practice in ontology relevant to development of behaviour change interventions as described by Wright et al. (Wright et al., 2020). That strategy involved defining the scope and key entities of the framework, an iterative process of literature annotation, discussion and revision, expert stakeholder review, disseminating and maintaining the framework.

Discussion within and across the groups was facilitated by desk reviews conducted by each WG when searching the existing terminology items and relevant definitions among the documents known to the team members. These reviews were informed by the standards accepted in the field of medication adherence research, in particular the ABC terminology and taxonomy (Vrijens et al., 2012), and the EMERGE guidelines (De Geest et al., 2018).

These steps allowed for drafting the first set of terms and definitions of adherence enabling activities. In order to facilitate a critical discussion about these results by all relevant stakeholders, a dedicated ENABLE workshop #1 was organised in a hybrid form in Malaga, Spain on 3 May 2022. Along with ENABLE, other professional associations were invited to join the meeting either onsite or online, e.g., the International Society for Medication Adherence (ESPACOMP), the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), and particularly, ISPOR's Medication Adherence and Persistence Special Interest Group, and European Drug Utilisation Group (EuroDURG) of International Society of Pharmacoepidemiology. The program of the workshop allowed for detailed presentation of each piece of proposed terminology in the context of the activities taken by relevant WGs.

Phase II: public consultations

Along with *ad hoc* discussion at the forum of the participants of the ENABLE hybrid workshop #1, which was recorded for future reference, a dedicated exercise was organised during this workshop to collect stakeholders' feedback on presented terms and definitions. Namely, an anonymous interactive survey was conducted among workshop participants, based on provided instructions. The survey, powered by the eDelphi software (eDelphi.org), was made available online. Individual questions concerned basic participants' characteristics, as well as their level of agreement with, and the clarity of relevant terms and definitions presented. Whenever relevant, individual items were assessed with visual scales, allowing to select a location on a 9-point two dimensional graph representing levels of agreement and clarity. The respondents could also share their free text comments on every item in the survey. Stakeholders who were not able to participate in the consultations in real time could fill in the survey later. To further encourage online participation, additional advertising efforts were directed towards engagement of the stakeholders' community.

Results of the survey were analysed with descriptive statistics, similarly to those described in more detail elsewhere (Nabergoj Makovec et al., 2022). The respondents' socio-demographic characteristics were summarized in terms of level of education, profession, primary field of work, years of experience, age, gender, country and participation in ENABLE. The level of agreement on the terms and definitions proposed was described for each item for both relevance and clarity, using the interpercentile range adjusted for symmetry (IPRAS), and the disagreement index (DI), *i.e.*, the ratio between the interpercentile range (IPR) and IPRAS. We considered DI > 1 (*i.e.*, IPR > IPRAS) as indicating disagreement. The median values of relevance and clarity and the DI was used to define different levels of agreement and steer decisions on modifying terms and definitions, as described in (Nabergoj Makovec et al., 2022). In order to analyse whether there were any patterns or differences in the level of consensus reached during voting according to respondents' characteristics, relevant variables with acceptable distributions were examined using Wilcoxon rank sum tests with Bonferroni correction for multiple testing.

All this allowed for the critical analysis of the definitions provisionally agreed on in Phase I. This analysis was informed by the feedback obtained from both internal (ENABLE community) and external resources. Results of the analysis were presented at the next round of public stakeholder consultations, in a dedicated ENABLE workshop #2, organised in a hybrid form in Oslo, Norway, on 25 June 2022. During the meeting, the participants were updated on the process and provisional outcomes of the drafted set of terminology definitions. The feedback provided by the participants of online stakeholder consultations was overviewed, and their free text comments were summarised. This was followed by open discussion on every item of the proposed terminology, which was voice-recorded. Online chat with remote participants was also recorded for further analysis.

Phase III: in-depth analysis of stakeholder feedback and final fine-tuning of definitions

The final round of fine-tuning of the terms and definitions included an in-depth analysis of all the sources of feedback provided by the stakeholders in Phase I and II, namely:

1) Verbatim transcript of recording of discussion and hand notes taken at Hybrid workshop #1
2) Verbatim transcript of recording of discussion and chat notes taken at Hybrid workshop #2
3) Free text comments collected during online stakeholder consultations

All these resources were subject to a stepwise qualitative content analysis. In the first step, individual comment items were extracted from the verbatim transcript and transferred to a spreadsheet. Then, the items were ascribed one or more corresponding terminology elements, to allow for their assessment according to the owner. The original spreadsheet was divided into parts belonging to each Working Group, which clustered the comments of similar thematic content, and ascribed each cluster one of the three values: high importance

TABLE 1 Terminology of medication adherence enabling and supporting activities–across the phases of the fine-tuning process.

Phase	Item	Definition
PHASE 0	MATech	MATech are devices, procedures or systems developed based on evidence to support patients to take their medication as agreed with the healthcare providers (to initiate, implement and persist with medical regimen)
	MAEIs	MAEIs are broadly defined as any formalised activities taking place within, or in association with the healthcare system, that in any way could positively affect medication adherence at the individual patient level
	REIMBURSEMENT	Reimbursed MAEIs are those MAEIs which are subject to reimbursement by various organizations, such as public healthcare systems, governments, public or private insurance options, pharmaceutical companies, patient organizations, or others. However, interventions paid only through out-of-pocket by individual patients are not regarded as 'reimbursed MAEIs'
PHASE I	MATech	Medication Adherence Technologies (MATech) are evidence-based health technologies (i.e., devices, techniques, procedures/services, or systems) used in management of medication adherence by diverse stakeholders (i.e., patients, caregivers, healthcare professionals, *etc.*)
	MAEIs	MAEIs are any formalised activities taking place within, or in association with the healthcare system, that in any way could positively affect medication adherence at the individual patient level
	REIMBURSEMENT	Reimbursement relates to public or private insurers' payment to providers for covering the costs of delivering MATechs and/or MAEIs
Phase III	**MATech**	**Medication Adherence Technologies (MATech) are evidence-based health technologies used in the management of medication adherence by different stakeholders**
	MAEIs	**MAEIs are any structured activities taking place within, or in association with the healthcare system that have evidence on their positive effect on medication adherence at the individual patient level**
	REIMBURSEMENT	**Reimbursement refers to payments made to providers or patients by relevant stakeholders to cover, partly or entirely, the costs of providing MATechs and/or MAEIs**
	BEST PRACTICE	**Best practice in medication adherence is evidence-based practice enhancing medication adherence**

("very useful"), medium importance ("to be considered"), and low importance ("not important at all"). Results of this process were provided for cross-check and approval by another Working Group (e.g., clusters created by WG1 were approved by WG2, *etc.*). Only high importance items were to be considered in the final round of terminology fine-tuning.

In the final step, approved clustering results were discussed at the forum of cross-WG terminology working panel, which allowed to agree the final wording of the terminology definitions. Additionally, consensus on the definition of best practice was reached via an online tool.

Results

Initial definitions adopted by various WGs of ENABLE ("Phase 0 definitions", see Table 1) and used as a starting point for this process, are described below.

- Working on a repository of Medication Adherence Technologies (MATechs), WG 2 adopted a definition of MATech (Nabergoj Makovec et al., 2022) The initial definition of MATech was informed by i) the WHO definition of health technologies (World Health Organization WHO, 2007), ii) the ABC definition of medication adherence (Vrijens et al., 2012) and iii) the WHO definition of adherence to long-term therapies (World Health Organization, 2003)
- For the purpose of their search of reimbursed Medication Adherence Enhancing Intervention (MAEIs) across Europe, WG 3 adopted definitions of MAEI as well as 'Reimbursement' applicable to medication adherence enabling and supporting activities (Kardas et al., 2022)
- The discussion over the definition of 'Best Practices' applicable to medication adherence enabling and supporting activities adopted by WG 1 was guided by the definition of best practice in healthcare proposed by the European Commission (Perleth et al., 2001).

Compared to these initial definitions applied by the ENABLE Working Group prior to the terminology design process, the definitions were modified significantly in the iterative process of fine-tuning in Phases I, II and III, as described below.

MATech phase I definition

For the Phase I consultation on definitions during the Hybrid workshop #1, the MATech definition v2 was used. This version was the upgraded version of 'Phase 0' v1 definition, being informed by the results of the Delphi survey conducted for the benefit of the planned repository of MATechs.

> **Medication adherence technologies MATech definition v2.0**
>
> Medication Adherence Technologies (MATech) are evidence-based health technologies (i.e., devices, techniques, procedures/services, or systems) used in management of medication adherence by diverse stakeholders (i.e., patients, caregivers, healthcare professionals, *etc.*).

Particular elements used in this definition are described in more detail below.

- evidence-based encompasses the requirement of using available evidence for development of MATech as

well as producing evidence that shows the contribution of the technology to medication adherence management;
- health technologies (i.e., devices, techniques, procedures/services or systems) emphasize the inclusion of all types of technologies aimed at managing medication adherence, irrespective of their mode of delivery or included technical elements/solutions;
- used in management of medication adherence by diverse stakeholders (i.e., patients, caregivers, healthcare professionals, *etc.*) encompasses the contribution of the technology to medication adherence management–either directly in patients' self-management, or by supporting professionals in offering such services to patients through all types and phases of medication adherence.

MAEI phase I definition

The Phase I definition of MAEI was a slight modification of the previous Phase 0 version (Kardas et al., 2022). To ensure consistency, the phrase "are broadly defined" was removed from its initial wording.

Medication adherence enhancing intervention definition of phase I

MAEIs are any formalised activities taking place within, or in association with the healthcare system, that in any way could positively affect medication adherence at the individual patient level.

Reimbursement phase I definition

The Phase I definition of reimbursement was inspired by the ISPOR definition of reimbursement, which is the following: 'Reimbursement relates to public or private insurers' payment to providers for the delivery of healthcare products and services' (Bingefors et al., 2003).

Reimbursement definition of phase I

Reimbursement relates to public or private insurers' payment to providers for covering the costs of delivering MATechs and/or MAEIs.

Best practice phase I definition

Discussion on the best practices was inspired by various available definitions of the best practices, i.e.,.

- "Best practices are health practices, methods, interventions, procedures or techniques based on high-quality evidence in order to obtain improved patient and health outcomes." (Makic et al., 2013)
- "Best practice in healthcare are defined as the 'best way' to identify, collect, evaluate, disseminate, and implement information about as well as to monitor the outcomes of healthcare interventions for patients/population groups and defined indications or conditions." (Perleth et al., 2001)
- According to WHO, "best practice" is commonly defined as "a technique or methodology that, through experience and research, has proven reliably to lead to a desired result." It is also defined as "knowledge about what works in specific situations and contexts, without using inordinate resources to achieve the desired results, and which can be used to develop and implement solutions adapted to similar health problems in other situations and contexts." (WHO, 2008).

However, it is noteworthy that the 'best practice' was not defined in Phase I.

Phase II

As many as 111 participants took part in the online stakeholder consultations, of which 75 participants came from 26 EU countries, and another 36 from non-EU countries. Approximately 2/3 of the survey participants were female (68.5%), mainly representing academia and healthcare sectors. Over 2/3 of the respondents had a PhD degree, and 64.0% were ENABLE members. For detailed characteristics of the respondents, see Table 2.

Cumulative results of the stakeholder consultations are presented in Table 3. Of a note is that there were no significant differences in agreement and clarity among participants depending on their clinical or academic experience or ENABLE membership. Geographical differences could not be examined due to the limited number of participants from different countries. According to the low values of the Disagreement Index (range 0.12–0.38), none of the assessed terms or definitions was a subject of disagreement as to their clarity and content. Therefore, all the assessed items were retained in the target terminology.

MATech

In the online stakeholder consultations, MATech v2 definition received 39 comments and/or suggestions for clarification or modification. They referred to 4 main topics.

1. The term 'evidence-based'. Some participants advised to exclude this term, while others commented on the difficulty to agree on which evidence would be recommended or sufficient for a technology to be considered a MATech. After careful consideration, it was decided that the term should remain unchanged as it aligns with the European Commission's definition of best practice and the evidence base represents a specific domain in the framework defining the repository and the knowledge management system intended to accompany it.
2. The term 'health technologies' was suggested to impose too broad scope, and was suggested to be changed for procedures, services, *etc.*, as well as to be limited to an electronic or digital area only. Upon careful deliberation, it was determined that retaining the term in its current form is appropriate as it is widely accepted and easy to understand, also being inclusive enough to cover a broad range of contexts.
3. The term 'medication adherence management' was deemed inappropriate by some participants and some advised to replace it with terms specifying the promotion or enhancement of medication adherence. Upon detailed consideration, the decision was made to

TABLE 2 Characteristics of the participants of the online stakeholder consultations.

	Values	Frequencies (%)
Gender (%)	Female	76 (68.5)
	Male	34 (30.6)
	Do not wish to answer	1 (0.9)
Age (%)	18–30	15 (13.5)
	31–40	25 (22.5)
	41–50	36 (32.4)
	51–60	18 (16.2)
	61–70	13 (11.7)
	70+	2 (1.8)
	Do not wish to answer	2 (1.8)
Country (%)	Albania	2 (1.8)
	Austria	2 (1.8)
	Belgium	2 (1.8)
	Bosnia and Herzegovina	2 (1.8)
	Bulgaria	3 (2.7)
	Croatia	3 (2.7)
	Cyprus	1 (0.9)
	Czech Republic	3 (2.7)
	Denmark	1 (0.9)
	Estonia	1 (0.9)
	Finland	1 (0.9)
	France	2 (1.8)
	Germany	3 (2.7)
	Hungary	4 (3.6)
	Iceland	1 (0.9)
	Ireland	3 (2.7)
	Israel	1 (0.9)
	Italy	4 (3.6)
	Lithuania	1 (0.9)
	Luxembourg	1 (0.9)
	Montenegro	1 (0.9)
	Netherlands	8 (7.2)
	North Macedonia	2 (1.8)
	Norway	2 (1.8)
	Poland	2 (1.8)
	Portugal	7 (6.3)
	Romania	4 (3.6)
	Serbia	1 (0.9)
	Slovakia	1 (0.9)
	Slovenia	2 (1.8)
	Spain	10 (9.0)
	Sweden	3 (2.7)
	Switzerland	4 (3.6)
	Turkey	3 (2.7)
	United Kingdom	8 (7.2)
	Other	12 (10.8)
Education (%)	Bachelor	1 (0.9)
	Doctorate (PhD)	76 (68.5)
	High school diploma	3 (2.7)
	Master	22 (19.8)
	Speciality Degree (healthcare)	9 (8.1)
Expertise (%)	Data Science/Statistics	4 (3.6)
	Economy/Management	1 (0.9)
	Medicine	20 (18.0)
	Nursing	9 (8.1)
	Pharmacy	63 (56.8)
	Psychology	4 (3.6)
	Sociology	1 (0.9)
	Other	9 (8.1)
ENABLE membership (%)	Yes	71 (64.0)
	No	40 (36.0)
TOTAL		111 (100.0)

(Continued in next column)

retain the term in its original form as it aligns with the ABC taxonomy and encompasses both measurement and intervention regarding medication adherence. To clarify this aspect, it was decided to include an explanatory text accompanying the definition.

4. The term 'stakeholders' was deemed sufficient and not requiring any examples in the definition sentence (rather in the explanatory text). 'Different' was suggested as a more appropriate adjective in English that 'diverse'. This suggestion was considered for modification in v3 of the definition and explanatory text.

MAEI

The term MAEI received 17 comments in the online stakeholder consultations exercise, of which most suggested other options for 'enhancing', such as 'supportive', 'promoting', 'enabling' and 'optimizing'. After careful consideration, it was determined that the term should remain unchanged due to its comprehensive meaning, encompassing both the promotion of high performance and the enhancement of current outcomes.

TABLE 3 Median values and indicators of agreement for ratings of clarity and agreement regarding terms and definitions subject to the online stakeholder consultation.

Question	Outcome	Median	IPR	IPRAS	DI
MATech definition	Clarity	7.02	1.94	5.35	0.36
MATech definition	Agreement	7.01	1.77	5.49	0.32
MAEI term	Clarity	8.00	0.91	6.83	0.13
MAEI term	Agreement	7.97	1.23	6.30	0.20
MAEI definition	Clarity	7.04	1.98	5.30	0.37
MAEI definition	Agreement	6.98	1.72	4.95	0.35
Reimbursement definition	Clarity	7.57	1.24	6.07	0.20
Reimbursement definition	Agreement	6.99	2.05	5.32	0.38

Notes: IPR: Interpercentile Range 30–70, IPRAS: interpercentile range adjusted for symmetry, DI: Disagreement Index (ratio IPR/IPRAS; indicates disagreement if > 1).

The definition of MAEI received 32 comments and/or suggestions for clarification or modification. They referred to 4 main topics.

1. The term 'formalised', which was suggested to be replaced by 'structured'. The suggestion was accepted as it more accurately conveyed the original intentions of MAEI, which was to provide a framework that could be replicated consistently.
2. The term 'within, or in association with the healthcare system', which was questioned due to creating an unnecessary limitation, as some interventions could be provided without any association with a healthcare system. The decision was made to retain the term in its current form to prevent a loose interpretation of the relationship between the intervention and medication adherence, as broadening the definition would risk diluting its specificity (e.g., universal school education is certainly effective in developing the ability to understand the need for medication adherence among people, yet this is not an intervention targeting adherence directly, nor primarily).
3. The term 'in any way', which was suggested to be simply deleted. This suggestion was accepted to ensure the definition remains concise and clear.
4. The term 'at individual patient level', which was questioned due to the fact that potentially, adherence can be helped at a higher level, such as the healthcare facility or healthcare system level. After careful consideration, it was determined that the term should remain unchanged, as the entire concept of patient adherence, as defined by the ABC taxonomy, is centred around the individual patient, with his/her own characteristics, and promotes individualised approach to individual challenges. For example, general availability of more affordable drugs (e.g., generics) promotes adherence, yet it cannot be assumed to be an intervention designed and implemented for a particular combination of patient, condition, drug and external factors.

Reimbursement

In the online stakeholder consultations, definition of "reimbursement" in relation to MATechs/MAEIs received 34 comments referring to 6 main topics.

1. There exist multiple definitions of reimbursement for pharmaceuticals or medical devices. Therefore, respondents questioned the need for a separate reimbursement definition for MATechs/MAEIs. However, adherence technologies and interventions differ significantly from pharmaceuticals or medical devices, and hence, may require distinctive reimbursement considerations.
2. The term "public or private insurers" may not accurately reflect all the possible sources of reimbursement for MATechs/MAEIs. Therefore, this term was removed from the definition and instead a more inclusive wording was used that encompasses all relevant stakeholders who may finance these technologies and interventions.
3. Some respondents noted that payment pathways for adherence interventions may vary, and patients may also be eligible for reimbursement related to these interventions, not just providers. This feedback was taken into consideration and the definition was updated accordingly.
4. Suggestions were made to modify the term 'covering the costs' to reflect the extent of reimbursement, including whether it covers the entire cost or only a portion of it. Additionally, it was suggested to include cost elements in the definition. After careful consideration, we incorporated the extent of reimbursement (partly or entirely) in the definition. However, it was decided not to include cost elements, as it would overcomplicate the definition.
5. The term "delivering" was found to be unclear in the context of the definition. Therefore, it was decided to replace it with the term "providing" for more clarity.
6. Several respondents criticized the use of the terms "MATechs/MAEIs" in the definition of "reimbursement" due to a lack of understanding of the definitions of MATech and MAEI. Some suggested removing "MATechs" from the definition of "reimbursement", arguing that technologies alone cannot improve medication adherence and therefore should not be the target of reimbursement. After defining MATech and MAEI, it was decided that both terms should be included in the definition.

Best practice definition

In total, 71 respondents (81 comments collected) shared their opinions on the definition of "best practice" regarding MATech/MAEI, referring to 2 main merged topics.

TABLE 4 Statistics of the process of final definition fine-tuning in Phase III.

Definition of	Items#			Clusters			
	Merged notes	Online stakeholder consultations	Total	Not relevant	To be considered	Very useful	Total
MATech	18	34	52	3	4	2	9
MAEI	25	44	69	2	1	2	5
Reimbursement	8	34	42	1	4	0	5
Best Practice$	10	71	81	1	4	1	6
TOTAL	61	183	244	7	13	5	25

Note: # items extracted from individual comments; one comment could be extracted from multiple items; $ No definition of 'Best practice' was available in Phase II; comments provided with regard to the dimensions that this definition was believed to cover.

1. Best practice should be outcome-oriented (42% of responses). Respondents believed that best practice represents MATechs/MAEIs which make most patients adherent to their medications, provide the best medication adherence results or improve medication adherence. Additional 14 comments expressed an opinion that MATech/MAEI should be cost-effective to be considered 'best practice'.
2. Relation of best practice and evidence-based. Twenty-two respondents (33% of responses) related "best practice" to evidence-based. The use of general definition was suggested. As an option, the following was proposed: "Best practices are health practices, methods, interventions, procedures or techniques based on high-quality evidence in order to obtain improved patient and health outcomes".

Respondents agreed that the best practice definition is related to both MATech/MAEI. Other comments and suggestions after content analyses were considered to be irrelevant to the definition of best practice.

Phase III

The iterative approach applied to the fine-tuning of the definitions allowed for designing the final set of definitions which constitute the ENABLE terminology.

In the first step, original verbatim transcripts of workshop #1 and #2 discussion recordings, onsite hand notes and chat notes allowed for identification of 55 comments, out of which as many as 61 comment items were extracted, and ascribed to each of the four definitions (Table 4). Online stakeholder consultations provided another 183 items, thus making the total number of comment items as high as 244. Through a meticulous content analysis, it was possible to cluster these items into 25 distinct groups. Out of these clusters, 6 pertained to the definition of "Best Practice", 9 focused on defining MATech, while 5 referred to the definition of MAEI and another 5 were related to the definition of "Reimbursement". However, only 5 of these clusters were assessed to be of high importance ("very useful"), and therefore, were subject of modifications of Phase II definitions, and approval at the forum of the cross-WG terminology working panel.

MATech

In the case of the definition of MATech, two highly important suggestions concerned 1) exclusion of the list of technologies, and 2) exclusion of the list of stakeholders. Both of these options were accepted to simplify the definition, resulting in the final version of MATech definition v3.0.

MAEI

In the case of the definition of MAEI, two highly important suggestions concerned 1) changing 'formalised' into a more relevant term, e.g., 'structured', and 2) adding a reference to evidence to the definition. Both of these options were accepted because they conveyed the intended meaning of the definition more clearly. Additionally, the reference to evidence was consistent with the other elements of the final set of definitions.

Reimbursement

As regards the definition of 'Reimbursement', three crucial recommendations were made: 1) to exclude the list of stakeholders who may be responsible for paying the reimbursement, 2) to include patients as beneficiaries of the reimbursement, and 3) to incorporate the extent of reimbursement into the definition, regardless of whether it covers the entire cost or only its portion. All these recommendations were accepted, resulting in a simpler yet more comprehensive definition.

Best practice

In the case of the 'Best Practice' definition, only one highly important suggestion was found, namely, adding a reference to evidence to the definition. Similarly to the MAEI definition, this option was accepted because it conveyed the intended meaning of the definition more clearly.

In the WG1 workshop held on 29 March 2023 in Zagreb, Croatia, the members of the steering committee and the members of WG3 and WG4 groups discussed the issue of theories behind the term "best practice". Afterwards, the following definition was suggested: "Best practice in adherence is evidence-based practice enhancing medication adherence", where evidence-based practice is the integration of clinical expertise, patient values, and the best research evidence into the decision-making process for patient care (Sackett et al., 1996; Sackett et al., 2000). Consensus was reached through the online tool asking WG1 members to agree with the suggested definition. The 7-point Likert scale was used, where 1 indicated "strongly disagree" and 7 "strongly agree". Points 5 to 7 were calculated as an agreement

and consensus was reached at 80% (28 out of 35). According to the concluding suggestions from the panellists, the final definition was updated to: "Best practice in medication adherence is evidence-based practice enhancing medication adherence".

Hence, the example of the best practice could be providing patients with feedback on their drug taking based on its electronic monitoring, due to clear evidence that such an approach is effective (Demonceau et al., 2013). On the other hand, relying solely on physicians' assessments of their patients' adherence is not a best practice as there is ample evidence that physicians fail to correctly identify which of their patients are non-adherent (Hines and Stone, 2016).

Final set of definitions

The final set of definitions forms a cohesive taxonomy, as presented in Table 1, establishing an interconnected ecosystem. MATechs encompass various technologies that can be utilized in the context of MAEIs. A specific MAEI may incorporate one or multiple MATechs, while it is also conceivable to have MAEIs that do not rely on any MATechs (such as, e.g., medication regimen management-based interventions). Reimbursement represents a critical parameter for both MATechs and MAEIs, and best practice in medication adherence involves the practical application of MATechs and MAEIs in real-life settings. Therefore, within both scientific and clinical contexts, multiple terms from this taxonomy can be employed simultaneously.

Discussion

Certainly, adherence itself is not the ultimate aim, but rather a means to achieve improved health outcomes. On the other hand, the link between the two is strong: the better the adherence, the greater the effectiveness of therapies. Therefore, given the current low levels of adherence, this factor becomes extremely important among the modifiable determinants of public health.

Unfortunately, despite half a century of adherence research, and a number of excellent publications devoted to the review of available approaches (Nieuwlaat et al., 2014; Mbuagbaw et al., 2015; Mistry et al., 2015; Morrissey et al., 2016), no consensus has yet been reached as to the terminology that should be used to describe medication adherence bettering activities. This scenario entails far-reaching consequences, ranging from hindering scientific research to negatively impacting the benchmarking of current interventions, and even inhibiting the adoption of best practices in healthcare policy. Consequently, available tools and methods are not promoted, and effective ways of supporting medication adherence are underused. This scenario is illustrated perfectly well by a recent survey conducted in 38 European countries and Israel, which identified 13 reimbursed MAEIs in nine countries only (Ágh et al., 2022).

The taxonomy proposed by ENABLE collaboration is a first set of cohesive terminology that attempts to cover this large gap. Being the result of an iterative process of fine tuning and co-design with stakeholders, it might be expected to lay conceptual foundations for more rigorous scientific research, and facilitate taking more objective and well-informed decisions in clinical practice and healthcare policy.

It is noteworthy that the final elements of the ENABLE taxonomy place great importance on evidence. This is not a coincidence. On the contrary, this is an approach similar to those adopted for general adherence terminology by the ABC taxonomy (Vrijens et al., 2012), and for reporting of the scientific studies by the EMERGE guidelines (De Geest et al., 2018). Therefore, these three guidance documents could be perceived as a cohesive ecosystem.

Moreover, we hope that the set of the definitions proposed by the ENABLE taxonomy is complete, and that there is no overlap between the individual terms. In particular, MATech stands for technological part of medication adherence bettering activity, whereas MAEI represents an entire intervention. Of course, most of the MAEIs use one or multiple MATechs. However, MATech may also be a stand-alone product, and finally, the same MATech might be applied in various MAEIs.

Of course, the proposed taxonomy has some limitations. Obvious one is the language used to express the terms and definitions. As it is currently only English, it may require validated translations into other languages in the future. Moreover, the scope of the terminology is definitely reflecting European roots of the ENABLE collaboration, putting much attention to the dimension of reimbursement of adherence-enhancing actions. Indeed, in a short-term perspective, this taxonomy will be used by ENABLE in its own activities, such as the repository of MATechs, or further search of reimbursed MAEIs. For that reason, it prioritizes healthcare system-related perspective, putting much less attention to other (e.g., social) determinants of health. Specifically, it restricts the MAEI definition to those targeting individual patient level interventions. This approach excludes interventions at other levels, such as community-based initiatives. While such interventions can somehow impact adherence, assessing their effects accurately can be quite challenging. Finally, this first of its kind terminology needs extensive 'real life testing' regarding its usability and added value, that will come with further studies. Nonetheless, we firmly believe that it will prove useful to many stakeholders and, in a longer perspective, encourage further discussion on effective methods for promoting medication adherence.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: Zenodo - https://zenodo.org/record/8356621

Author contributions

PK: Conceptualization, Investigation, Methodology, Supervision, Visualization, Writing–original draft, Writing–review and editing. EA:

Conceptualization, Methodology, Writing–review and editing. TA: Conceptualization, Methodology, Writing–review and editing. JV: Conceptualization, Methodology, Writing–review and editing. AD: Conceptualization, Methodology, Writing–original draft, Writing–review and editing. CG: Conceptualization, Methodology, Writing–review and editing. FK: Conceptualization, Methodology, Writing–review and editing. GP: Conceptualization, Methodology, Writing–review and editing. UN: Conceptualization, Methodology, Writing–original draft, Writing–review and editing. IT: Conceptualization, Methodology, Writing–original draft, Writing–review and editing.

Funding

This paper is based upon work from COST Action CA19132 "ENABLE," supported by the COST (European Cooperation in Science and Technology).

Acknowledgments

Experts participating in the online stakeholder consultations were: TA, Obreniokibo Ibifubara Amiesimaka, Lucrezia Armando, Susan J Bartlett, Rebecca Bartlett Ellis, Yasemin Cayir, Aurelia Cretu, Maria Dimitrova, Mark Duman, Marie Ekenberg, Dalma Erdősi, CG, Anne Gerd Granas, João Gregório, Rob Heerdink, Anita Hogg, Nejc Horvat, Dyfrig Hughes, Freyja Jónsdóttir, FK, Elena Kkolou, Thomas Kubiak, Francisca Leiva-Fernández, Katerina Mala-Ladova, Sara Malo, Karin Martin-Latry, Enrica Menditto, Mitar Popović, Martin Schulz, Michael Scott, Agnieszka Skowron, Katarina Smilkov, Vashti NMF Tromp, JV, Eliska Voriskova, Vesna Vujić-Aleksić.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 17 October 2023
DOI 10.3389/fphar.2023.1266095

OPEN ACCESS

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RECEIVED 24 July 2023
ACCEPTED 21 September 2023
PUBLISHED 17 October 2023

CITATION
Vázquez-González N, Leiva-Fernández J, Cotta-Luque VM, Leiva-Fernández F, Rius-Díaz F, Martos-Crespo F, Martín-Montañez E and Barnestein-Fonseca P (2023), Effectiveness of an educational intervention about inhalation technique in healthcare professionals in primary care: a cluster randomized trial. *Front. Pharmacol.* 14:1266095. doi: 10.3389/fphar.2023.1266095

Effectiveness of an educational intervention about inhalation technique in healthcare professionals in primary care: a cluster randomized trial

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Background: Incorrect inhalation technique (IT) is an important issue for chronic obstructive pulmonary disease (COPD) patients and healthcare professionals. Studies in which counseling is carried out with healthcare professionals beforehand so that they can properly educate their patients are required. The objective of the present trial is to assess the improvement in the performance of the IT in subjects with COPD and prescribed inhaled therapy after the implementation of an educational intervention conducted by their general practitioners.

Methods: A cluster randomized clinical trial was conducted. A total of 286 COPD patients received scheduled inhalation therapy from 27 general practices in seven primary care centers. A teach-back educational intervention was implemented for both healthcare professionals and patients. The primary outcome of this study was the performance of the correct inhalation technique. It is considered a good technique if all steps in the inhalation data sheet are correctly performed. The secondary outcomes were assessed using forced spirometry, the basal dyspnea index, the Medical Research Council dyspnea scale, St George's Respiratory Questionnaire (SGRQ), and EuroQoL5D-5L for health-related quality of life. A one-year follow-up was conducted using an intention-to-treat analysis.

Results: After the intervention, incorrect IT was observed in 92% of professionals and patients, with rates reaching 50% and 69.2%, respectively. The effectiveness in patients was significant, with a number needed to treat of 2.14 (95% CI 1.79–2.66). Factors related to correct IT in patients included the type of intervention, length of intervention (>25 min), good pulmonary function, age (youngest <=65, oldest >83), and less limitation of activity due to dyspnea. There was no relation with the cluster.

Conclusion: This study shows the effectiveness of direct inhaler technique training provided by a trained professional on an appropriate timescale (for example, a specific consultation for medication reviews), aiming to help subjects improve their performance using the teach-back method. This could be an encouraging intervention to improve medication adherence and health promotion in people with COPD.

Clinical Trial Registration: clinicaltrials.gov, identifier ISRCTN93725230.

KEYWORDS

chronic obstructive pulmonary disease, inhalation technique, educational intervention, primary care, healthcare professionals, cluster randomized controlled trial

1 Introduction

Medication adherence, referring to the level of participation in terms of individuals taking medications as prescribed, is known to be a central health problem, especially important in the treatment of chronic diseases. After half a century of adherence-related research and increased knowledge of the factors involved in its implementation (>200), adherence rates remain fairly stable (Vrijens et al., 2012; Conn and Ruppar, 2017; Ellis et al., 2023). Thus, although the rates observed in clinical trials are considered to be very high (70%–90%), they vary between 10% and 40% in clinical practice (WHO, 2015; Bhattarai et al., 2020). Adherence to medication is essential for individuals to receive the potential therapeutic benefits of the prescription, especially in those conditions where the application of the treatment is much more complex than taking a pill. Lack of adherence is associated with considerable morbidity/mortality (Ellis et al., 2023).

Chronic obstructive pulmonary disease (COPD) is among the significant health challenges worldwide (Duarte-de-Araújo et al., 2019; Lindh et al., 2019) due to its high prevalence (11.7%) (Padmanabhan et al., 2019), the high healthcare costs it leads to (Barja-Martínez et al., 2019; Padmanabhan et al., 2019; Rincon-Montaña and Rosselli, 2019), and the negative effects it has on the quality of life (Rincon-Montaña and Rosselli, 2019). The treatment relies primarily on inhaled medication (Barja-Martínez et al., 2019; Duarte-de-Araújo et al., 2019; Padmanabhan et al., 2019) through currently available devices, which include dry powder inhalers (DPIs), metered-dose inhalers (MDIs), pressurized metered-dose inhalers (pMDIs), and soft mist inhalers (SMIs) (Rincon-Montaña and Rosselli, 2019; Dekhuijzen et al., 2022; Lindh et al., 2022). These devices require many steps, which may be complex, making them difficult to use (Melzer et al., 2017; Takaku et al., 2017; Dekhuijzen et al., 2022). Therefore, the incorrect use of these devices becomes a major problem, leading to reduced therapeutic effects, increased symptoms, and ineffective disease control (Vila Jato, 2020; Dekhuijzen et al., 2022). Increased hospitalization, emergency room visits, and the need for antibiotics and corticosteroids have also been reported, increasing the cost of the disease and leading to adverse effects and a reduction in therapeutic alternatives (Vila Jato, 2020; Dekhuijzen et al., 2022).

To acquire proficiency in handling inhalers, it is essential to provide proper training to patients (Poureslami et al., 2016; Dhadge et al., 2020; Luley et al., 2020; Rodrigues et al., 2021; Lindh et al., 2022; Sulku et al., 2022), since education on the proper use of inhalers is received by only a small number of them (Poureslami et al., 2016; Dekhuijzen et al., 2022).

Furthermore, COPD clinical practice guidelines pay particular attention to proper advice and instruction on inhaler management as a vital part of treatment. They state that the first time a device is prescribed, the IT should be explained and a demonstration should be performed for the patient, training the patient as many times as necessary to achieve a proper IT and confirming that the patient can use it properly. Subsequently, the patient should demonstrate, with their own device, how they perform the IT at each visit to ensure successful execution (Andaluz de Salud, 2019; Global Iniciative for COPD, 2022; Miravitlles et al., 2022). The accessibility of patients to healthcare providers is important for a correct IT because professionals will have more opportunities to assess the patient periodically and train them appropriately (Yawn et al., 2012).

Healthcare professionals (e.g., general practitioners, respiratory physiotherapists, community pharmacists, or health educators) also need to be properly trained, as evidence suggests that their knowledge of the use of inhaled medicines can be improved (Al-Otaibi, 2020; Cvetkovski et al., 2020). IT also improves for them after training, either by attending educational workshops (Al-Otaibi, 2020) or conferences (Takemura et al., 2011), providing explanatory leaflets (Cvetkovski et al., 2020; Matsuyama et al., 2022), or demonstrations with placebo devices (Basheti et al., 2008) or through videos (Cvetkovski et al., 2020; Matsuyama et al., 2022).

This highlights the importance of conducting studies in which the educational intervention is carried out beforehand with public and community health personnel so that they can properly counsel their patients. To the best of our knowledge, no trial of educational intervention concerning the IT has been carried out among general practitioners (GPs) to assess its effectiveness on COPD patient IT performance. Therefore, this study aimed to implement a cluster randomized trial among healthcare professionals at primary care centers (PCCs) to evaluate the effectiveness of an educational intervention on the improvement in the performance of the IT in patients with COPD and prescribed inhaled therapy after the implementation of this educational intervention with their GPs.

2 Materials and methods

2.1 Study design

A pragmatic cluster randomized controlled trial (ISRCTN93725230) was conducted. The cluster has a two-level design: at the higher or second level is the GP (the recipient of

the educational intervention), and at the lower or first level are the patients (who provided consent for their participation and received the educational intervention from their GP). The PROF-EPOC trial gained approval from the Malaga Provincial Ethical Committee (12/12/13). The protocol of the study was broadly described by Leiva-Fernández et al. (2016). We adhered to the CONSORT reporting guidelines (Schulz et al., 2010).

2.2 Setting, participants, recruitment, and follow-up

A total of 286 patients with a diagnosis of COPD who were receiving scheduled inhalation therapy were chosen by a non-random consecutive sampling method from 27 general practices in seven PCCs in Málaga and Almería, Spain.

The sample size was determined to detect a 25% difference in the percentage of the correct IT between the groups, aiming for a statistical power of 80%, confidence level of 95%, and design effect (DE) of 2.3 (Christie et al., 2009; Bunker et al., 2012; Thompson et al., 2012). A potential loss of 40% was estimated.

The inclusion criteria were as follows: patients with a COPD diagnosis receiving clinical attention at the PCC included in the trial, those who had been prescribed scheduled inhalation treatment, and those who had given their consent to participate in the trial by signing an informed consent form. The exclusion criteria were the presence of another respiratory illness not included in the definition of COPD and cognitive impairments that make it impossible for the individual to complete the outcome questionnaires or fully engage with the educational intervention. These criteria were all ascertained from the patient's clinical record.

The GPs included were required to be physicians caring for patients included in the COPD Process of the Andalusian Health Service Guidelines (COPD PAI) (Andaluz de Salud, 2019) and who had signed the informed consent form. The exclusion criteria were reluctance to participate or leaving the job during the trial.

Twenty-seven GPs were chosen using a non-probabilistic consecutive sampling method: 14 GPs were used as the control group (CG) and 13 as the intervention group (IG). GPs were invited to participate and randomized to one of the two groups using a block randomization technique. The GP's baseline visit was undertaken once the randomization had been completed. The study variables were collected during this time, and the IT of the various inhalers (Handihaler®, Accuhaler®, Turbuhaler®, Breezhaler®, and pressurized metered-dose inhalers) was assessed through a step-by-step test that was specifically designed for the study, following guidelines of the Spanish Society of Pneumology and Thoracic Surgery (SEPAR, its acronym in Spanish) (Vila Jato, 2020).

Patients were contacted by telephone and asked to participate. An appointment was then arranged at their healthcare center. This first appointment (an inclusion visit) involved patients being given more detailed information about the study. If they then agreed to participate, the written consent form would be signed and a baseline visit carried out, where all the variables were measured (this included the assessment of the IT of the various inhalers they used). As for GPs, two groups of patients were established, depending on the group their GP was assigned to, the IG or CG.

A one-year follow-up was conducted after the initial visit. At the final visit (12 months), all variables were collected again, including the IT with all devices in patients and GPs. All measurements were performed by a research assistant who was unaware of the group to which the study subjects were assigned. For the IG subjects (patients), their GPs visited to reinforce IT at 3 and 6 months.

2.3 Interventions

2.3.1 GPs

GPs in the IG received group training (2–4 GPs) from the research team with a demonstration of the correct IT per device and the rationale for it. Participants were asked to show their technique with placebo inhalers. Then, using the teach-back method, they were asked to talk about the problems and errors they might have perceived with the technique, and they were then shown the proper technique with each device, in stages, with an explanation that included the importance of each one. Finally, GPs asked questions and practiced the techniques until they achieved good performance.

GPs in the CG were asked to show their technique, but there was no further intervention from the researcher other than correcting critical errors (this is known as a rescue mechanism). A critical error was defined as one that would considerably reduce the deposition of the drug in the lungs (Melani et al., 2017). No other educational intervention was carried out.

2.3.2 Patients

Subjects included in the IG were asked to show their technique with placebo inhalers by their GP. The GP, via the teach-back method, would then ask about the problems and apparent errors with the technique before demonstrating the proper technique with the various devices, step by step, explaining the importance of each. Finally, patients were encouraged to ask questions and practice the techniques until they were performed correctly or until they became tired. Follow-up visits reviewed the IT, corrected errors, and cleared up any doubts. The main purpose at this stage was for patients to identify errors and to give as many demonstrations as necessary to remind them of the proper technique. GPs scheduled patients for follow-up IT visits at 3 and 6 months after the initial visit.

The CG patients had their usual care without any reinforcement interventions.

2.4 Outcomes

2.4.1 Individual variables/first-level variables (patients)

The primary outcome was the performance of the correct IT by patients (this was assessed via a step-by-step test designed specifically for each inhaler). This test was designed especially for this study based on SEPAR recommendations (Supplementary Material S1) (SEPAR, 2017; Vila Jato, 2020). It is considered that the IT was appropriate if all the steps for the device were performed correctly.

The step template designed consists of two parts:

- First part: Steps necessary for a correct inhalation technique for each of the devices studied (Handihaler®, Accuhaler®, Turbuhaler®, Breezhaler®, and Metered Dose Inhalers), considering several attempts for the patient to perform the inhalation technique. The steps that the patient does not perform correctly in each attempt are marked with a cross.
- Second part: The so-called critical errors have been marked with an asterisk (*). These errors are corrected and considered a rescue mechanism. They are noted as an incidence to be taken into account in the data analysis.

It is considered a good technique if all steps in the inhalation data sheet are correctly performed.

Secondary outcomes included functional status, which was measured by forced spirometry (Garcia-Rio et al., 2013), the dyspnea index, measured using the basal dyspnea index (BDI) (Mahler et al., 1984), and the modified Medical Research Council dyspnea scale (mMRC) (Devon and Holman, 1966). The St George's Respiratory Questionnaire (SGRQ) (Ferrer et al., 1996) and EuroQoL5D-5L (Herdman et al., 2001) were used to measure health-related quality of life.

The SGRQ is a disease-specific instrument designed to measure the impact on overall health, daily life, and perceived wellbeing in patients with obstructive airway disease. It is sufficiently sensitive to reflect changes in disease activity (Ferrer et al., 1996) (Supplementary Material S2). It should preferably be self-administered, but administration by personal interview is also acceptable. Scores range from 0 to 100, with higher scores indicating more limitations.

The independent variables are age, sex, level of education, inspiratory peak flow, smoking history (patient-reported smoking habit and the number of packs per year), comorbidities, time since the diagnosis of COPD, number of exacerbations/year, total visits to health centers and visits because of COPD, mental and/or cognitive status (Mini-Mental State Examination (MMSE) (Folstein et al., 2000; Lobo et al., 2002)), types of inhalers, previous training in the use of the technique, types of errors in the technique, clinical significance of failure (CSF) (Melani, 2021), time for inhaler training (including a test of how the IT is performed on all devices used by the patient), and prescribed treatment for COPD.

2.4.2 Group variables/second-level variables (GPs)

Group and second-level variables were the correct performance of the ITs by GPs (measured using a step-by-step test specific to each inhaler, the same as that used for patients) and knowledge about COPD and its treatment (assessed with a questionnaire designed especially for this study, based on COPD PAI (Andaluz de Salud, 2019), the Spanish COPD Guidelines (Miravitlles et al., 2022), and the GOLD guidelines (GOLD Report, 2022)).

The independent variables were age, sex, level of education, and access to the COPD clinical practice guidelines.

2.5 Statistical analysis

The analysis used an intention-to-treat procedure, considering all patients who were randomized, regardless of what happened during follow-up. For the primary outcome variable, lost data were handled using the worst-case scenario, assuming that the control group losses performed the IT correctly, while the intervention group losses performed the IT incorrectly. For the other variables, a multivariate imputation was performed.

A descriptive statistical analysis was carried out for each of the study variables. The mean and standard deviations were calculated for the quantitative variables, while the absolute and relative frequencies were evaluated for the qualitative variables. The univariate analyses included the following comparisons: an inter-group comparison at baseline, a comparison between the initial and final samples (aimed at assessing the impact of losses on sample structure), and a comparison between the intervention and control branches at the 12-month follow-up. This was conducted with an analysis of variance (ANOVA) or chi-square test, as applicable. The relative risk reduction (RRR), absolute risk reduction (ARR), and number needed to treat (NNT) were calculated with a confidence interval (CI) of 95%.

Multivariate analyses: A logistic regression model was used to analyze the primary outcome (proper IT at 12 months), with the intervention held to be the predictive variable and adjusting for independent variables as modifying factors of the effect of the intervention. A classification tree based on the Chi-square Automatic Interaction Detector (CHAID) technique (Kass, 1980) was made for the main outcome—correctly performing the IT—with all independent variables showing a statistically significant relationship with the dependent variable in the bivariate analysis and/or those included in the study hypothesis or those the literature deems to be clinically relevant. Blocks of variables were established by fields of study (GP and cohort) and sociodemographic variables: age, sex, educational level, and MMSE. There are three blocks with variables related to IT: performance of IT with each device, previous instruction for IT, time since receiving it, who gave the instruction (primary care physician, pulmonologist, community nurse, and community pharmacist), how the instruction was given (demonstration with or without a device and explanation with or without a device or by handout), and quality of life (EuroQol-5D-5L and SGRQ); variables related to functional status: spirometry pattern, severity, % FEV1, and dyspnea (BDI and mMRC) including the time of intervention.

A 5% significance level ($\alpha = 0.05$) and the SPSS statistical package, version 25.0, were used to run the aforementioned analysis.

3 Results

3.1 Participant recruitment and follow-up

Various health areas of Andalusian Health Services were contacted to recruit GPs from different healthcare centers. Ultimately, 27 GPs were recruited. In total, 1,958 possible participants, identified through health records of the participating GPs in the study, were approached. Finally, 286 patients participated.

Sixty-seven patients were lost to follow-up (dropout rate 23.4%): 31 patients (21.3%) from the IG and 36 (25.5%) from the CG. However, these dropouts did not change the initial characteristics of the study sample. Figure 1 shows the CONSORT flow diagram.

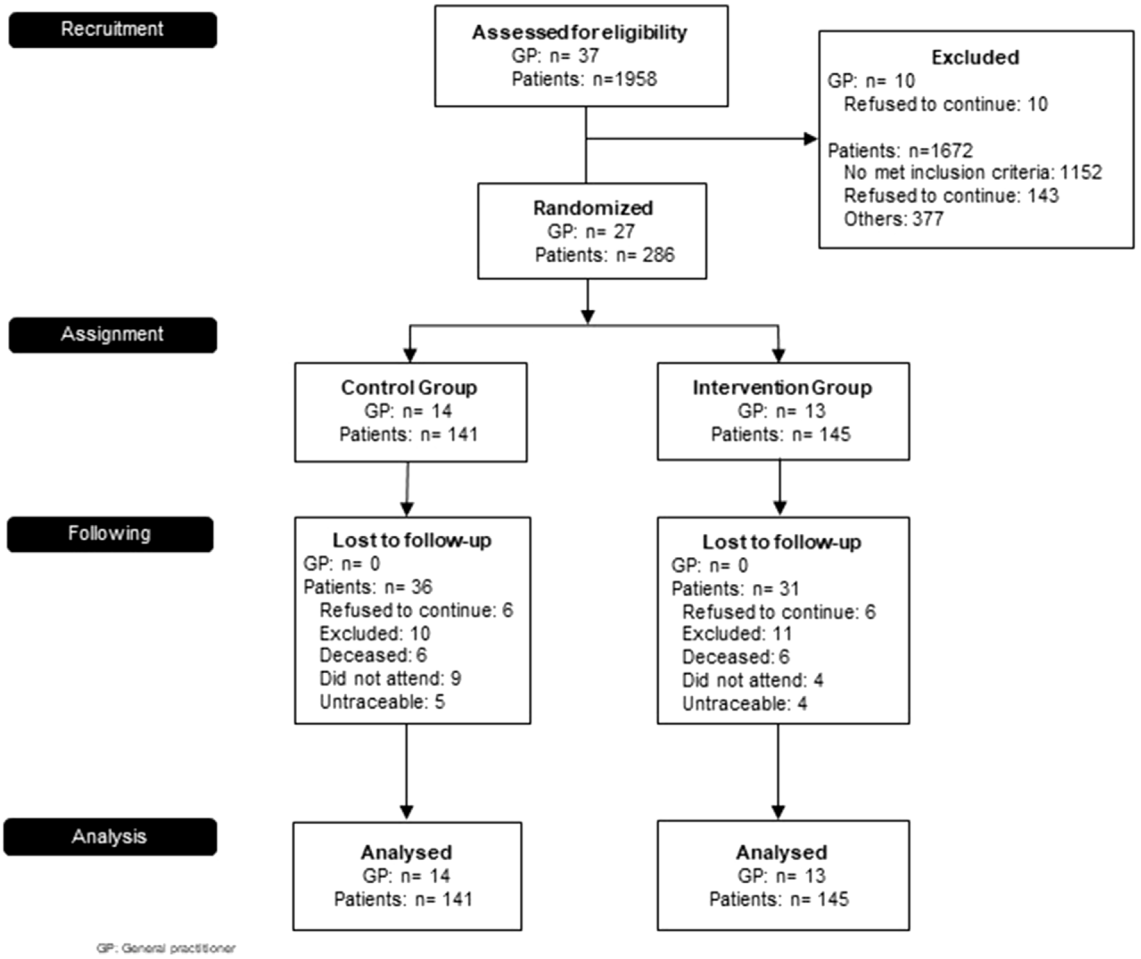

FIGURE 1
PROF-EPOC CONSORT Flow Diagram.

3.2 Patients' baseline characteristics

The 286 study subjects were predominantly male (84.3%), with an average age of 69.8 (95% CI, 69.25–70.43) and a low education level. More than half (58.7%) had been smokers (x = 49.46 packs per year, 95% CI, 28.74–47.36), with 33.2% being active smokers. With respect to COPD, they suffered an average of 1.12 exacerbations in the preceding year (95% CI, 1.02–1.21). The mean pFEV1 was 62.1% (95% CI, 60.85–63.35); the mixed pattern was 56.8%. Furthermore, a large number also had comorbid chronic diseases, at least one, with high blood pressure (HBP) being the most frequent (53.8%). The quality of life was negatively affected.

Table 1 shows the baseline characteristics of the sample per group. The comparison between branches showed significant differences in the use of Turbuhaler® (CG used less; $p = 0.007$), educational level (CG had a higher educational level; $p = 0.038$), the pneumologist's instructions (CG was better instructed in the IT, $p = 0.045$), and the type of previous instruction for the IT (CG had been previously instructed more through demonstration with the device, $p = 0.024$, and less using explanation with the device, $p = 0.003$).

With regard to the IT, 263 patients (92%) did not perform correctly. The Turbuhaler® was prescribed in 134 (46.9%), the pMDI in 105 (36.7%), the Handihaler® (33.6%) in 96, the Accuhaler® (22.2%) in 64, the Breezhaler (19.6%) in 56, and other inhalers (23.1%) in 66 subjects. Incorrect IT was observed in 120 patients (89.6%) with Turbuhaler®, 103 (98.1%) with pMDI, 86 (89.6%) with Handihaler®, 50 (78.1%) with Accuhaler®, and 50 (78.1%) with Breezhaler®. Two hundred and sixty-five patients (93%) had been given some type of IT training, and the average time elapsed from this education to recruitment was 40.09 months (95% CI, 37.41–42.77). GPs carried out the majority of educational training (144 subjects; 50.9%), followed by pulmonologists (99 subjects; 35%). The most common way in which this instruction was performed was through an explanation of the device (124 subjects; 43.7%), followed by demonstration with the device (89 subjects; 31.3%), explanation without the device (31 subjects; 10.9%), and demonstration and explanation without the device (17 subjects; 6%). In four patients (1.4%), the training consisted of handing over a descriptive brochure.

The most common errors, not related to the device, included i) incomplete exhalation before inhaling (84.6%), ii) failure to hold breath or experiencing shortness of breath after inhalation (67.6%), and iii) non-optimal inhaling force (23.7%). These all have moderate clinical significance. The most repeated errors associated with the

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TABLE 1 Baseline sample characteristics and baseline comparison according to the study arm.

Variables	Control group (n = 141)	Intervention group (n = 145)
Sex, n (%), male	123 (87.2)	118 (81.4)
Age (years) [mean, CI 95%]	69.30 (67.70–70.89)	70.36 (68.66–72.06)
Low educational level, n (%)	112 (80)*	128 (88.9)*
Smokers, n (%)	48 (34)	47 (32.4)
Packets/year [mean, CI 95%]	51.03 (45.01–57.04)	47.94 (42.14–53.73)
Comorbidities		
AHT, n (%)	78 (55.3)	76 (52.4)
OP, n (%)	40 (28.4)	53 (36.6)
DM, n (%)	29 (20.6)	35 (24.1)
Diagnostic time (months) [mean, CI 95%]	86.30 (76.45–96.16)	94.46 (83.39–105.52)
COPD pattern, n (%)		
Obstructive	33 (24.6)	27 (19.7)
Restrictive	24 (17.9)	25 (18.2)
Mixed	74 (55.2)	80 (58.4)
COPD severity, n (%)		
Mild	24 (17.8)	26 (19)
Moderate	75 (55.6)	72 (52.6)
Severe	29 (21.5)	37 (27)
FEV1% [mean, CI 95%]	61.30 (57.67–64.93)	62.90 (59.51–66.28)
Inspiratory peak flow [mean, CI 95%]	182.18 (168.42–195.93)	176.42 (165.58–187.26)
Number of exacerbations/year [mean, CI 95%]	1.15 (0.87–1.42)	1.09 (0.82–1.36)
Total visits to HC [mean, CI 95%]	6.22 (5.32–7.12)	6.45 (5.55–7.34)
Visits to HC because of COPD [mean, CI 95%]	2.10 (1.64–2.56)	2.06 (1.68–2.44)
Prescribed treatment, n (%)		
Anticholinergic	92 (67.2)	84 (57.9)
Beta-2 adrenergic	121 (88.3)	131 (90.3)
Inhaled corticosteroids	89 (65)	101 (69.7)
SGRQ [mean, CI 95%]		
Total	33.07 (29.76–36.38)	34.72 (31.76–37.69)
Activities	46.81 (42.72–50.91)	47.16 (43.42–50.90)
Symptoms	41.18 (37.11–45.24)	44.33 (40.68–47.98)
Impact	25.09 (21.88–28.29)	25.50 (22.61–28.38)
EuroQol-5D n (%) with no problems		
Mobility	86 (61)	98 (67.6)
Self-care	119 (84.4)	124 (85.5)
Usual activities	114 (80.9)	118 (81.4)
Anxiety/depression	102 (72.3)	99 (68.3)
Pain/discomfort	78 (55.3)	67 (46.2)
VAS	66.06 (62.07–70.04)	63.57 (59.90–67.25)
BDI, n (%)		
Functional impairment	19 (13.5)	19 (13.1)
Magnitude of task	27 (19.1)	18 (12.4)
Magnitude of effort	28 (19.9)	19 (13.1)
MMRC, n (%)	47 (33.3)	36 (24.8)
MMSE [mean, CI95%]	27.82 (27.32–28.32)*	27.03 (26.5–27.57)*

AHT, arterial hypertension; BDI, baseline dyspnea index; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; EuroQol-5D, European Quality of Life-5 Dimensions; VAS, Visual Analog Scale; FEV1, forced expiratory volume in 1 s; HC, health center; MMRC, Modified Medical Research Council Dyspnea Scale; MMST, Mini-Mental Status Examination Test; OP, osteoarticular pathology; RT, randomized trial; SGRQ, St. George Respiratory Questionnaire. *, statistically significant differences ($p < 0.05$).

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TABLE 2 Inhalation technique by type of device.

Incorrect IT n (%)									
Handihaler®		Accuhaler®		Turbuhaler®		Breezhaler®		pMDI	
BV	FV	BV	FV	BV	FV	BV	FV	BV	FV
86 (89.6)	31 (64.6)	50 (78.1)	21 (48.8)	120 (89.6)	61 (58.7)	50 (89.3)	32 (62.7)	103 (98.1)	50 (60.2)
Most frequent mistakes									
No full exhale before inhalation n (%)									
CSF n (%)									
78 (81.3)	30 (62.5)	51 (78.5)	20 (46.5)	114 (85.1)	59 (56.7)	47 (83.9)	28 (56)	86 (82.7)	43 (51.8)
CSF2: 78 (100)	CSF2: 30 (100)	CSF2: 51 (100)	CSF2: 20 (100)	CSF2: 114 (100)	CSF2: 59 (100)	CSF2: 47 (100)	CSF2: 28 (100)	CSF1: 86 (100)	CSF1: 43 (100)
Not pushing the button correctly n (%)									
CSF n (%)									
20 (20.8)	8 (16.7)	7 (10.9)	2 (4.7)	48 (35.8)	8 (7.6)	4 (7.3)	9 (18)	24 (23.3)	10 (12)
CSF2: 15 (75)	CSF2: 8 (100)	CSF3: 7 (100)	CSF3: 2 (100)	CSF3: 48 (100)	CSF3: 8 (100)	CSF1: 1 (25)	CSF2: 9 (100)	CSF2: 6 (25)	CSF2: 3 (30)
CSF3: 5 (25)						CSF2: 2 (50)		CSF3: 18 (75)	CSF3: 7 (70)
						CSF3: 1 (25)			
Not placing lips correctly on the mouthpiece n (%)									
CSF n (%)									
2 (2.1)	0	2 (3.1)	0	2 (1.5)	0	0	0	13 (12.6)	6 (7.2)
CSF1: 1 (50)		CSF2: 2 (100)		CSF2: 1 (50)				CSF1: 3 (23.1)	CSF3: 6 (100)
CSF3: 1 (50)				CSF3: 1 (50)				CSF2: 6 (46.2)	
								CSF3: 4 (30.8)	
Non-optimal strength of inhalation n (%)									
CSF n (%)									
8 (8.3)	1 (2.1)	7 (10.8)	0	11 (8.2)	2 (1.9)	3 (5.5)	0	72 (69.9)	24 (28.9)
CSF1: 5 (62.5)	CSF1: 1 (100)	CSF1: 3 (42.9)		CSF1: 2 (18.2)	CSF2: 2 (100)	CSF1: 1 (33.3)		CSF2: 72 (100)	CSF2: 24 (100)
CSF2: 3 (37.5)		CSF2: 4 (57.1)		CSF2: 7 (63.6)		CSF2: 2 (66.7)			
				CSF3: 2 (18.2)					
No or short breath hold after inhalation n (%)									
CSF n (%)									
65 (67.7)	18 (37.5)	40 (61.5)	14 (32.6)	81 (60)	33 (31.7)	40 (72.7)	22 (44)	77 (74.8)	33 (39.8)
CSF2: 65 (100)	CSF2: 18 (100)	CSF2: 40 (100)	CSF2: 14 (100)	CSF2: 81 (100)	CSF2: 33 (100)	CSF2: 40 (100)	CSF2: 22 (100)	CSF2: 77 (100)	CSF2: 33 (100)

BV: baseline visit; CSF: clinical significance of the failure: CSF1: mild, CSF2: moderate, CSF3: critical error; FV: final visit; IT: inhalation technique.

devices were pressing the button (Turbuhaler® 35.8%, Handihaler® 20.8%, pMDI 23.3%, and Breezhaler® 7.3%) and shaking the pMDI device (52.4%). Table 2 sets out the baseline characteristics of the IT per device and CSF.

3.3 GPs' baseline characteristics

The 27 GPs had an average age of 55.64 years (CI 95%, 56.62–54.66), and 59.3% were women. The majority (91.7%) were

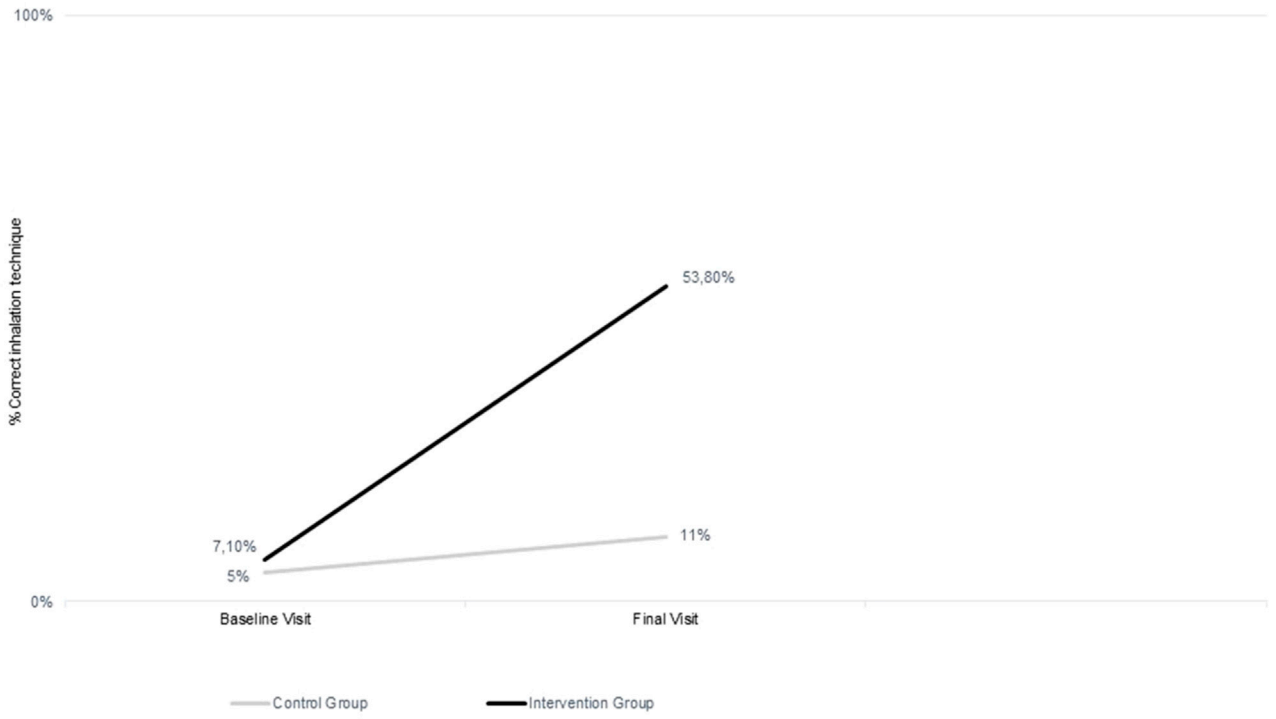

FIGURE 2
Evolution of correct inhalation technique.

family and community medicine specialists and 9.3% had completed their doctoral studies. About the last update on COPD, 41.7% had attended clinical sessions and reviewed national recommendations; 33.3% had taken courses; 20.8% had received other types of updates; 12.5% had reviewed international recommendations; and 4.2% had attended congresses.

Regarding the COPD guidelines, 62.5% knew the national guidelines (the Spanish COPD guide, GesEPOC, Integrated Care Process of COPD) and 37.5% knew the international guidelines (the Global Initiative for COPD, GOLD). As a result of the test of knowledge about COPD diagnosis and management, no professional answered the full questionnaire correctly. If we split the questionnaire into questions related to the diagnosis, classification, and management of COPD, we found the correct answers in 3 (11%), 7 (26%), and 2 (7%) GPs, respectively.

Concerning IT, 91.7% (25) of the professionals performed it incorrectly, 92.3% in the IG and 92.9% in the CG. Incorrect IT was detected in 19 subjects (79.28%) with Turbuhaler®, 19 (86.4%) with pMDI, 22 (91.7%) with Handihaler®, 17 (70.8%) with Accuhaler®, and 20 (90.9%) with Breezhaler®.

Twenty GPs (74.4%) had been given some type of IT training, and the average time elapsed from this education to recruitment was 30.2 months (95% CI, 6.96–58.84). The pulmonologist carried out the majority of educational training (seven GPs; 25.9%), followed by Big Pharma courses (three GPs; 11.1%) and healthcare service courses (three GPs; 11.1%). The most frequent way in which this instruction was performed was through the demonstration with the inhaler (15 subjects; 55.6%), followed by instruction with device explanation (5 subjects; 18.5%), and in one GP (3.7%), the instruction consisted of a descriptive brochure.

The most recurrent errors, observed and not related with the device, included failure to hold breath or experiencing shortness of breath after inhalation (60.9%) and incomplete exhalation before inhaling (36.2%), with moderate clinical significance. The most frequent errors related to the inhalers were correct position for Turbuhaler® (16.4%), emptying the content for Handihaler® (75%) and Breezhaler® (77.3%), and coordination for pMDI (60%).

Regarding the review of the IT with their patients, 100% agree that it should be reviewed periodically: when the device is changed (41.7%), at the beginning of treatment (37.5%), at each consultation or each year (25%), when the patient requests it (12.5%), or every 6 months (4.2%).

GPs reported that they tended to review the IT in COPD patients when introducing a new device (79.2%), only once (16.7%), never (12.5%), or every 3 months (4.2%).

3.4 Intervention effectiveness

On finishing the study, the success IT rates were found to be 78 subjects (53.8%) for the IG and 10 subjects (7.1%) for the CG ($p < 0.0001$). Figure 2 shows the progression of the IT in both groups.

The effectiveness parameters calculated for this study were RR = 7.58 (CI 95%, 4.09–14.04), ARB = 6.57, AAB = 0.46 (95% CI, 0.37–0.46), and NNT = 2.14 (95% CI, 1.79–2.66), which means that, for every 2–3 patients who are trained by their GP, an additional clinical benefit is achieved (correct IT).

The mean time for device educational training was 5.21 min (CI 95%, 4.98–5.44) for the CG and 5.98 min (CI 95%, 5.49–6.47) for the

IG at baseline. On finishing the study, it was 5.21 min (CI 95%, 4.76–5.66) for the CG and 5.98 min (CI 95%, 5.01–6.95) for the IG.

For the step-by-step performance of the IT and also by devices, the comparison between baseline and the end of the study is summarized in Table 2.

For the GPs, the comparison between baseline and the final visit showed statistically significant differences for the correct performance of the IT in general and by devices for the IG. For the general IT, there was an improvement of 61.5% ($p < 0.0001$). No statistically significant differences were found for any other variable in either the IG or CG.

The comparison of secondary outcomes (patients) at the end of the trial is set out in Table 3. Statistically significant differences are shown for the VAS scale of EuroQoL-5D-5L, with better perceived health status in both groups (CG $p = 0.028$; IG $p < 0.0001$). Moreover, statistically significant differences were found for the SGRQ total scale ($p = 0.041$) and SGQR symptom scale ($p < 0.0001$) scales in the IG.

3.5 Intervention-related factors

Table 4 summarizes the multivariate analyses. A logistic regression analysis and a classification tree analysis were performed as multivariate analyses for this study. Both analyses showed the same results; so finally, classification tree analysis was

TABLE 3 Comparison between secondary outcome variables BV and FV.

Variables	Control group			Intervention group		
	BV (n = 141)	FV (n = 145)	*p*	BV (n = 141)	FV (n = 145)	*p*
EuroQol, n (%)						
Self-care problems	22 (15.6)	27 (25.8)	*0.113*	21 (14.5)	17 (14.9)	*0.940*
Usual activities problems	27 (19.1)	*32 (30.5)*	*0.117*	27 (18.7)	21 (19.3)	*0.554*
Pain/discomfort	63 (44.6)	56 (53.4)	*0.395*	78 (53.8)	50 (43.8)	*0.244*
Anxiety/depression	39 (27.6)	40 (38.1)	*0.092*	46 (31.8)	*30 (26.3)*	*0.244*
EuroQol VAS [mean, CI 95%]	66.06 (62.07–70.04)	72.29 (68.69–75.88)	*0.028**	63.57 (59.90–67.25)	72.37 (69.12–75.61)	*0.001**
SGRQ [mean, CI 95%]						
Total	34.32 (31.08–37.56)	34.17 (30.01–38.33)	*0.955*	35.48 (32.58–38.38)	31.07 (27.92–34.22)	*0.044**
Symptoms	42.73 (38.75–46.71)	38.73 (34.03–43.43)	*0.199*	45.29 (41.73–48.85)	34.76 (30.96–38.55)	*0.000**
Activities	46.81 (42.72–50.91)	46.86 (41.42–52.30)	*0.989*	47.16 (43.42–50.90)	43.22 (39.44–47.01)	*0.150*
Impact	25.09 (21.88–28.79)	25.44 (21.50–29.39)	*0.899*	25.50 (22.61–28.38)	22.35 (18.96–25.74)	*0.161*
Dyspnea, n (%)						
BDI functional impairment	122 (86.5)	122 (86.5)	*0.569*	126 (86.9)	126 (86.9)	*0.569*
BDI magnitude of task	114 (80.9)	114 (80.9)	*0.560*	127 (87.6)	127 (87.6)	*0.571*
BDI magnitude of effort	113 (80.1)	113 (80.1)	*0.559*	126 (86.9)	126 (86.9)	*0.569*
MMRc scale	47 (33.3)	36 (24.8)	*0.550*	47 (33.3)	36 (24.8)	*0.554*
FEV1% [mean, CI 95%]	61.3 (57.71–64.89)	62.9 (59.64–66.16)	*0.091*	56.73 (53.61–59.85)	64.38 (60.82–67.94)	*0.552*
Inspiratory peak flow [mean, CI95%]	182.18 (168.75–197.59)	176.42 (165.67–187.17)	*0.484*	175.19 (163.60–186.78)	185 (172.51–197.49)	*0.371*
COPD severity, n (%)			*0.393*			*0.821*
Mild	24 (17)	26 (17.9)		17 (12.1)	24 (16.6)	
Moderate	75 (53.2)	72 (49.7)		45 (31.9)	57 (39.3)	
Severe	36 (25.6)	39 (26.9)		36 (25.6)	26 (18)	

BDI, basal dyspnea index; BV, baseline visit; VAS, Visual Analogic Scale; FV, final visit; MMRc, Modified Medical Research Council Dyspnea Scale; SGRQ, Saint George Respiratory Questionnaire. The *p*-values are the marked in italic.

TABLE 4 Factors associated with the correct inhalation technique at the final visit.

Variables	% correct IT	*p*	Significance
Intervention group vs. control group	53.8 vs. 7.1	*0.0001**	Intervention group shows a better IT
Explanation with a device vs. others	72.1 vs. 48.5	*0.002**	IT improves using explanation with a device
pFEV	77.3 vs. 56.5	*0.0001**	Better pulmonary function improves the IT
SGRQ total scale	0 vs. 14.7	*0.013**	Having a better quality of life improves the IT
SGRQ activity scale	65.9 vs. 75	*0.0001**	
Intervention time ≥25 min	77.4 vs. 55.5	*0.0001**	IT improves if the interview is ≥25 min

IT: inhalation technique; SGRQ, Saint George Respiratory Questionnaire. The *p*-values are the marked in italic.

chosen to describe the results for this paper. Several analyses were performed with and without missing data, but the results were the same. In addition, the losses were less than those calculated for sample size, so it was decided to exclude dropouts from the analysis in order to avoid statistical artifacts from this cause.

With the classification tree analysis, it was observed that membership in the intervention group discriminated in favor of a better IT (53.8% IG vs 7.1% CG, $p < 0.0001$). Furthermore, the explanation with the device improved the performance of the IT (0% IG vs. 72.1% CG, $p = 0.002$). In the patients of the IG, good pulmonary function favored the good performance of the technique (56.5% vs. 77.3%, $p = 0.0001$). Likewise, among those with poorer pulmonary function, age influenced good performance ($p = 0.014$), with the youngest patients (≤65) and the oldest (>83) returning the best results, while the intermediate age group had the lowest percentage of good performance (34.5% vs. 90% and 100%).

A good IT is inversely associated with the quality of life in the CG regarding the total SGRQ scale ($p = 0.013$). For the IG, a relationship was found between a lower limitation of activity due to dyspnea (activity scale of SGRQ, $p < 0.0001$) and a good performance of the IT. Finally, an intervention lasting more than 25 min significantly improves the performance of a good IT (55.1 vs. 77.4, $p < 0.0001$). No relation was found between the prior IT trainer and dyspnea (BDI and mMRC).

With regard to the GPs, there was no influence of age, sex, previous IT performance, or knowledge about COPD and its treatment. Only membership in the intervention group is related to a better IT performance.

4 Discussion

The PROF-EPOC study shows that an educational intervention using the teach-back method with GPs has a significant and positive effect on GPs' performance of the IT and that of their patients after 1 year of follow-up. This improvement was associated not with the characteristics of the GP but with the intervention. This study found that good performance of the IT was related to demonstrating the proper technique with the device, having a good pulmonary function, being among the youngest (≤65) and the oldest (>83) patients, experiencing lower limitation of activity due to dyspnea, and undergoing an intervention lasting more than 25 min. This educational intervention involving GPs could be a promising approach to improving medication adherence and health outcomes in COPD patients.

There are few studies addressing interventions focused on the training of healthcare professionals on the IT, and fewer focused on GPs or COPD patients. Toumas et al. (2009) conducted a study with second-year pharmacy students who were given a brochure and found that 10% of the participants performed the technique properly as a result. However, when they were given a demonstration with the device, this percentage increased to 62%. Al-Otaibi (2020) performed the intervention on physicians, pharmacists, respiratory therapists, and health educators who attended a training course where an improvement in the inhaler handling questionnaire score of almost 40% was observed. Cvetkovski et al. (2020) carried out their study on primary care physicians, showing that only 0.88% of the professionals performed the IT incorrectly after reading a leaflet and witnessing an explanation with a device. The present study showed a similar increase for the proper IT for GPs.

Regarding the improvement of the IT in patients after the training of their GPs, there are few studies in the literature carried out on COPD patients, and most are conducted jointly with asthma patients. Aksu et al. (2016) conducted a prospective study of 108 patients with asthma and COPD. The physician made an initial visit where the patient's IT was corrected, and after 3 months, the IT was checked again. The percentage of patients with good IT improved (28%), showing how the practical training provided by physicians on the management of inhalers was an effective tool in the improvement of ITs. Takaku et al. (2017) carried out a prospective observational study with 216 subjects with asthma (the majority) and COPD. The counseling was performed by a pharmacist who had received prior training. They reported an improvement of 53% in the IT after the intervention. Takemura et al. (2013) performed a study training 81 community pharmacists to educate patients through a brochure. A review was conducted 4 years later, and it was observed that 39 patients had improved adherence and quality of life, including the IT. These studies show that training HCP improves the IT in their patients, in line with the results of our own study. However, these studies did not include effectiveness parameters. Only the study of Kim et al. (2021) reported an NNT of 3.3, which is similar to our result. Further studies are, thus, necessary to address this topic.

There is apparent agreement on the need to demonstrate the practical management of inhalers by professionals before prescribing them. The IT should be performed appropriately during every appointment at the healthcare center and should be controlled by healthcare professionals (Aksu et al., 2016; Lavorini et al., 2019; Melani, 2021; Global Iniciative for COPD, 2022). When a change in treatment takes place, a new demonstration must be repeated by both the healthcare professional and the patient (Dekhuijzen et al., 2022). Similar results were obtained in the present study by questioning GPs. The IT must also be reviewed periodically in order to be effective (Kim et al., 2021; Dekhuijzen et al., 2022; Global Iniciative for COPD, 2022), as a relationship between regular instruction and adherence has been observed (Martínez Ibán et al., 2019; Ahn et al., 2020; Efil et al., 2020), with an improvement in the quality of life (Martínez Ibán et al., 2019; Efil et al., 2020; Luley et al., 2020; Lindh et al., 2022) and a reduction in the need for hospital admission of up to 80% (Martínez Ibán et al., 2019; Efil et al., 2020). Thus, the professionals considered that the IT should be checked periodically, although they did not agree on how often it should be checked. However, previous studies carried out in the same environment showed that reminders about the IT for COPD patients should take place every 3 months (Barnestein-Fonseca et al., 2023). Other studies suggest the same frequency of 3 months improves IT and adherence (Takaku et al., 2017; Ahn et al., 2020), while another recommends a lesser frequency (Lee et al., 2016; Yoo et al., 2017).

It is clear that suitable instruction can improve IT (Klijn et al., 2017; Barnestein-Fonseca et al., 2023). However, due to varying educational levels, different teaching techniques are used. Essentially, these teaching techniques can be classified into two types: brochures and practical demonstrations. The studies of educational IT interventions (Toumas et al., 2009; Bosnic-

Anticevich et al., 2010; Klijn et al., 2017; Jia et al., 2020; Melani, 2021; Barnestein-Fonseca et al., 2023) showed that interventions including a face-to-face or video demonstration showing how to use inhalers are effective. In the same way, after testing which educational interventions were the most appropriate for COPD patients in our environment, it was decided to include an educational intervention based on a practical demonstration of the IT (Barnestein-Fonseca et al., 2011; Barnestein-Fonseca et al., 2023).

Our work shows fewer IT improvements than most studies carried out, although there are some exceptions (Giner et al., 2002; Cabedo García et al., 2010; O'Dwyer et al., 2020). This may be because the analysis was performed considering the intention-to-treat principle, while the other authors did not take into account the dropouts.

Although many patients indicated that they had received IT instruction, the rate of incorrect techniques was high. This fact could be due, in part, to the limited knowledge of the professionals who prescribe these medicines on how to manage inhalers and the teaching techniques (Aksu et al., 2016; Plaza et al., 2018; Al-Otaibi, 2020; Cvetkovski et al., 2020), as well as to a lack of regular IT verification with reminders and to the kind of training chosen (Klijn et al., 2017; Takaku et al., 2017; Kaplan and Price, 2018; Lavorini et al., 2019; Melani, 2021; Lindh et al., 2022). These results agree with the findings of this work, where the GPs manifested a high level of incorrect IT in their patients and where the reminders of the IT were performed with inappropriate periodicity.

In addition, it is essential to consider that reminders are important not only for patients but also for professionals so that the training they provide to their patients will also be correct. Some authors claim that GPs may be served by less frequent updating of skills in the management of particular inhalers compared to others (Takemura et al., 2011; Bosnic-Anticevich et al., 2018; Cvetkovski et al., 2020). Although regular educational interventions do indeed improve the long-lasting consistency of the IT (Takemura et al., 2011), from the perspective of GPs, illness management should be prioritized (Cvetkovski et al., 2020). It is clearly demonstrated that motivation plays an essential role in the IT, as it is not just a physical skill (Bosnic-Anticevich et al., 2018). Whether GPs have the time and disposition to educate COPD patients about the IT and implement strategies to improve adherence and proper use of medicines remains unanswered (Cvetkovski et al., 2020).

Several works indicated that from 50% to 94% of patients are not able to carry out the inhalation technique correctly (Chrystyn et al., 2017; Adib-Hajbaghery and Karimi, 2018; Duarte-de-Araújo et al., 2019; Rincon-Montaña and Rosselli, 2019; Dhadge et al., 2020; Vila Jato, 2020; Dekhuijzen et al., 2022; Sulku et al., 2022), even though the success of the treatment depends on it (Chrystyn et al., 2017; Adib-Hajbaghery and Karimi, 2018; Duarte-de-Araújo et al., 2019; Lindh et al., 2019; Padmanabhan et al., 2019; Rincon-Montaña and Rosselli, 2019; Rodriguez-Garcia et al., 2020; Schreiber et al., 2020; Dekhuijzen et al., 2022). The errors found in all the devices are similar to those reported by Melani (2021) in a review. Previous works revealed that the errors depended on the subject's preparedness and physical ability to execute the technique. The most common errors found were to achieve lower peak inhalation flow, lower MMSE scores, fewer appointments with the pulmonologist, and not receiving previous educational management of inhalers (Leiva-Fernandez et al., 2013; Barnestein-Fonseca et al., 2022). Errors associated with inhalers are less frequent and are linked to different positions (in the case of Turbuhaler®) and flows (coordination in the case of pMDI) (Chrystyn et al., 2017; Duarte-de-Araújo et al., 2019; Lindh et al., 2019). Despite improvements and breakthroughs in technology, most subjects do not intuitively reach full competence with the inhaler by themselves (Harb et al., 2020; Melani, 2021). Studies using real-world data inform us that, as of yet, there is no easy-to-use inhaler available.

A poor IT leads to a reduction of its beneficial effect, lower symptom control, and therefore, poor COPD control (Padmanabhan et al., 2019; Vila Jato, 2020; Dekhuijzen et al., 2022). It may also be associated with an increase in the number of emergency room visits, hospitalizations, or the use of antibiotic and corticosteroid treatments, ultimately increasing the cost of COPD management, increasing adverse reactions, and limiting therapeutic alternatives (Martínez Ibán et al., 2019; Efil et al., 2020; Vila Jato, 2020; Dekhuijzen et al., 2022). The performance of the correct IT has been related, in this study as well, to a better FEV1, perhaps because correct performance allows for better FEV1, potentially slowing down functional deterioration, and it then improves the technique because there are steps that are related to good pulmonary function, such as deep inhalation of the aerosol (Melani et al., 2011; Padmanabhan et al., 2019; Efil et al., 2020; Vila Jato, 2020). Among those with poorer lung function, the percentage of those performing the correct IT was influenced by age; specifically, those under 65 and over 83 years of age demonstrated a higher percentage of correct technique. These findings could be associated with a greater concern for the progression of COPD in younger and older people with shorter and longer diagnosis times, respectively. It has been found that the performance of the correct IT is related to QoL measured by SGRQ in both groups. In the CG, the modification is observed at the global scale, and there is a higher percentage of subjects with the correct technique among those who have a poorer quality of life. This could be explained by the fact that, feeling worse, they make a greater effort to take advantage of the benefits that the treatments can provide for them. In the IG, the differences are observed on the activity scale. The subjects with higher scores (bad quality of life) perform the technique less well than those with lower scores. Poor performance of the technique makes it difficult to perform daily activities (Melani et al., 2011; Padmanabhan et al., 2019).

Finally, when the visit lasts longer than 25 min, there is a higher percentage of patients who perform well on the IT (Weheida et al., 2017; Efil et al., 2020; Lindh et al., 2022). This finding correlates with the methods used for training the patients. The intervention includes the feedback of the patients until they develop a correct IT, so to obtain a higher percentage of good results, it is necessary to spend time on correct training. However, when the training is fixed, the time of intervention decreases during the follow-up visits (Kim et al., 2021; Barnestein-Fonseca et al., 2023).

Overall IT performance for GPs showed the same errors as the patients, those related to their preparation before performing the technique. However, when analyzed by devices, the most frequent errors among GPs are related to the device itself, even if the type of error is the same. This is perhaps because they do not have lung capacity problems, as their patients do. The consistency in the type of error over different devices is understandable, given that they have

the same characteristics (Dekhuijzen et al., 2022). However, are the errors subject related rather than device related? Could there be a transfer of knowledge between inhalers (Dekhuijzen et al., 2022)? This was partially noted in this study, with GP errors related to their preparation for the technique. Thus, focusing education on the most common known errors could help improve full IT competence, regardless of the inhaler used.

The main strength of this study is the use of an intervention that is quick, easy, and reproducible to improve the IT, based on the practical demonstration of the IT using the teach-back method, previously tested in clinical trials (Barnestein-Fonseca et al., 2011; Barnestein-Fonseca et al., 2023). With these methods, patients can demonstrate their inhaler handling and subsequently receive specific feedback from the instructor. In addition, the dropout percentage was found to be lower than expected, and there were no differences between the initial and final samples. Therefore, the internal validity of the study is guaranteed.

This work also has limitations. First, the missing data lead to a loss of estimation accuracy. To address this, the sample size was increased by 40% (i.e., the expected losses), telephone calls were made to unreachable patients at different times, and extra appointments for clinic visits were scheduled; these resulted in lower losses than expected. Moreover, we applied data imputation to complete the lost data. Second, randomization was applied at the second level before the recruitment of participants from the first level, where the impact of the intervention was measured, which could lead to selection bias at this level. To minimize this bias, external research assumed the patients' selection and their follow-up; this person did not know the GP randomization. In addition, different motivations among randomized professionals could lead to different recruitment rates, as control GPs may be less willing to cooperate. To counteract this lack of motivation, control professionals received the same training as intervention professionals at the end of the trial (Basheti et al., 2008; Ahn et al., 2020). Another potential bias could have come from the selective correction of only critical errors in the control group patients, which could have worked in favor of the study hypothesis by increasing the rate of the incorrect technique in this group, considering that all the steps indicated in the template had to be fulfilled in the assessment of the technique. Another limitation could be interviewer bias in the measurement of variables based on the application of questionnaires due to the involvement of different interviewers in administering them. To minimize these biases, the interviewer monitors were previously trained to ensure that the visits were as homogeneous as possible. To avoid this bias among the health professionals in the intervention group, who were, therefore, in charge of training their patients in the correct inhalation technique, they were thoroughly trained and provided with a common data collection booklet and an explanatory manual on how to collect each of the variables that were measured in the follow-up visits of their patients.

The results of this research could have a major impact on the prognosis of the disease, making it a promising approach. This is an easy-to-implement intervention with high potential for real-life efficacy in improving medication adherence and health outcomes in COPD patients. As a recommendation for implementation in the clinical setting, this training could be extended to all professionals involved in the care of COPD patients; it would represent a more effective strategy that could benefit a larger number of individuals. It is also important to consider changing the inhaler used or applying a spacer, especially for those who have greater difficulties handling the different devices due to their age and physical and/or mental disability.

As a group of patients still struggled to manage their inhalers, a more detailed analysis of patient characteristics would be necessary to modify certain phases of the training (e.g., frequency of reminders for both professionals and patients). In conclusion, this study shows the efficacy of direct training using the teach-back method in the inhaler technique in patients by a trained professional (general practitioner) with sufficient time (e.g., specific consultation for medication review).

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Comité Ética Investigación provincial de Málaga. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

NV-G: formal analysis, investigation, writing—original draft, and writing—review and editing. JL-F: conceptualization, funding acquisition, project administration, resources, supervision, and writing—review and editing. VC-L: data curation, investigation, and writing—review and editing. FL-F: conceptualization, methodology, writing–original draft, and writing—review and editing. FR-D: formal analysis and writing—review and editing. FM-C: formal analysis and writing—review and editing. EM-M: resources, writing—original draft, and writing—review and editing. PB-F: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, writing–original draft, and writing—review and editing.

Funding

The authors declare that financial support was received for the research, authorship, and/or publication of this article. This research project was funded by Fondo de Investigaciones Sanitarias (FIS), Instituto de Salud Carlos III (PI-0170-2013), Spain, and II Plan Propio de Investigación, Transferencia y Divulgación Científica de la Universidad de Malaga, Spain.

Acknowledgments

The authors thank the general practitioners and patients for their participation in this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1266095/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 17 October 2023
DOI 10.3389/fphar.2023.1254912

OPEN ACCESS

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RECEIVED 07 July 2023
ACCEPTED 05 October 2023
PUBLISHED 17 October 2023

CITATION
Kardas P, Mair A, Stewart D and Lewek P (2023), Optimizing polypharmacy management in the elderly: a comprehensive European benchmarking survey and the development of an innovative online benchmarking application. *Front. Pharmacol.* 14:1254912. doi: 10.3389/fphar.2023.1254912

Optimizing polypharmacy management in the elderly: a comprehensive European benchmarking survey and the development of an innovative online benchmarking application

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Background: Polypharmacy, defined as the simultaneous use of multiple medications by a patient, is a worldwide problem of rising prevalence. Paving the way for drug interactions, adverse drug reactions and non-adherence, it leads to negative health outcomes, increased use of healthcare services and rising costs. Since it is closely related to multimorbidity, it peaks in older adults. So far, not many polypharmacy management programs in the elderly have been introduced in practice. However, due to the rapid ageing of European societies, there is an urgent need to implement them more widely.

Objective: The aim of this study was to benchmark polypharmacy management programs in the elderly available in Europe and creating a dedicated benchmarking application.

Methods: It was a cross-sectional study based on an online survey targeting healthcare professionals and other stakeholders across European countries. Data collected in the survey were reused to design an online benchmarking application.

Results: As many as 911 respondents from all but two EU countries took part in this study. Out of the survey participants, 496 (54.4%) reported availability of various activities or formal programs targeting polypharmacy in the elderly that were known to them. These programs had multiple goals, of which improved patient safety was indicated as the most common objective (65.1% of the cases). The most typical settings for such programs was primary care (49.4%), with pharmacists and primary care doctors being indicated most often as those providing the programs (61.7% and 35.5% of cases, respectively). Vast majority of programs applied diverse forms of drug reviews. The identified programs were assessed against four predefined dimensions of effectiveness, applicability, scalability and cost-effectiveness. The lowest scores were obtained within the last of these categories, due to unavailability of relevant data. Based on the survey results, a benchmarking application was constructed. It allows for comparing an individual polypharmacy management program targeting the elderly against the other ones, and particularly, against the national and European context.

Conclusion: By providing strong evidence, the findings of this study, coupled with the benchmarking application, can prove valuable in aiding clinicians and policymakers in the implementation and expansion of polypharmacy management programs for the elderly.

KEYWORDS

polypharmacy, elderly, older adults, chronic conditions, benchmarking, survey, multimorbidity

1 Introduction

Polypharmacy is most often referred to as the simultaneous use of multiple medications by a patient to treat their conditions. Still lacking a standard definition, it is usually operationalised as a scenario of concurrent use of five or more prescribed drugs (Kurczewska-Michalak et al., 2021).

Over the last 2 decades, polypharmacy has become a major public health concern, and a subject of multiple scientific publications. The reason for this is twofold. On the one hand, polypharmacy entails a number of profound consequences. Although the correct multidrug treatment in patients with complex medical problems can improve clinical outcomes, quality of life and life expectancy, polypharmacy is also associated with an increased risk of avoidable harm. Of course, first of all this is true in the case of improper use of multiple medicines, i.e., the so called "inappropriate polypharmacy". Nevertheless, the more drugs are used concurrently, the higher are the chances that polypharmacy becomes inappropriate. Indeed, particularly in older adults polypharmacy leads to increased prevalence and severity of medication-related problems, such as drug interactions, adverse drug reactions and medication errors, some of which are severe enough to result in profound health repercussions or even death. Polypharmacy can also pave the way to medication non-adherence, with up to 50% of community-dwelling older people who receive four or more medications not taking them as prescribed (Franchi et al., 2021). In older adults it leads to occurrence and worsening of geriatric syndromes. Apart from safety issues concerning individual patients, it also has far-reaching public health, social, and economic consequences, which translates into increased use of healthcare services and costs (Fried et al., 2014). Particularly in older adults, it leads to a higher risk of hospitalization and institutionalization, along with greater healthcare expenditures (Maher et al., 2014).

Another reason for the growing interest in polypharmacy is that its frequency has been rising dramatically (Charlesworth et al., 2015; Carmona-Torres et al., 2018; Zhang et al., 2020). A recent analysis proves that within just 5 years, the prevalence of polypharmacy nearly doubled in the United States, and more than doubled in the Netherlands (Oktora et al., 2019). These negative trends are more than certain to continue, as a number of factors responsible for this problem are also on the rise. This is particularly true for ageing and multimorbidity, i.e., the two interlinked factors which are becoming more and more prevalent globally (Guthrie et al., 2015). However, the current paradigm of healthcare, being generally based on fragmented care and single-disease oriented guidelines, seriously increases the chances of multidrug therapy as well. Unfortunately, clinical trials seldom include the elderly and rarely focus on polypharmacy (Giardini et al., 2018). Hence, clinical guidelines only infrequently address the complex nature of multimorbidity and take the patient's perspective into consideration, prioritize certain conditions or treatments, and consequently, help to reduce the burden of prescribed drugs (Montori et al.; Farmer et al., 2016).

Another indirect consequence of the above-described interrelationships is that both the prevalence and the magnitude of the problem caused by polypharmacy is the greatest in older adults. An analysis of a large European cohort has found polypharmacy to be present in 32.1% of citizens aged 65 years or above (Midão et al.). Recent data from Poland prove that the older the patients, the more prevalent the polypharmacy. In 2019, it affected 42.1% of individuals aged 65+, and 55.0% of those aged 80+ (Kardas et al., 2021a). As many as 19.1% of the national 65+ cohort was subject to chronic polypharmacy, in the vast majority (68.6%) continuing this status for the period of the whole studied year (Kardas et al., 2021b).

There is a variety of tools aimed at reducing inappropriate polypharmacy (Kaufmann et al., 2014). A recent scoping review identified numerous interventions, of which most involved various types of drug reviews based on either implicit (judgement-based) or explicit (item list-based) criteria (Kurczewska-Michalak et al., 2021). However, even those interventions which are simplified by the use of explicit criteria, such as, e.g., STOPP/START, Beers and Medication Appropriateness Index (MAI), and/or supported by the computerised decision support systems, are used infrequently.

In general, polypharmacy management in older adults is underused, and practical implementation of available interventions is very limited. In fact, healthcare professionals are often either unaware of such tools or disregard them as not being user-friendly (Mc Namara et al., 2017). Indeed, application of various forms of drug reviews was reported in only half of the 32 European countries studied (Bulajeva et al., 2014). At the higher level, polypharmacy does not attract much attention of decision makers either. Despite the significance of the problems created by polypharmacy in older adults, this subject is only seldom tackled in a systematic way. An extensive search for polypharmacy guidance documents across Europe has identified only five countries that actually have such instruments targeting older patients (Stewart et al., 2017a).

As a consequence, there is an urgent need to change the current scenario, and reduce the negative impact that polypharmacy has on both individual patients and whole societies. This requirement is even more appealing due to the fact that not only were many tools created, but also several complete interventions were implemented successfully, mostly on the local level. Such interventions need to be identified, and compared, in order to select the best ones, and allow

for their multiplication and scaling up. The SIMPATHY Project (Stimulating Innovation Management of Polypharmacy and Adherence in The Elderly), a European scientific collaboration supported by the Horizon 2020 grant, aimed at introducing of relevant system changes that could facilitate implementation of polypharmacy management programs (Mair et al., 2020). To accomplish this objective, SIMPATHY focused on analysing of current healthcare models and practices for management of inappropriate polypharmacy across the EU, as well as stimulating exchange and adoption of the best practices (Mair et al., 2017a). Therefore, the aim of this study, stemming from the SIMPATHY Project, was to benchmark polypharmacy management programs in the elderly available in Europe. In order to increase usability of the obtained results, and stimulate wider implementation of the best practices in real life settings, we also aimed at creating a benchmarking application—an online tool allowing for comparing an individual polypharmacy management program targeting the elderly against other similar solutions, and particularly, against the national and European context.

2 Methods

It was a cross-sectional study based on an online survey targeting healthcare professionals and other stakeholders, which aimed at collecting data on practices of polypharmacy management in older adults across European countries, benchmarking the identified programs, and ultimately designing an online benchmarking application. This study was a part of a larger analysis including both patients and professionals, performed within the framework of SIMPATHY project (Mair et al., 2017a). In this paper, however, we report data collected for various types of professional respondents only. In following paragraphs, the methodology of the study is described in more detail, following the STROBE guidelines (von Elm et al., 2007).

2.1 Designing the benchmarking survey questionnaire

The benchmarking survey was designed on firm theoretical grounds, constructed under the framework of the SIMPATHY project, which included a systematic literature review (Stewart et al., 2017a), 9 national case studies and reflection over change management mechanisms (McIntosh et al., 2018), and results of the online survey in polypharmacy experts. Detailed analysis of results of all these works allowed for preliminary identification of four major dimensions against which specific strategies of polypharmacy management were to be assessed, i.e., effectiveness, cost-effectiveness, applicability and scalability. Also, an initial list of relevant parameters could be drafted. It covered 170 items, ranging from the high of 54 for "Effectiveness" dimension, to the low of 36 for "Scalability" dimension. In order to reduce this number, a Delphi-like process of fine-tuning of the list of benchmarking parameters has been implemented. In this process, each domain was filtered-out of the least well-matched items so that the number of items in each of the domains did not exceed 25. As a result of five rounds of iterative reduction, the number of the items was reduced to 88. In the next step, the list of the parameters prepared for the questionnaire was validated by external experts. Assuming that validity refers to the appropriateness, meaningfulness and usefulness of a measure for a specific purpose (Jensen, 2003), this process covered aspects of content validity (operational question: are all the dimensions covered?), construct validity (operational question: how well is each of the dimensions covered?), and criterion validity (synonym: predictive validity—to which extent is a measure able to predict important outcomes?). The list of items was presented to a selected number of external polypharmacy experts who were asked to choose up to seven items within each dimension, and rank them from 1 (for top priority) to 7, for each of the two areas of process and outcome. The experts could also propose new items and provide their comments. Based to the results of prioritising of the preselected items, the first version of the survey questionnaire was prepared. It included 42 criteria items. An intensive internal discussion within the SIMPATHY consortium allowed for further fine-tuning of the questionnaire. Its sixth version was approved for piloting in a limited number of stakeholders in preselected SIMPATHY partner countries (Greece, Poland and the United Kingdom), either in the original English version, or local translation. The survey questionnaire was made available in a dedicated online surveying system, with relevant skip options, according to the previous answers given by the respondents. In order to assess the questionnaire itself, all the respondents were directed to the last section, in which they were to give their opinions on its length and content. In total, 40 responses to the pilot survey were obtained. Following discussion, several minor modifications were introduced, and the final English version of the questionnaire was agreed on and approved for use in the benchmarking survey (see Supplementary Appendix S1).

2.2 Benchmarking survey fieldwork

The final version of the benchmarking survey questionnaire was translated from English into eight European languages: Dutch, French, German, Greek, Italian, Polish, Portuguese and Swedish. All these versions were made available online at the Survey Monkey website, with relevant skip options provided. Thus, the participant could answer various number of questions, depending on the responses already given. Survey fieldwork was started on 12 June 2016. Diverse methods were used in order to attract the target population which included healthcare providers, members of professional organizations, policymakers, payers, government authorities, and all other kinds of relevant stakeholders. Invitations to take part in the survey were sent via e-mail to a number of individual stakeholders identified in all 28 Member States. A snowball method was also adopted to increase participation in the survey. The SIMPATHY Ambassadors and several collective bodies (such as major professional organisations active in the field of medicine, pharmacy and nursing, as well as patient organisations, *etc.*) were asked to invite other participants. The links to the survey in all the nine language versions were also made available on the SIMPATHY project website.

According to the benchmarking study protocol, a target number of respondents accepted was 560 (i.e. 20 per each out of 28 EU

countries, on average). When the number was reached, according to the continuous analysis of both the number and distribution of the respondents, the decision was made to extend the time to collect survey data by 11 September 2016. This was assumed to increase the response rate in underrepresented groups of stakeholders, such as politicians or policymakers.

2.3 Statistical analysis of survey data

The survey data collected in the Survey Monkey system were downloaded and saved in separate files created for each of the nine language versions of the survey. Then, after combining all the nine individual files, single master database was set up. Non-English responses were translated into English (based on the English version of the questionnaire, used for the international survey). Relevant variables were created to assess, in a cumulative way, performance of individual programs within each of the four dimensions (effectiveness, applicability, scalability and cost-effectiveness), along with a composite cumulative variable to assess overall performance (for details and relevant thresholds, see Supplementary Appendix S2). Free-text entries were analysed case-by-case and encoded in a cohesive way. Before running the final test, the master database was quality-checked and debugged.

IF≥90% of responses per country indicated lack of a polypharmacy program in that country; such an example was deemed to be "no intervention country".

Data exploration included descriptive statistics of characteristics of polypharmacy management programs and their analysis with cumulative variables for each of the four dimensions studied, as well as the overall composite measure. In the benchmarking analysis, cumulative data for the country level were compared.

2.4 Design of the benchmarking application

Based on the results of the benchmarking survey, an online benchmarking application was created. The application questionnaire was designed to use the original phrasing of the questions of the SIMPATHY Benchmarking survey in order to collect data on performance of individual programs with regard to the four dimensions (effectiveness, applicability, scalability and cost-effectiveness). A graphical interface of the application was designed to produce figures in which characteristics of individual programs were benchmarked against both national and European data.

3 Results

3.1 Characteristics of the respondents

The total number of 911 responses were collected in the survey. They were obtained from all but two (Luxemburg nor Malta) EU countries (please note that at the time of conducting the survey execution, the United Kingdom was one of the EU Member States). Additionally, 29 responses came from four non-EU European countries (Faroe Islands, Norway, Switzerland and Ukraine), and another 15 from eight non-European countries. More than half of the respondents (52.8%) represented different classes of pharmacists, 12.8% were doctors, whereas 8.9% were nurses, social workers and other healthcare providers. Detailed characteristics of the respondents are presented in Table 1. The distribution of the respondents varied across the countries (e.g., 33.7% of nurse respondents in Poland vs. 0% in both Belgium and Sweden, 75.5% of pharmacist respondents in Belgium vs. 22.7% in Germany, *etc.*).

3.2 Availability and characteristics of the polypharmacy management programs

The respondents were asked whether they had any knowledge about an activity or a formal program targeting polypharmacy in the elderly. More than half of them (496, i.e. 54.4%) indicated availability of such programs. In most of the cases, the programs were known to respondents in a direct way, from their workplace (54.8%). However, some of the respondents knew about such programs despite the fact that they did not have any direct contact with them, as they were only available in their region or country only (45.2% in total, for detailed distribution see Figure 1).

Out of the 26 EU countries from which the responses to the benchmarking survey were collected, polypharmacy management activities or programs for the elderly were reported by all but two countries. On average, more than half of the respondents (53.5%) from the EU countries reported availability of such programs. Due to fulfilling the predefined criterion of programs reported by <10% of the respondents, three EU countries, i.e., Bulgaria, Estonia and Poland, were deemed to be 'no intervention courtiers', providing availability of programs in 0%, 0% and 9.2% of their reports, respectively. On the other hand, as many as 14 EU countries reached the level of 50% or more of the respondents reporting availability of polypharmacy management programs for the elderly (these being Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Latvia, Lithuania, Netherlands, Slovakia, Spain, Sweden, and the United Kingdom). Among them, seven countries reached a level of 75% or more of the respondents reporting availability of such programs. For detailed distribution of percentages of the respondents reporting availability of polypharmacy management programs for the elderly in their countries, see Figure 2.

Programs known to the respondents had multiple goals often; of these, improved patient safety was provided most often (65.1% of programs). They were followed by programs focused on improved patient health outcomes and reduced medication errors, both reaching the level above 50% of responses (Table 2). Close to this level, there were programs aimed at reduction of hospitalizations number (45.4%), and improved patient adherence to medication (44.6%). The objective of approximately one-third of the programs was cost reduction.

The most typical setting for the programs was primary care (49.4%), with hospitals and community pharmacies being more than twice less common locations (22.8% and 20.8%, respectively). However, pharmacists were indicated as those providing the programs most often (61.7%), with GPs (general practitioners, i.e., primary care doctors) being pointed at much less frequently (35.5%). The programs were often based on teamwork; out of several options, a teamwork of doctors and pharmacists was the most prevalent one

10.3389/fphar.2023.1254912

TABLE 1 Characteristics of the respondents of the benchmarking survey.

Countries of the respondents[a]	N	%
EU countries	867	95.2
Austria	6	0.7
Belgium	49	5.4
Bulgaria	1	0.1
Croatia	5	0.5
Cyprus	5	0.5
Czech Republic	6	0.7
Denmark	3	0.3
Estonia	8	0.9
Finland	1	0.1
France	11	1.2
Germany	44	4.8
Greece	52	5.7
Hungary	6	0.7
Ireland	6	0.7
Italy	57	6.3
Latvia	1	0.1
Lithuania	10	1.1
Netherlands	29	3.2
Poland	98	10.8
Portugal	122	13.4
Romania	6	0.7
Slovakia	2	0.2
Slovenia	5	0.5
Spain	41	4.5
Sweden	48	5.3
United Kingdom[b]	245	26.9
• England	140	15.4
• Northern Ireland	11	1.2
• Scotland	84	9.2
• Wales	10	1.1
Non-EU European countries	**29**	**3.2**
Faroe Island	1	0.1
Norway	13	1.4
Switzerland	14	1.5
Ukraine	1	0.1
Other countries	**15**	**1.6**
Australia	1	0.1
Canada	1	0.1
India	1	0.1

(Continued on following page)

TABLE 1 (*Continued*) Characteristics of the respondents of the benchmarking survey.

Countries of the respondents[a]	N	%
Israel	2	0.2
Malaysia	1	0.1
Palestine	1	0.1
Turkey	2	0.2
United States	6	0.7
Respondent category	**N**	**%**
Doctors, all	**117**	**12.8**
primary care doctors	54	5.9
geriatricians	25	2.7
outpatient consultant doctors	9	1.0
hospital based doctors	29	3.2
Pharmacists, all	**481**	**52.8**
community pharmacists	114	12.5
primary care pharmacists	149	16.4
hospital pharmacists	118	13.0
clinical pharmacists	100	11.0
Other healthcare professionals, all	**81**	**8.9**
nurses	63	6.9
social workers	4	0.4
other healthcare providers	14	1.5
Other stakeholders, all	**232**	**25.5**
managers, health system managers	37	4.1
policymakers	20	2.2
politicians	8	0.9
healthcare commissioners	7	0.8
healthcare scientists/researchers	99	10.9
education regulators/commissioners	12	1.3
other	49	5.4
TOTAL NUMBER OF RESPONDENTS	**911**	**100.0**

[a]a healthcare professional's country of work.
[b]at the time when the survey was conducted, the United Kingdom was a member of the European Union.

(30.2%), followed by a teamwork of doctors, pharmacists and nurses (21.6%). Also, only in some cases there were incentives in place for healthcare professionals providing the program (of which the financial ones were reported for 17.7% of programs only). Techniques applied within the program most often included a prescription review (i.e., a technical review of the list of a patient's medicines; 54.0%), followed by a treatment review (i.e., a review of medicines with the patient's full notes; 52.0%) and a clinical medication review (i.e., a face-to-face review of medicines and condition; 47.0%). Other frequently used tools included electronic patient health records accessible to both the doctors and pharmacists involved in the program (42.3%), and a checklist for the intervention designed to help program providers (39.9%).

3.3 Effectiveness, applicability, scalability and cost-effectiveness of the polypharmacy management programs

Out of all the 496 respondents, who declared to know about existence of polypharmacy management programs in the elderly, only 148 (29.8%) confirmed awareness of several effectiveness outcome measures of the programs, and were redirected to more detailed questions on this issue. Even fewer respondents (128, i.e. 25.8%) provided answers to the questions assessing various effects of the programs on patients (Table 3). Among them, as many as 42.2% pointed to existence of evidence for a positive effect of the programs on patient satisfaction, whereas 33.6% pointed to evidence of their positive effect on patient health status. Less often, the respondents claimed the programs proved to positively affect patient health-related quality of life (27.3%) and medication adherence (25.0%). Interestingly, none of the respondents pointed to a negative effect of the programs. It is noteworthy, however, that up to half of the respondents answering these questions claimed that data on the effectiveness of these programs were not available, and another 20% chose the "don't know" option.

Parameters assessing the effectiveness of the programs in an objective way were provided very rarely (by 26 respondents only). In their opinion, an average number of drugs reduced after the program had been offered to an individual patient was 1.95+/-1.18 (mean +/-SD). The programs resulted in a mean reduction in

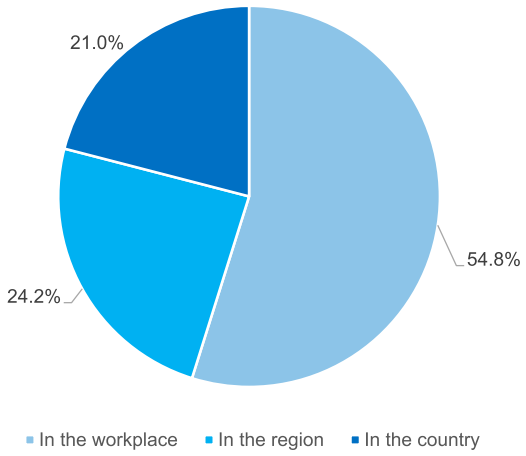


FIGURE 1
Availability of the polypharmacy management programs in the elderly by the level of their personal contact with the program (N = 496 respondents reporting availability of such programs).

medication-related problems by 40.3+/-25.7% on average, as well as reduction in primary care visits due to drug-related problems by 22.2+/-11.5%, and reduction in hospitalisations by 29.2+/-18.8%.

Not too many respondents were aware of the effect the program had on satisfaction among healthcare professionals (those providing the program). It is noteworthy, however, that a positive opinion on this effect was expressed 11 times more often than a neutral one (39.3% vs. 3.6% of the respondents who answered this question). Moreover, literally none of the respondents had a negative opinion.

The respondents who knew about existence of polypharmacy management programs were asked to assess several dimensions of applicability and scalability of these programs. As many as 309 valid answers were provided to this section (corresponding to 62.3% of the programs). From among that number, 56.0% of the respondents declared that the program had been created according to evidence-based (EBM) guidelines (Table 4). In 50.8% of the cases, the respondents reported that the development of skills allowing for multidisciplinary teamwork had been supported in order to help implementation of the program. At first, the support came in the form of educational measures, much less often in the form of financial contributions, via policy initiatives, or through contractual obligations.

When assessing applicability and scalability of these programs, various enablers were identified. For example, 41.7% of the relevant respondents indicated that there was a regional or national body coordinating and responsible for the program. The presence of dedicated ICT (Information and Communications Technology) solutions that facilitated implementation of the program was indicated by 32.7% of the respondents only. Moreover, the opinions of the respondents on the current level of support the ICT solutions provided to the programs were far from positive, and as many as 60.3% of them assessed them as either somewhat insufficient, or not sufficient.

Several factors may aid effective scalability of the polypharmacy management programs. One of them is undoubtedly the issue of dissemination of guidelines on polypharmacy management. Among the respondents who provided their answers in the applicability and scalability sections of the questionnaire, 62.8% reported that the process of dissemination of guidelines for polypharmacy management had been supported (Table 4). Most often that support came from health authorities (39.5%) and professional organisations (38.8%). In 40.5% of cases the programs were integrated within practitioners' training, of which most often in undergraduate and postgraduate training of pharmacists (in 29.1%, and 18.1% of respondents, respectively). It seems that there are some activities taken to raise patient awareness of polypharmacy

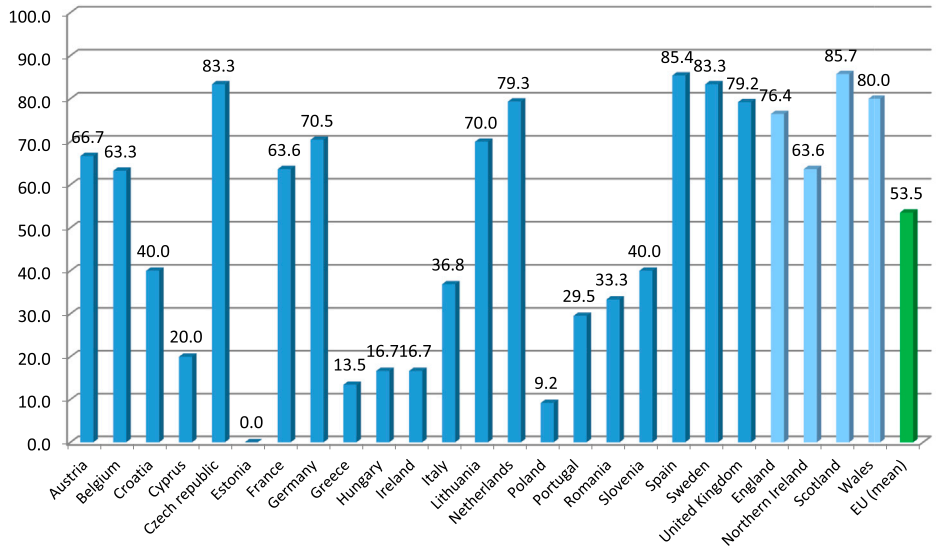


FIGURE 2
Percentage of the respondents reporting availability of polypharmacy management programs for the elderly across countries of Europe. Note: Countries with at least five responses to the benchmarking survey presented (therefore, Bulgaria, Finland, Latvia, Slovakia and Denmark are not included).

TABLE 2 Characteristics of the activities or formal programs targeting polypharmacy in the elderly known to the survey respondents.

Program characteristics	N	%
Major goal of tde program*		
to improve patient safety	323	65.1
to improve patient health outcomes	261	52.6
to reduce medication errors	249	50.2
to reduce the number of hospitalizations	225	45.4
to improve patient adherence to medication	221	44.6
to reduce costs	175	35.3
other goals	34	6.9
don't know	4	0.8
Program setting*		
primary care	245	49.4
hospital	113	22.8
community pharmacy	103	20.8
hospital pharmacy	48	9.7
other setting	51	10.3
Professionals providing the program*		
pharmacists	306	61.7
GPs (primary care doctors)	176	35.5
other doctors	96	19.4
nurses	76	15.3
other persons	48	9.7
Is the program using teamwork?		
yes: teamwork of doctors + pharmacists	150	30.2
yes: teamwork of doctors + pharmacists + nurses	107	21.6
yes: other patterns of teamwork	47	9.5
no	26	5.2
don't know	19	3.8
Incentives for healthcare professionals providing the program		
it is their contractual responsibility	98	19.8
there are financial incentives for professionals providing the program	88	17.7
it is their legal responsibility	50	10.1
there are other incentives	33	6.7
no incentives	93	18.8
don't know	50	10.1
The program is using*		
Prescription Review	268	54.0
Treatment Review	258	52.0
Clinical Medication Review	233	47.0

(Continued on following page)

TABLE 2 (*Continued*) Characteristics of the activities or formal programs targeting polypharmacy in the elderly known to the survey respondents.

Program characteristics	N	%
A validated medication appropriateness index	108	21.8
Is there a checklist for the intervention designed to help program providers?		
Yes	198	39.9
No	75	15.1
Don't know	73	14.7
Are electronic patient health records accessible to relevant professionals involved in the program?		
Yes: both to doctors and pharmacists	210	42.3
Yes: only to doctors	31	6.3
Yes: only to pharmacists	9	1.8
No, despite electronic patient health records existing for patients targeted for the program	19	3.8
No, electronic patient health records do not exist for patients targeted for the program	37	7.5
Don't know	39	7.9

Note: * The respondents could indicate several options at the same time, therefore, numbers do not sum up to the total.

management programs, e.g., through information disseminated in media (31.7% of positive responses). Unfortunately, very infrequently the funding is secured for scaling-up of the programs—this was observed by 15.5% of the respondents only.

Respondents provided wide range of the average percentages of healthcare institutions utilizing electronic prescribing in their country, ranging from 0% to 100.0%. On average, use of electronic prescribing systems was reported very often in primary care settings (91.3%+/-26.2%), and slightly less often in community pharmacies (75.7%+/-38.4%) and hospitals (67.5%+/-37.0%).

A similar pattern was observed for the average percentage of medical institutions trained in implementing such programs within a respondent's country or region: the highest were the results referring to primary care centres (64.2%+/-38.2%); they were followed by those concerning community pharmacies and hospitals, in which the training was provided twice less often (34.2%+/-38.7%, and 29.6%+/-36.9%, respectively).

Very few respondents were able to provide any evidence concerning the cost-effectiveness of polypharmacy management programs (33 persons, i.e. 6.7% of those who knew about such a program). Only five respondents provided data on the average cost of providing the program for healthcare professional for one patient; these ranged from '1 euro per day' (Switzerland) to 140 euro per drug review (the Netherlands). None of the respondents was able to provide valid estimation of the cost of one quality-adjusted life year (QALY) gained due to the program, and only one—to provide an estimation of the cost of one adverse drug event avoided due to the program (80–180 euro, for Northern Ireland), and one of the cost of one primary healthcare visit avoided due to the program (app. 1,300 euro, for Italy). For the cost of one unplanned hospitalization avoided due to the program, only three estimates were collected; they ranged from 600 to 9,000 euro for Northern Ireland to 2,500 GBP for England. Finally, only five respondents provided estimates of the average net effect of the program per patient (i.e., the difference between saved drug costs and cost of the program per patient), ranging from 35 GBP (Scotland) to 500 euro (Italy).

3.4 Benchmarking of the polypharmacy management programs

The parameters of effectiveness, applicability, scalability and cost-effectiveness of the identified programs were assessed according to the predefined criteria, and four cumulative variables were calculated for each program (V_EFFE, V_APPL, V_SCAL, and V_COST, respectively; for details see Methods section).

The results of these calculations show that the identified European programs were most effective within the dimension of applicability, reaching on average 2.57+/-2.07 points. This was followed by dimension of effectiveness (2.31+/-1.89), and scalability (1.80+/-1.59). It is noteworthy that within the dimension of cost-effectiveness, the identified programs reached a very low average score, due to the fact that very few respondents provided estimates of the parameters referring to this dimension. As a consequence, the total average percentage of points collected within all four dimensions for the identified programs, as summarised by the composite measure, reached only 6.81+/-4.51 points (Table 5).

3.5 Online benchmarking application for polypharmacy management programs

A freely accessible online benchmarking application for polypharmacy management programs has been launched and is available at https://www.zmr.lodz.pl/SIMPATHY-benchmarking-app/.

After the application questionnaire is filled in, a graphical report is produced automatically, along with its printable version (Figure 3). In this report, characteristics of an individual program of polypharmacy management in the elderly are provided with

TABLE 3 Parameter assessing effectiveness of polypharmacy management programs in the elderly.

Opinion on existence of evidence which proves that the program affects	N	%
Patient health status		
Yes—positive effect	43	33.6
Yes—neutral effect	4	3.1
Yes - negative effect	0	0.0
No data available	56	43.8
Don't know	25	19.5
Patient health-related quality of life		
Yes—positive effect	35	27.3
Yes—neutral effect	4	3.1
Yes - negative effect	0	0.0
No data available	62	48.4
Don't know	24	18.8
Missing entries	**3**	2.3
Patient satisfaction		
Yes—positive effect	54	42.2
Yes—neutral effect	0	0.0
Yes - negative effect	0	0.0
No data available	47	36.7
Don't know	25	19.5
Missing entries	**2**	1.6
Patient adherence		
Yes—positive effect	32	25.0
Yes—neutral effect	2	1.6
Yes - negative effect	0	0.0
No data available	63	49.2
Don't know	28	21.9
Missing entries	**3**	2.3
TOTAL[a]	**128**	100.0

Note: [a]N = 128 patients who provided valid answers to at least one of four survey questions addressing general effectiveness of the programs.

reference to four dimensions, i.e., effectiveness, applicability, scalability and cost-effectiveness. It is also benchmarked to the mean national and European data coming from the SIMPATHY benchmarking survey. Moreover, for the sake of transparency, additional information is provided on the number of responses collected in the benchmarking survey for the country concerned.

4 Discussion

This extensive survey included more than 900 respondents representing practically all the EU countries. Most of the survey participants provided a perspective of various classes of healthcare professionals as a majority of them were pharmacists, doctors and nurses. An important finding was big proportion of the study participants—over half of the respondents - reporting availability of different activities or formal programs targeting polypharmacy in the elderly that they were aware of. This is slightly surprising because an extensive search for polypharmacy guidance documents (both those published in scientific journals and made available as grey literature) conducted across Europe within the SIMPATHY Project identified only five countries that actually have such documents targeting older patients (Stewart et al., 2017a). Of course, this might be related to the voluntary nature of the survey, which favoured respondents deeply interested in

TABLE 4 Parameters assessing applicability and scalability of polypharmacy management programs in the elderly.

Applicability parameters	N	%
The program was created according to evidence-based (EBM) guidelines		
Yes	173	56.0
No	40	12.9
Don't know	93	30.1
Missing data	**3**	1.0
Dedicated Information and Communications Technology (ICT) solutions (helping implementation of the program) exist		
Yes	101	32.7
No	128	41.4
Don't know	70	22.7
Missing data	**10**	3.2
There is a regional or national body coordinating and responsible for the program		
Yes	129	41.7
No	116	37.5
Don't know	57	18.4
Missing data	**7**	2.3
The development of skills allowing for multidisciplinary teamwork has been supported in order to help implementation of the program		
Yes	157	50.8
No	71	23.0
Don't know	56	18.1
N/A	22	7.1
Missing data	**3**	1.0
Scalability parameters		
The process of dissemination of guidelines for polypharmacy management and adherence is supported	194	62.8
of which		
• by health authorities	122	39.5
• by professional organisations	120	38.8
• by patients organisations	33	10.7
• by regions	58	18.8
Is not supported	45	14.6
Don't know	52	16.8
Missing data	**18**	5.8
The program is integrated into undergraduate and/or postgraduate training of practitioners	125	40.5
of which		
• undergraduate training of medical doctors	28	9.1
• postgraduate training of medical doctors	49	15.9
• undergraduate training of pharmacists	56	18.1
• postgraduate training of pharmacists	90	29.1
• undergraduate training of nurses	9	2.9
• postgraduate training of nurses	18	5.8
Is not integrated	81	26.2
Don't know	83	26.9

(Continued on following page)

TABLE 4 (*Continued*) Parameters assessing applicability and scalability of polypharmacy management programs in the elderly.

Applicability parameters	N	%
Missing data	**20**	6.5
The funding is secured for scaling-up of the program		0.0
Yes	48	15.5
No	132	42.7
Don't know	112	36.2
Missing data	**17**	5.5
There is an activity taken to raise patient awareness of the program		
Yes	98	31.7
No	115	37.2
Don't know	74	23.9
Missing data	**22**	7.1

Base: N = 309 participants who provided at least one answer to the relevant question regarding applicability and scalability of polypharmacy management programs; ICT, Information and Communications Technology.

TABLE 5 Average benchmarking scores per country. See chapter IV.3 'Statistical analysis of survey data' for details of calculation of cumulative variables (V_EFFE, V_APPL, V_SCAL, and V_COST).

V10 [Q1] which country do you work or live in	No. of responses*	Measure of effectiveness (V_EFFE)	Measure of applicability (V_APPL)	Measure of scalability (V_SCALA)	Measure of cost-effectiveness (V_COST)	Composite measure of benchmarking (V_COMPO)
Belgium	16	1.69	1.44	1.56	0.00	4.69
England	75	2.35	2.21	0.99	0.20	5.75
France	7	2.20	2.15	1.11	0.14	5.60
Germany	24	1.38	1.00	1.17	0.04	3.58
Italy	16	2.56	2.31	1.44	0.19	6.50
Netherlands	18	2.94	3.39	3.22	0.22	9.78
Poland	5	3.40	1.60	1.40	0.40	6.80
Portugal	22	1.27	2.09	1.82	0.00	5.18
Scotland	56	2.68	3.34	1.82	0.21	8.05
Spain	23	2.74	3.52	2.22	0.00	8.48
Sweden	31	2.42	2.90	2.42	0.10	7.84
Other European country	32	2.44	2.94	2.28	0.09	7.75
Other non-European country	25	2.36	2.68	2.40	0.16	7.60
TOTAL*	**350**	**2.31**	**2.57**	**1.80**	**0.13**	**6.82**

Base: 351 individual reports of the respondents who indicated availability of such a program known to them, and provided at least one valid parameter of benchmarking, * number of individual responses providing at least one valid parameter of benchmarking.

polypharmacy management in elderly. However, this fact may be also explained by a high number of the identified programs or activities being local initiatives only, and not necessarily having its reflection in the published literature. Indirectly, this emphasizes the value our survey has in terms of illustrating activities otherwise not recorded.

The geographical distribution of the reported programs seems to be far from random. On the one hand, there were countries reporting polypharmacy management programs in the elderly that were available very often (e.g., United Kingdom, Sweden and Spain). On the other hand, only single reports came from some other coutries, and none was obtained from Bulgaria or Estonia. Therefore, the last two, along with Poland with <10% of positive reports, were deemed "no intervention countries". Considering the fact that the previously mentioned search resulted in finding

SIMPATHY Stimulating Innovation Management of Polypharmacy and Adherence in The Elderly

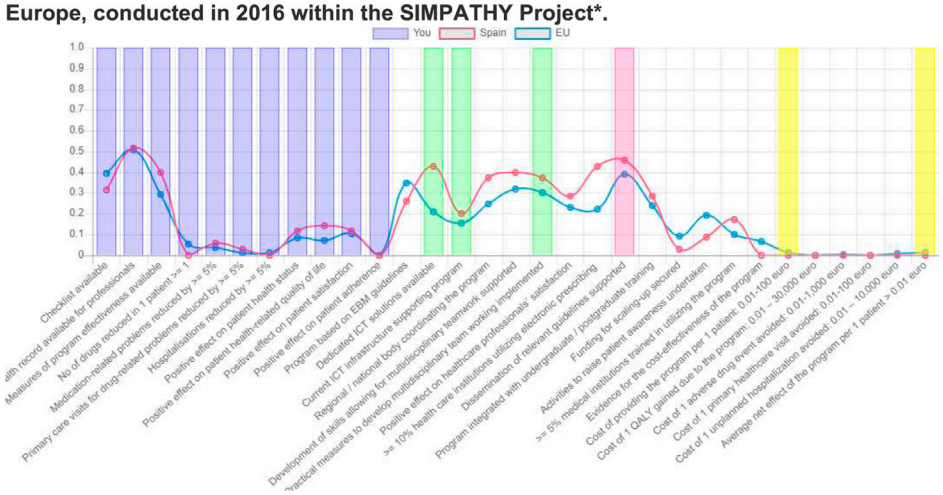
UNIWERSYTET MEDYCZNY W ŁODZI

Thank you for using the SIMPATHY BENCHMARKING APP FOR POLYPHARMACY MANAGEMENT PROGRAMS!

PROGRAM NAME: SPECIMEN

COUNTRY: Spain

Below, please find out your program, benchmarked against the national and European data. This data come from the international survey of the polypharmacy management programs in elderly currently available in Europe, conducted in 2016 within the SIMPATHY Project*.



Country mean presented for [Spain] are based on the analysis of [31] individual reports provided by the SIMPATHY benchmarking survey participants.

Note: country means calculated for 5 or less individual reports are the subject of large bias due to the low number of projects analysed.

Dimension EFFECTIVENESS

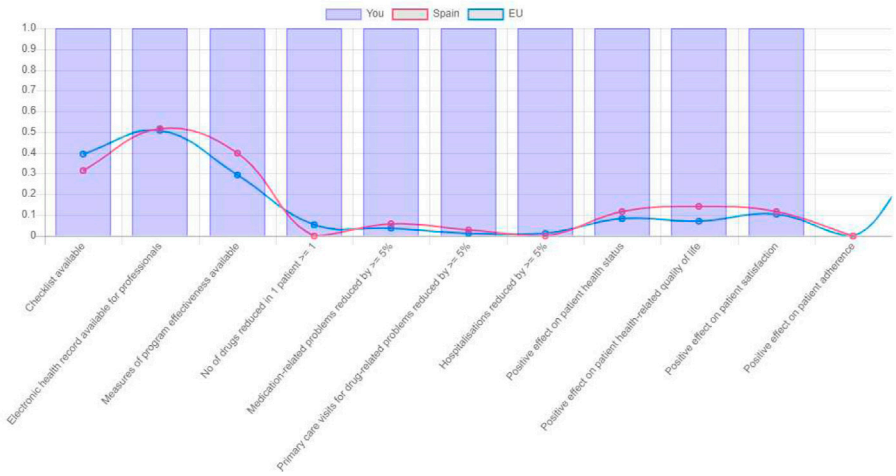


FIGURE 3
Example of benchmarking of an individual program (specimen) against the trajectory of national, and European means—copy of the report produced by the SIMPATHY benchmarking app available at https://www.zmr.lodz.pl/SIMPATHY-benchmarking-app/(first page presented only).

TABLE 6 Major lessons learnt due to the SIMPATHY benchmarking survey of polypharmacy management programs in the elderly across the EU countries.

- According to the benchmarking survey results, diverse PMPE are undertaken in most of the EU countries
- PMPE are known to the healthcare professionals
- Most of the PMPE are provided in primary care settings
- PMPE combine patient benefits with cost containment
- There is evidence for effectiveness of PMPE, whereas data on their cost-effectiveness are scarce
- Current ICT infrastructure does not provide effective support for PMPE
- There is a need for better integration of PMPE within practitioners' undergraduate and postgraduate training
- Wide use of indicators of effectiveness and cost-effectiveness of PMPE is advisable
- The funding for scaling-up of PMPE is not widely available
- Targeted activities within the change management domain are advisable in order to increase the number of PMPE implemented across the European Union

Note: PMPE, polypharmacy management program in the elderly.

guidelines for polypharmacy management in the elderly available in selected countries only (i.e., Germany, Spain, Sweden, the Netherlands and United Kingdom) (Stewart et al., 2017a), this uneven distribution is not surprising. The right question to be asked, however, is whether the low number of reported programs in the other countries reflects their unavailability, or rather low awareness of the polypharmacy problem among healthcare professionals, or maybe both. Further studies are required to shed more light on this issue.

It should be stressed that the programs were not incentivised so often, and the use of financial incentives for professionals providing the program was reported by 1/4 of the respondents only. This does not seem to be an optimal approach. Even small financial incentives proved to motivate primary care teams to devote more attention to polypharmacy, which eventually led to significant reductions in related emergency admissions to hospital (Drei et al., 2016). In the light of these data, financial incentives seem to be fully justified even from the economic point of view.

As regards the content of interventions provided within these programs, nearly all of them were based on various forms of drug reviews. In this study, we have not explored any details of these reviews. Therefore, we are lacking information on which tools have been used to conduct them. However, a pragmatic approach to polypharmacy management in the elderly advocates the application of several available explicit criteria-based tools, such as, e.g., STOPP/START, Beers' criteria, *etc.*, preferably, which may be implemented through a computerized decision-support system (Kurczewska-Michalak et al., 2021).

An interesting finding of our survey is that the respondents assessing the effectiveness of the programs believe that interventions brought several benefits, i.e., they lowered the number of drugs used by a patient, decreased medication-related problems, reduced primary care visits for drug-related problems, and the number of hospitalisations. Similarly, evidence for positive effects of the program has been reported in terms of patient satisfaction, patient health status, patient health-related quality of life, and patient adherence to medication. Unfortunately, the value of these findings is limited due to a low number of respondents providing this data, which was also true for the cost-effectiveness dimension.

As far as the applicability of the programs is concerned, there seems to be a discrepancy between more traditional and more modern tools used to promote them. The programs were often created according to evidence-based guidelines, and the educational measures were implemented to support development of skills facilitating multidisciplinary teamwork for the benefit of the programs. On the other hand, despite the fact that the availability of electronic prescribing was widely reported across the studied countries, the dedicated ICT solutions rather infrequently helped in implementation of the programs, and the majority of the respondents assessed this support to be either somewhat insufficient, or not sufficient. Indeed, computerised systems are extremely useful, yet they may have many disadvantages too. Not only are they often time-consuming but sometimes they also produce dozens of alerts, of which some are of low clinical usefulness, and therefore, subject to ignoring (Knight et al., 2019).

Also, contradictory vectors were observed within the scalability dimension of the identified programs. On the one hand, the process of dissemination of guidelines for polypharmacy management was supported—mostly by health authorities and professional organisations. On the other hand, training in polypharmacy management in the elderly was definitely too rarely integrated into undergraduate and postgraduate education of practitioners. Moreover, activities to raise patient awareness of polypharmacy management programs were probably underused, which is a very common problem (Simões et al., 2022). Finally, the funding for scaling-up of the programs was secured extremely seldom.

To conclude, out of the four predefined dimensions, polypharmacy management programs in the elderly showed the best results within the dimension of applicability, effectiveness and scalability. However, the score for the dimension of cost-effectiveness was significantly lower, in large part due to unavailability of relevant information.

Nevertheless, there are grounds for hope since the respondents who did not know any activity or program targeting polypharmacy management in their workplace, region, or country, expressed their interest in such a program. Indeed, even in countries where polypharmacy management programs do not currently exist, there is a common understanding that polypharmacy is an important issue that needs to be addressed (Stewart et al., 2017b). However, it seems that without some active help, this change will not occur soon—very few found it very probable that such a program could be started in a region/country within the coming 3 years. Therefore, there is a need for further activities aimed at introducing changes in the field of management. To address this need, the SIMPATHY consortium has developed a vision reaching 2030, trying to explore how healthcare management programs can be implemented to improve medication safety and prevent patient harm by addressing the appropriate use of multiple medications (Mair et al., 2017b). Some inspiration can be also found in the Care Pathways, i.e., guiding documents developed by Italian regional health authorities (Dell'Anno et al., 2023).

A recent systematic review identified many cultural and organisational barriers to deprescribing in primary care. As major facilitators of effective deprescribing it listed resources, improved communication, collaboration, patient-centred care and shared decision-making (Doherty et al., 2020). To be effective, the measures to improve the appropriateness of drug use in older people should be implemented across the whole management continuum, from prescription and its acceptance by patient, up to continuous monitoring of adherence and risk-benefit profile (Lunghi et al., 2022).

The results obtained in this study are of high importance. Major lessons learnt from the benchmarking survey of polypharmacy management programs in the elderly conducted across the EU countries are listed in Table 6. Upcoming programs may greatly benefit from these findings. The pattern of future programs should be based on the teamwork of doctors, pharmacists and nurses. It is advisable to make complex interventions, combining medication review with the use of electronic resources (e.g., electronic prescriptions, electronic patient records), which can be implemented thanks to computerised decision-support systems applying one of the validated implicit-criteria based tools. Perhaps, the best results could be obtained with sharing these data among healthcare providers, and overpassing the barriers created by privacy legislation. The use of objective indicators of both effectiveness and cost-effectiveness is more than needed. This is particularly true for the ones generally accepted by the respondents in our survey, such as "reduction in inappropriate prescribing", "reduction in medication-related problems" and "reduction in hospitalizations due to adverse drug reactions or side effects", for effectiveness, and "the cost of 1 unplanned hospitalization avoided" for cost-effectiveness. Finally, it would be reasonable to consider financial incentives for institutions and/or individuals providing such programs. When searching for existing gold standards, or designing new schemes, the SIMPATHY benchmarking application might be of great help.

On the other hand, one needs to be aware that the data collected in our survey has to be interpreted carefully. Various numbers of the respondents in particular countries, their different background, and underrepresentation of several important stakeholders groups have to be considered. In countries such as Spain and Italy, which have their healthcare systems organised and governed at the regional level, generalization of the findings to the national level is less well supported. In countries such as Spain and Italy, whose healthcare systems are organized and managed at the regional level, generalization of conclusions to the national level should be done with caution. Also, the study has some limitations, related to its voluntary nature and on-line design, namely, the fact that some questions were not answered by many participants. The type of the study did not make it possible to follow up the participants and thus understand the reasons why some of them left the survey before the end. Descriptive nature of this research creates additional limitations. Last but not least, many data—and particularly those related to the cost-effectiveness dimension—may be simply not available for various programs. Moreover, it was not possible to check the quality and reliability of the responses. Therefore, it should be assumed that some of the participants might have given inaccurate answers. However, addressing the survey to the targeted groups of potentially interested stakeholders, we feel that we have minimised the chance of such bias.

These are typical challenges associated with all voluntary surveys, and particularly those made available online. However, this methodology has substantial benefits also, allowing to reach relevant stakeholders living in different geographical locations, and finally, to attract attention of a great number of participants from a large group of countries. In fact, to our knowledge, this was the first study of this kind referring to practical cases and covering the whole Europe. Moreover, approximately 60% of the survey respondents had the opportunity to observe the performance of the projects in their workplace, which means that they shared their own opinions based on their personal experience, rather than other people's points of view.

5 Conclusion

In the coming years, addressing the challenge of polypharmacy in the elderly will be increasingly vital for public health. Consequently, widespread adoption of polypharmacy management programs is an imperative step. To achieve this objective, an evidence-based guidance is essential, aiding clinicians and policymakers in setting realistic drug treatment goals and implementing the most effective strategies available. The findings of this study directly address this need, presenting valuable evidence to guide clinicians and policymakers in the selection and successful implementation of polypharmacy management programs tailored for the elderly. This first-of-its-kind study provides a comprehensive review of polypharmacy management programs for the elderly available across Europe against the criteria of effectiveness, applicability, scalability, and cost-effectiveness. The development of an easy to use benchmarking application adds practical value, encouraging the utilization of these findings. Therefore, the study results, along with the benchmarking application, have the potential to positively affect the trajectory of polypharmacy management, and shape a more effective and sustainable future in elderly care.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Author contributions

PK: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing–original draft, Writing–review and editing. AM: Conceptualization, Methodology, Writing–review and editing. DS: Conceptualization, Methodology, Writing–review and editing. PL: Conceptualization, Methodology, Writing–review and editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This publication stems from the project 663082/SIMPATHY which has received funding from the European Union's Health Programme (2014–2020).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1254912/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 25 October 2023
DOI 10.3389/fphar.2023.1283135

OPEN ACCESS

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RECEIVED 25 August 2023
ACCEPTED 03 October 2023
PUBLISHED 25 October 2023

CITATION
Achterbosch M, Vart P, van Dijk L and van Boven JFM (2023), Shared decision making and medication adherence in patients with COPD and/or asthma: the ANANAS study.
Front. Pharmacol. 14:1283135.
doi: 10.3389/fphar.2023.1283135

Shared decision making and medication adherence in patients with COPD and/or asthma: the ANANAS study

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Background: Medication adherence to inhalation medication is suboptimal in patients with COPD and asthma. Shared decision making (SDM) is proposed as an intervention to improve medication adherence. Despite its wide promotion, evidence of SDM's association with greater medication adherence is scarce. Also, it is unknown to what degree patients presently experience SDM and how it is associated with medication adherence.

Objective: To (i) assess the level of SDM and (ii) medication adherence, (iii) explore the relation between SDM and medication adherence and iv) investigate possible underlying mechanisms.

Methods: Cross-sectional observational study. A survey was distributed among Dutch patients with COPD and/or asthma using inhaled medication. Medication adherence was measured using the Test of Adherence to Inhalers (TAI-10), and SDM by the 9-item Shared Decision-Making questionnaire (SMD-Q-9). Feeling of competence, relatedness and feeling of autonomy from the Self-Determination Theory (SDT) were considered as possible mechanisms. The primary outcome was adherence.

Results: A total of 396 patients with complete information on relevant covariates were included. Mean SDM-Q-9 score was 26.7 (SD 12.1, range 0–45) and complete adherence was 41.2%. The odds ratio for the association of SDM with adherence was 1.01 (95% CI: 0.99, 1.02). This only changed minimally when adjusted for mediators (mediating effect <3%).

Conclusion: The patient experienced level of SDM in daily practice and medication adherence have room for improvement. No association between SDM and medication adherence was observed. Factors related to feeling of competence, relatedness and feeling of autonomy did not meaningfully explain this finding.

KEYWORDS

COPD, chronic obstructive pulmonary disease, asthma, lung patients, medication adherence, inhalation medication, shared decision making

Abbreviations: COPD, chronic obstructive pulmonary disease; HCP, healthcare professional; SDM, shared decision making; SDT, self-determination theory.

Introduction

Up to half of patients with COPD and asthma do not adhere to their maintenance medication, despite the fact that medication is crucial for controlling their disease (World Health Organization, 2004; Dekhuijzen et al., 2018; Dima et al., 2019; Vervloet et al., 2020). Medication adherence is defined as "the extent to which a patient participates in a treatment regimen after he or she agrees to that regimen" (Balkrishnan, 2005; Vrijens et al., 2012). Nonadherence to the medication impacts both patients and society greatly. It results in more disease-related health complaints such as exacerbations, poor symptom control, a higher mortality risk and higher healthcare costs (Simpson et al., 2006; Vestbo et al., 2009; Mäkelä et al., 2013).

Many factors influencing medication adherence have been identified. Given the wide range of factors, a wide variety of adherence enhancing strategies have been proposed. Among those, shared decision making (SDM) is increasingly promoted (Gina Main Report, 2022). SDM is described as 'a process in which patients are involved as active partners with the clinician in clarifying acceptable medical options and in choosing a preferred course of clinical care' (World Health Organization et al., 2008). Currently, it is unknown how patients with COPD and/or asthma experience SDM in discussing and deciding about their inhaled treatment. Despite the increasing promotion of SDM and its association with healthcare and disease related outcomes, not much is known about its association with medication adherence. Only a limited number of studies have been performed in the field of asthma and COPD (Joosten et al., 2008; Shay and Lafata, 2014; Hauser et al., 2015; Bukstein et al., 2020).

A positive effect of SDM-based interventions on medication adherence was found in two randomized controlled trials for patients with asthma (George et al., 2020; Granados-Santiago et al., 2020). For COPD, only one randomized controlled study has been performed, which showed a positive relation (Wilson et al., 2010). In patients with other medical conditions such as diabetes, cardiovascular disease, severe mental disorders and arterial hypertension, no significant positive associations have been found between SDM and medication adherence (Joosten et al., 2008; Shay and Lafata, 2014; Hauser et al., 2015).

Overall, there seems to be limited evidence available for the overall uptake of SDM in daily practice and the association between SDM and medication adherence. The overabundance of SDM and medication adherence definitions is further complicating study comparisons. Furthermore, a theory-based explanation regarding the association of SDM with medication adherence is lacking. To improve medication adherence and health outcomes in patients with both COPD and asthma, it is valuable to further investigate this relation and how it could support daily clinical practice. Therefore, this study aimed to assess;

(i) the level of SDM uptake in daily practice;
(ii) the level of medication adherence;
(iii) to explore the potential relation between SDM and medication adherence and finally;
(iv) to investigate possible underlying mechanisms regarding the relation between SDM and medication adherence.

To explore the underlying mechanisms for the relationship between SDM and adherence the Self-Determination Theory by Ryan and Deci is a suitable theory as it explains under which circumstance people feel motivated in their behaviour (Ryan and Deci, 2000; Deci and Ryan, 2008). It states that people feel more autonomously motivated when three fundamental psychological needs are met: 1) feeling autonomous, 2) feeling competent and 3) feeling related towards certain behaviour or action. This type of motivation—autonomous motivation—is a stronger and more sustainable type of motivation compared to other types of motivation such as extrinsic motivation (Ryan and Deci, 2000; Deci and Ryan, 2008).

Notably, these three fundamental needs for persistent behaviour could be identified in the process of SDM. Bomhof-Roordink and others (2019) found that the four most recurring elements in all models and definitions of SDM are i) *taking patients preference into account*, ii) *deliberating between patient and healthcare professional,* iii) *create choice awareness* and iv) *learn about the patients' preferences* (Bomhof-Roordink et al., 2019). Creating choice awareness in the patient and letting the patient be part of the conversation about treatment options can both be seen as making the patient more autonomous in relation to their health and treatment (*create choice awareness* and *deliberating between patient and healthcare professional*). More specifically, when it is discussed with the patient starting or changing the inhalation medication should be considered since the COPD or asthma is not well controlled and discussing the different medication options and the pros and cons of these options, the patient is aware of the options. With this awareness and knowledge, the patient is more autonomous in regulating his or her own health and medication. Concurrently, patients can become more competent regarding their treatment when there is more deliberation with the healthcare professional and preferences for treatment are being discussed (*taking the preferences into account* and *deliberating between patient and healthcare professional*). For example, if a complex inhalation technique is required for a certain type of medication, the required inhalation technique then can be practiced making the patient competent or a less complex option can be discussed. Lastly, patients could be feeling closer related to their healthcare professional when they experience their healthcare professional is willing to get to know the patient to make the best treatment plan (*learn about the patients' preferences* and *taking the preferences into account*). More specifically, if a patient for example, prefers not to have a pink-coloured inhaler or does not want to use the inhalation medication at work and the HCP takes this into account when making a medication plan, the patient could possibly feel taken more seriously by the HCP and therefore more connected to the HCP.

Summarizing, SDM contains different key elements that could enhance autonomous motivation, and this could possibly result into more medication adherent behaviour. Based on this SDT and these key elements of SDM the following four hypothesis are postulated:

1. The higher the degree of SDM experienced by patients with COPD and asthma, the more likely that they adhere to their medication.
2. SDM results in patients feeling more autonomous in relation to their inhalation medication, which leads to patients being more likely to adhere to their medication.

3. SDM results in patients feeling more competent in relation to their inhalation medication, which leads to patients being more likely to adhere to their medication.
4. SDM results in patients feeling more related to their physician, which leads to patients being more likely to adhere to their medication.

Materials and methods

Study design

This was a cross-sectional observational study and registered at the Centre for Open Science (OSF) with number https://doi.org/10.17605/OSF.IO/QW623.

Setting and data collection

Data were collected using an online survey distributed from March 2020 till May 2021 in the Netherlands. Participants were recruited via six community pharmacies from different geographical regions including both urban and rural areas. Pharmacists identified all patients that redeemed prescriptions for inhaled respiratory medication (Anatomic Therapeutic Chemical [ATC]-code for inhalation medication (i.e., R03) during the last 12 months. This included both patients who recently started inhalation medication and patients who had been using respiratory medication for over a longer time. All eligible patients were invited by their pharmacist to participate in this study using an email invitation. Data collection was anonymous using an online survey created in REDCap software.

Participants

Patients were eligible if they were: i) 18 years and older; ii) living in the Netherlands; iii) proficient in the Dutch language, iv) living in their own house (with or without home care); v) independent medication intake, vi) diagnosed with COPD, asthma or with both (self-reported); and vii) had a recent (last year) appointment with an healthcare professional (HCP) to discuss their medication use for COPD and/or asthma or if they started or switched medication for their COPD and/or asthma. It was not differentiated if these patients were recently diagnosed and therefore also recently started inhalation medication or were diagnosed a long time ago. If any criterion was not fulfilled, the survey was terminated.

Study outcomes

Study outcomes included i) the extent of SDM, ii) the extent of medication adherence and iii) the association between SDM and medication adherence.

Extent of SDM

The exposure was the extent of SDM during the prescription of asthma/COPD medication. SDM was measured using the validated 9-item Shared Decision-Making questionnaire (SDM-Q-9) (Kriston et al., 2010).Answers were recorded on a Likert scale from 1–5 (total score 9–45). Here, it was specified that it concerned SDM during any consultations (also online and by phone) concerning the medication treatment for COPD and/or asthma with an involved HCP (general practitioner, nurse, physician). The higher the total score, the more the patients feels involved in the decision making process concerning the inhalation medication. Of note, two questions concerning the COVID-19 pandemic—whether the frequency in contact and whether the amount of experienced participation with their HCP in relation to their inhalation medication was changed - and one question concerning health insurance—whether the prescribed medication was different from the medication received at the pharmacy–in relation to SDM were added because of their possible impact on the study results.

Extent of medication adherence

Extent of medication adherence Medication adherence was measured using the 10-item Test of Adherence to Inhalers (TAI) (Plaza et al., 2016). Each TAI-item represents one cause of adherence and was recorded on a Likert scale from 1-5 resulting in a total score ranging from 10–50. With the total TAI-score, the level of non-adherence (good, intermediate, poor) and the type of non-adherence (sporadic, deliberate) can be differentiated (Joseph-Williams et al., 2014). Here, the TAI is used as binary to differentiate non-adherence (total score ≤49) and complete adherence (total score = 50) and as binary to differentiate poor adherence (total score ≤45) and intermediate to good adherence (total score of 46–50). Sporadic and deliberate non-adherence are shown exploratively.

Underlying mechanism of SDM and medication adherence

Drivers of a potential mechanistic link between SDM and medication adherence included feeling of autonomy, level of competence, relatedness to the healthcare provider. Autonomy was measured using the 6-item Healthcare Climate Questionnaire (HCCQ-6) (total score range 6–42) (Czajkowska et al., 2017). the HCCQ-6 is proven to be internally consistent (Cronbach's alpha of 0.91) and reliable (correlation coefficient of 0.54) (Czajkowska et al., 2017). This questionnaire has been used to measure the patient feeling of autonomy in a wide variety of illnesses and settings and is also linked to the Self-Determination Theory. (Czajkowska et al., 2017)' The level of competence was measured with the Perceived Competence cale (PCS) (total score range 7–28) (Williams et al., 1998). This instrument is also suggested for measuring patient feelings of competence in relation to the Self-Determination Theory and has been used in a diverse range of illnesses. The PCS demonstrates a good internal consistency (Cronbach's alpha 0.80–0.94) (Williams et al., 1998) Relatedness to the healthcare provider was measured using the Inclusion of Other in the Self Scale (IOS scale) (total score range 1–7) (Aron et al., 1992). This scale is used mainly in psychology and behavioral research and is adjustable to the relation you are measuring, e.g., patient-physician relation, while remaining reliable and consistent (Aron et al., 1992).

Covariates

Perceived illness severity, social support, ethnicity, educational level, socioeconomic status, age, and gender have also been shown to have a significant impact on shared decision making and/or medication adherence and are therefore taken into account (Kardas et al., 2013; Mathes et al., 2014). To

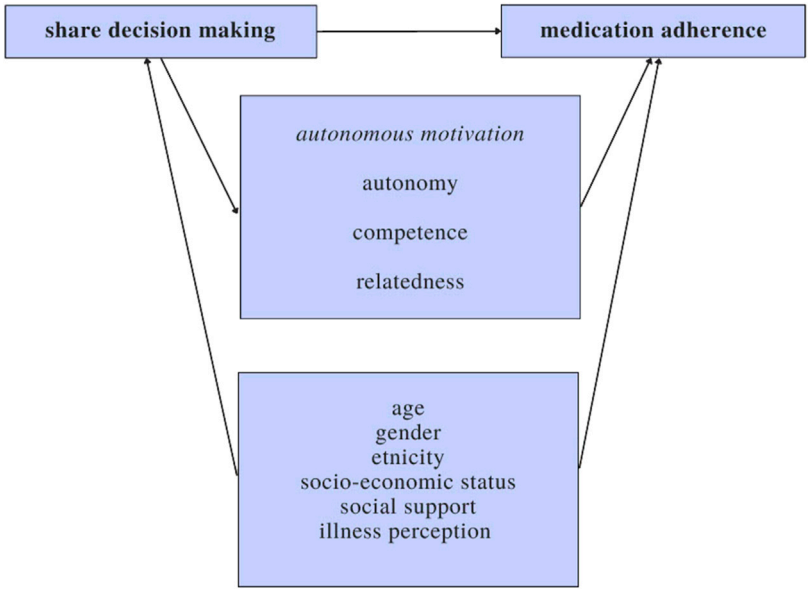

FIGURE 1
Theoretical model of the relation between SDM and therapy adherence.

determine the perceived illness severity, the Illness Perception Questionnaire (IPQ) was used (Broadbent et al., 2006). To measure social support, we used the 12-item Social Support List-Interactions (SSL-I-12) (van Eijk et al., 1994; Kempen and Van Eijk, 1995). Socioeconomic status was measured using educational level–a key measurement for socioeconomic status and an important indicator for health literacy–and ethnicity was measured using the country of birth of the patient and the country of birth of the patients' parents (Zhang et al., 2014; Stormacq et al., 2018).

Figure 1 represents the model of the hypothesized relation between SDM and medication adherence, the proposed mechanisms, and the influencing determinants.

Demographic data

Baseline demographic information that was collected included age (years), gender (female, male, different), ethnicity (country of birth of respondent, mother, and father), living environment (urban or countryside), and educational level (lower education, higher education, university).

Sample size and statistical analysis

Sample size calculation was based on a minimum of 10 events per predictor variable rule (Concato et al., 1995; Peduzzi et al., 1996). Assuming 24% in patients with asthma and 36% in patients with COPD according to a Dutch report and consideration of 10 covariates for inclusion in the logistic model, we aimed to include between 278 and 417 patients (Infographic).

For the analysis, individuals with missing information on key variables were excluded. Data were transformed as follows: Total scores of the variables were calculated as the sum of the individual items of the variables for the variables *shared decision making* (SDM-Q-9), *medication adherence* (TAI-10), *autonomy* (HCCQ-9), *competence* (PCS), *social support* (SSL-I-12) and *illness perception* (brief IPQ). In addition, the total score for medication adherence measured with the TAI was transformed into:

1) a binary variable with total scores of '50' being a '1' (fully medication adherent) and total scores of '≤49' being a '0' (medication non-adherent);
2) a categorical variable with total scores of '50' (good adherence), total scores of '46–49' being '1' (intermediate adherence) and total scores of '0–45' being '2' (poor adherence);
3) a binary variable with total scores between '46–50' being '1' (medication adherent) and total scores of '≤45' being a '0' (medication non-adherent);
4) a binary variable with TAI item 1-5 total scores of '25' being '0' '(sporadic non-adherence) and scores of '0–24' being '1' (sporadic adherence);
5) a binary variable with TAI items 6–10 total scores of '25' being '0' '(deliberate non-adherence) and scores of '0–24' being '1' (deliberate adherence) (Plaza et al., 2016).

Summary data of study participants are presented using descriptive statistics (e.g., mean, standard deviation, median and percentages) and all variables included in the model were checked for bivariate associations. Bivariate associations were calculated using the Spearman's ρ for continuous variables, the adjusted R square from ANOVA for continuous and bivariate variables, the Cramer's V for categorical variables and the $\chi 2$ from Kruskall Wallis H-test was used for correlation between ordinal and continuous variables. Also, data were collected during the COVID-19-pandemic and a change in health insurance coverage. Therefore these data were analyzed descriptively in addition to the study aims.

The relation between the outcome *medication adherence* (TAI-10) and the exposure *shared decision making* (SDM-Q-

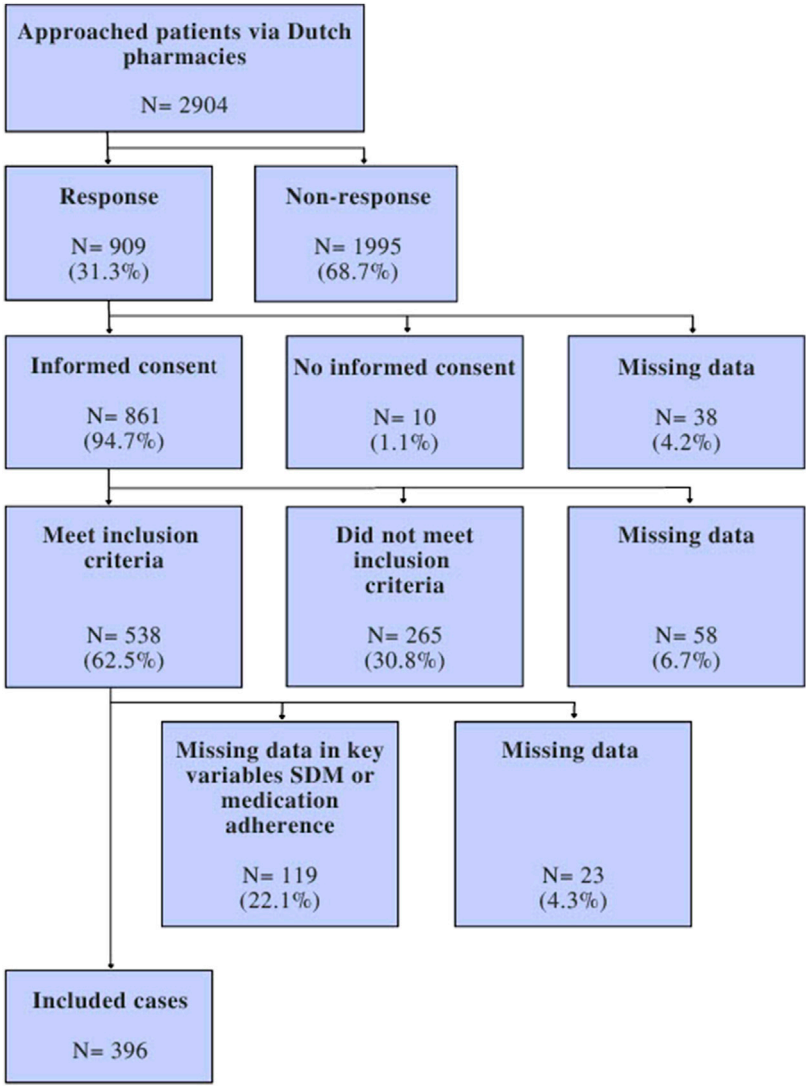

FIGURE 2
Flowchart of patient inclusion.

9) was analyzed using logistic regression analyses, firstly without (model 1) and secondly with the covariates (model 2). Subsequently, mediation analysis were performed with the Baron and Kenny approach (Baron and Kenny, 1986). The proposed mediating variables *autonomy* (HCCQ), *relatedness* (IOS) and *competence* (PCS) were added separately (model 3, model 4 and model 5). Lastly, the complete model was analyzed including the exposure variable *shared decision making,* the covariates and three mediating variables (model 6). For mediation analysis, we used binary variations of the TAI.

All model assumptions and fits were checked using the Box Tidwell test and the Hosmer-Lemeshow test and models were tested with the SDM as continuous variable as well. Additionally, we explored the interaction between disease type (COPD/Asthma) and SDM for its association with adherence.

All analyses were performed for the total study population and for patients with COPD (+/-asthma) and patients with asthma separately. Used software for analyses was IBM SPSS Statistics 28.

Ethics

The study protocol was assessed by the medical ethical board of the University Medical Centre Groningen (the Netherlands) against the Medical Research Involving Human Subjects Act (METC Nr: 2021/149) and was exempted from full ethics review given the observational non-invasive nature of the study. Participants were informed about the content and the purpose of the study and provided online written consent.

Results

Study population

Figure 2 shows the inclusion flow of the study population. In total, 2,904 patients with asthma and/or COPD were invited to participate in the study and received the survey. The response rate

TABLE 1 Characteristics of total study population (N = 396) and the subgroups of patients with COPD (+/-asthma) and patients with asthma.

Characteristics		N (% of total) or mean (±SD) of total study population (N = 396)	N (% of total 194) or mean (±SD) of patients with COPD (+/-asthma) (N = 194)	N (% of total 202) or mean (±SD) of patients with asthma (N = 202)
Age		63.1 (13.8) (%)	69.2 (9.6)	57.2 (14.7)
Sex	Female	55.8	47.9%	63.4%
	Male	44.2	52.1%	36.6%
Ethnicity (Dutch)	Respondent	94.9	94.8%	95.0%
	Mother	93.7	94.3%	93.1%
	Father	94.9	96.9%	93.1%
Diagnosis	COPD only	33.3	68%	-
	Asthma only	51.0	-	100%
	COPD and asthma	15.7	32%	-
Living environment	Urban total	74.5	72.2%	77.2%
	Rural total	25.3	27.8%	22.7%
Educational level	Lower education	27.3	34.0%	20.8%
	Secondary vocational education	36.1	39.7%	32.7%
	Higher professional education	36.3	26.3%	46.5%

was 31% (N = 909). After exclusion of patients with missing informed consent or relevant covariates, a total of 396 patients remained available for analysis.

Table 1 shows the characteristics of the study population. The mean age of the population was 63.1 years (SD 13.8), 55.8% were female and the vast majority had Dutch ethnicity (93.1%–96.9%). Most patients were living in an urban environment (74.4%). About half of the respondents (51.0%) were diagnosed with asthma and the other half (49.0%) with COPD (+/-asthma).

Extent of shared decision making

A consistent level of experienced shared decision making was found within the total study population (mean 26.7, SD 12.1) and asthma (mean 26.4, SD 10.8) and COPD (mean 27.1, SD 13.3) (Table 2). Regarding the context of SDM, it is worth noting that during the COVID-19-pandemic almost half of the patients had less contact with their HCP (47.0%), while a smaller group (5.8%) had more contact since the outbreak of the pandemic. Despite these differences in the amount of contact, most patients (85.1%) experienced the same amount of involvement in relation to their inhalation medication plan with their HCP since the outbreak of the COVID-19-pandemic (Supplementary Figure E1 in the Online Repository Text). Also, no noticeable relation between SDM and the change in level of experienced participation was found (Supplementary Table E5 in the Online Repository Text). In addition, most patients received the same inhaler by the pharmacy as prescribed with their HCP (84.6%). A minority (9.3%) received a different inhaler as prescribed due to changes in health insurance coverage (Supplementary Figure E1 in the Online Repository Text).

Extent of medication adherence

The mean total TAI-10 score for medication adherence was 46.9 (SD 4.8) (Table 2). The TAI-items which were most often scored lowest were TAI-1 ('How many times did you forget to take your regular inhalers in the last 7 days?'), TAI-3 ("When you are feeling well, you stop taking your inhalers.") and TAI-8 ('You take fewer inhalations than prescribed by your doctor') (Supplementary Table E1 in the Online Repository Text). Overall, 41.2% of the included subjects reported to be fully adherent to their inhalation medication. Patients with COPD (+/-asthma) reported significantly higher rates of complete adherence (49.5%) compared to patients with asthma (33.2%) (OR = 0.507, 95% CI = 0.338–0.761, $p < 0.001$). More nuanced, of all non-adherent patients, 36.4% scored intermediate levels of adherence and 22.5% poor levels of adherence (Table 2). When looking specifically at sporadic and deliberate adherence, nonadherence rates were 53.0% and 38.1% respectively. In both patients with COPD (+/-asthma) and patients with asthma, more sporadic non-adherence was found compared to deliberate non-adherence. Figure 3 shows the percentage of non-adherent patients (TAI ≤49) in the total study population and according to diagnosis (COPD (+/-asthma), asthma), age (<64 years, ≥65 years) and sex

TABLE 2 Medication adherence, shared decision making and covariates in the total study populations and in the subgroups of patients with COPD and COPD/asthma and patients with asthma.

Variable	Instrument	Total study population (N = 396)		COPD (+/-asthma) (N = 194)		Asthma (N = 202)	
		Mean (SD) or % of total	Median IQR (Q_3-Q_1)	Mean (SD) or % of total	Median IQR (Q_3-Q_1)	Mean (SD) or % total	Median IQR (Q_3-Q_1)
Medication adherence		46.9 (4.8)	4.0 (50.0–46.0)	47.5 (4.8)	3.0 (50.0–47.0)	46.3 (4.8)	5.2 (50.0–44.8)
Level of medication adherence	TAI-10						
Poor *(≤45)*		22.5%		16.0%		28.7%	
Intermediate *(46–49)*		36.4%		34.5%		38.1%	
Good *(50)*		41.2%		49.5%		33.2%	
Type of medication non-adherence							
Sporadic *(<25)*	TAI 1–5	53.0%		43.8%		61.9%	
Deliberate *(<25)*	TAI 5–10	38.1%		30.9%		45.0%	
Shared decision making	SDM-Q-9	26.7 (12.1)	17.7 (36.0–18.3)	27.1 (13.3)	19.3 (36.3–17.0)	26.4 (10.8)	15.2 (35.0–19.8)
Autonomy	HCCQ-6	30.3 (9.3)	13.0 (37.0–24.0)	30.3 (9.9)	14.3 (38.3–24.00)	30.2 (8.7)	12.3 (36.3–24.00)
Competence	PCS	24.7 (4.3)	5.0 (28.0–23.0)	24.6 (4.6)	5.0 (28.0–23.0)	24.8 (4.0)	4.0 (28.0–24.0)
Closeness	IOS	5.0 (1.9)	2.0 (6.0–4.0)	5.0 (1.9)	3.0 (7.0–4.0)	4.7 (1.8)	2.0 (6.0–4.0)
Illness perception - brief	Brief IPQ	53.0 (9.5)	12.8 (58.8–45.9)	53.0 (10.6)	16.5 (61.3–44.8)	51.4 (8.2)	10.7 (57.0–46.3)
Social support	SSL-I-12	31.5 (7.2)	9.0 (36.0–27.0)	30.3 (7.3)	11.0 (36.0–25.0)	32.6 (6.9)	8.0 (36.0–28.0)
Socioeconomic status							
lower education		27.3%		34.0%		20.8%	
secondary vocational education		36.1%		39.7%		32.7%	
higher professional education		36.6%		26.3%		46.5%	
Age—in years		63.1 (13.8)	17.0 (73.0–56.0)	69.2 (9.6)	11.0 (75.0–64.0)	57.2 (14.7)	20.0 (68.0–48.0)
Sex—female		55.8%		47.9%		63.4%	

(male, female). While there were differences in adherence between the subgroups, the levels of SDM hardly varied (Figure 3).

Association between SDM and medication adherence

For the proposed mediator variables, a mean of 24.7 (SD 4.3, max. score 28) was found for the feeling of competence, and for feeling relatedness to their physician or other HCP who is involved in the inhalation medication the mean score was of 4.84 (SD 1.8, max. score 7). Concerning the feeling of autonomy, a mean of 30.3 (SD 9.3, max. score 42) was found. Table 3 shows the mediation analysis for the total study population and subgroups COPD (+/-asthma) and asthma. Before the mediation analysis, all bivariate correlations were determined (Supplementary Table E2–E4 in the Online Repository Text). No correlation between SDM and medication adherence (0–49 *versus* 50) was found (Spearman's $\rho = -0.002$; $p > 0.05$). Also, no associations were found between the three possible mediating variables - *autonomy*, *competence,* and *relatedness*—and medication adherence (Spearman's $\rho = -0.002$; $p > 0.05$; Spearman's $\rho = -0.000$; $p > 0.05$; Spearman's $\rho = 0.001$; $p > 0.05$, respectively). In contrast, these three variables positively correlated with SDM although not strongly (Spearman's $\rho = 0.512$; $p < 0.01$; Spearman's $\rho = 0.299$; $p < 0.01$; Spearman's $\rho = 0.355$; $p < 0.01$, respectively). These findings were similar in the mediation analysis within the subgroups of COPD (+/-asthma) and asthma (Supplementary Table E2-E Online in the Repository Text). When adjusted for potential confounders, SDM was also not significantly associated with medication adherence (0–49 *versus* 50) (OR = 1.004, 95% CI = 0.987–1.021) (Table 3). Change in OR of SDM was minimal when adjusted for the three mediators independently. The fully adjusted model

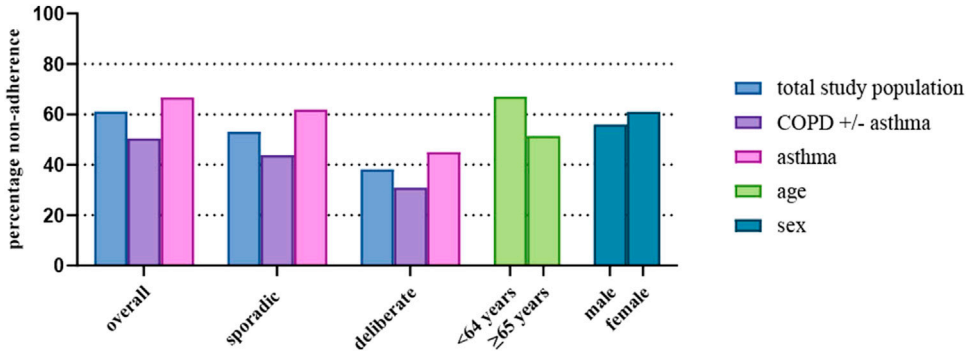

FIGURE 3
Percentage % overall non-adherence (TAI total score <50), sporadic non-adherence (TAI score items 1–5 <25) and deliberate non-adherence (TAI score items 6–10 < 25) in the total study population and in the subgroups diagnosis (COPD and COPD (+/-asthma), asthma), age (<64 years, ≥65 years) and sex (male, female).

TABLE 3 The relative chance of being medication adherend dependent on the level of shared decision making, the role of three suggested mediators and controlled for the covariates.

	TAI binary (0–49 versus 50)						TAI binary (0–45 versus 46–50)	
	Total study population (N = 396)		COPD (+/-asthma) (N = 194)		Asthma (N = 202)		Total study population (N = 396)	
	OR (95% CI)	% Attenuation	OR (95% CI)	% Attenuation	OR (95% CI)	% Attenuation	OR (95% CI)	% Attenuation
Baseline model 1	1.005 (0.988–1.022)	NA	1.010 (0.989–1.032)	NA	0.994 (0.967–1.021)	NA	1.001 (0.981–1.020)	NA
Plus covariates [a]	1.004 (0.987–1.021)	−0.1%[c]	1.008 (0.985–1.031)	−0.2%[c]	0.993 (0.966–1.021)	−0.1%[c]	1.000 (9.979–1.021)	−0.1%[c]
Plus autonomy	1.004 (0.984–1.024)	0.0%[d]	1.009 (0.979–1.039)	0.1%[d]	0.995 (0.967–1.025)	0.2%[d]	0.998 (0.974–1.023)	−0.2%[d]
Plus competence	1.001 (0.983–1.019)	−0.3%[e]	1.007 (0.983–1.031)	−0.2%[e]	0.990 (0.962–1.018)	−0.5%[e]	0.993 (0.971–1.016)	−0.5%[e]
Plus relatedness	1.003 (0.985–1.021)	−0.1%[f]	1.003 (0.980–1.027)	−0.4%[f]	1.011 (0.968–1.029)	2.1%[f]	0.998 (975–1.020)	0.2%[d]
Fully adjusted model [b]	1.002 (0.982–1.023)	−0.2%[g]	1.008 (0.978–1.038)	−0.5%[g]	0.997 (0.966–1.029)	−1.4%[g]	0.994 (0.969–1.020)	−0.6%[g]

[a]age, sex, illness perception, social support, socio-economic status.
[b]baseline model with all covariates, autonomy, competence and relatedness.
[c]Percent attenuation= $(\beta_{\text{model 1 + covariates}} - \beta_{\text{model 1}})/(\beta_{\text{model 1}}) \times 100$.
[d]Percent attenuation= $(\beta_{\text{model 1 + covariates + autonomy}} - \beta_{\text{model 1+ covariates}})/(\beta_{\text{model 1+ covariates}}) \times 100$.
[e]Percent attenuation= $(\beta_{\text{model 1 + covariates + competence}} - \beta_{\text{model 1+ covariates}})/(\beta_{\text{model 1+ covariates}}) \times 100$.
[f]Percent attenuation= $(\beta_{\text{model 1 + covariates + relatedness}} - \beta_{\text{model 1+ covariates}})/(\beta_{\text{model 1+ covariates}}) \times 100$.
[g]Percent attenuation= $(\beta_{\text{fully adjusted}} - \beta_{\text{model 1+ covariates}})/(\beta_{\text{model 1+ covariates}}) \times 100$.

including the confounders and all three mediators showed an OR of SDM of 1.002 (95% CI = 0.982–1.023) and a decrease in OR of 0.20% compared to the model with only the confounders. Similar results were found for the subgroups of patients with COPD (+/-asthma) and asthma with the less stringent medication adherence cut-off (0–45 *versus* 46–50) (Table 3). Note that the OR in all models is close to 1, suggesting a consistent lack of significant associations between SDM on medication adherence no matter the exact definition and model.

Additional analyses

Model diagnostics were assessed using the Box-Tidwell test and demonstrated no violation of assumptions. Also, the Hosmer-Lemeshow test showed all models fitted well to the data (Supplementary Table E6–E9 in the Online Repository Text).

All TAI variable variations were tested for their bivariate association with SDM and the relation and possible mediations between SDM and the TAI as continuous variable were checked

(Supplementary Tables E5 and E10 in the Online Repository Text). The TAI as continuous variable was first log-transformed since the variable was highly skewed. This analysis showed also no correlation and change with the mediators in the correlation between SDM and medication adherence (Supplementary Table E10).

Interaction between patient subgroups and SDM was not statistically significant for its association with medication adherence, although a trend is noticeable (p for interaction = 0.054).

Discussion

Main findings

In this study, we found that the level of SDM in patients with COPD and/or asthma in daily practice was intermediate, while the levels of self-reported medication adherence were relatively low with almost two-thirds being non-adherent. No clear association between SDM and medication adherence was identified. Autonomy, competence, and relatedness correlated positively with SDM, yet not with medication adherence and did not mediate the relationship between SDM and medication adherence.

Interpretation

The intermediate levels of perceived SDM in patients with asthma/COPD seem in line with previous findings regarding SDM in general. Indeed, SDM is not yet fully implemented in healthcare and although HCPs are generally positive towards SDM, their own reflection on, and performance of, SDM behavior is limited (Driever et al., 2022; Couët et al., 2015).

The self-reported levels of adherence as assessed by the TAI in this study were lower compared to a recent Dutch report (Infographic) We found that around 60% of COPD patients and two-thirds of asthma patients reported being not fully adherent compared to respectively 24% and 36% as reported by a previous report from Nivel in 2018 (Infographic) Differences in measurement methods could be one of the causes; while we used the TAI, the Nivel used the Medication Adherence Rating Scale (MARS). Both instruments are self-reported measurement instruments and a social desirability bias and/or effect of limited introspective ability is to be expected (Rosenman et al., 2011). Nevertheless, relatively low rates of complete adherence were found within this study. The anonymity of the survey, but even more so the good psychometric properties of the TAI and its comprehensiveness—the TAI covers all types and causes of non-adherence—advocates for the validity of our results.

Difference in measurement methods could also be one of the causes why we did not find any association between SDM and medication adherence in the asthma and COPD population, in contrast to previous findings (Wilson et al., 2010; George et al., 2020; Granados-Santiago et al., 2020). Since there is no gold standard for both measuring medication adherence and SDM, comparison of study results is complicated. Especially problematic in SDM research and the possibility to compare study results, is the lack of consistency in defining SDM and how SDM is performed. A recent study identified no less than forty unique definitions and models of SDM, and many HCP do not perform SDM, although they think they do (Bomhof-Roordink et al., 2019; Driever et al., 2022). Another factor that makes comparison and generalization of study results difficult and determining SDM interventions' effectiveness, is the context. For example, Grandanos-Santiago et al. (Granados-Santiago et al., 2020) examined the relation between SDM and adherence to inhalation medication in COPD patients during hospitalization, while Wilson et al. (Wilson et al., 2010) examined the same relation in patients with poorly controlled asthma using SDM in phone call encounters. Our study included a broad general outpatient population, i.e., patients were not hospitalized. Possibly, the context—patient population and setting—could be of influence on the effectiveness of SDM. For example, it could be that patients who are having their consultations over the phone could perceive lower levels of SDM or feeling less related to their HCP compared to patients who are hospitalized and speak to their HCP daily (moderation-effect). More specifically, the type of non-adherence—sporadic, deliberate, unconscious—could be crucial for the relation between SDM and medication adherence as well. For example, in patients who are unaware of the consequences of non-adherence, SDM—by informing and therefore making the patients more competent—could have a positive effect where in patients who are adherent due to forgetfulness SDM does not have an effect (mediation-effect). The type of non-adherence and context was not taken into account in previous studies and neither in this study but could be an underlying explanation for difference in findings in effect of SDM on medication adherence and a topic for further research. For example, some asthma patients may have been on a maintenance and reliever regimen, thereby not requiring complete adherence and therefore reporting deliberate nonadherence.

Furthermore, we did find that a feeling of autonomy, a feeling of competence and a feeling of relatedness correlated positively with SDM yet not with medication adherence. According to the SDT, this would signify when patients experience higher levels of SDM they are more autonomously motivated. The three factors of autonomous motivation did not correlate with medication adherence, and this could be a nudge to look into another possible mechanism e.g., white-coat adherence. This phenomenon reflects the intentional effort of patients to improve medication adherence before visiting the physician (Keemink et al., 2015). Possibly, not autonomous motivation but extrinsic motivation by social control—being supervised by a physician—is of greater influence compared to feeling more autonomously motivated in medication adherence. In other words, not SDM itself—and therefore also not autonomous motivation—but the appointment the patients have planned with an HCP and the feeling of being observed and assessed by that HCP would motivate the patient extrinsically which would result in higher levels of medication adherence. Lastly, we must consider the possibility that SDM has no or limited impact on medication adherence in patients with COPD and asthma, but is just a more desired communication style from an ethical perspective.

Strengths and limitations

This is the first study to measure the experienced levels of SDM in the general population of patients with COPD and asthma and is unique in also exploring the underlying mechanism within the

relation of SDM and medication adherence using a social behavior theory.

Another strength, but also a limitation, is the study design, a real-world observational study. Therefore, study findings give a comprehensive overview of the current situation when it comes to SDM and medication adherence in patients with COPD and asthma. Secondly, the external validity of observational studies is greater compared to RCTs and our study findings are therefore more generalizable. On the other hand, RCTs remain the golden standard for effectiveness studies and self-reported measurements have been used. Self-reported measurements are accompanied by a variety of biases such as recall errors and social desirability which limits the validity of our measurements and results (Rosenman et al., 2011).

The use of patient perspective is a strength and limitation as well. Although patient perspective and self-report measurements are not objective, and are therefore less reliable, the patient perspective is essential when we want to understand and interfere in patients' motivation and behavior as well as in underlying mechanisms. Additionally, we only measured whether patients experienced SDM, but not whether that was also their preferred level of involvement. Although research shows asthma patients prefer most often an active or collaborative role, not all patients prefer SDM or are capable to participate in it (Caress et al., 2005; Mathes et al., 2014). Notably, we also did not take into consideration if patients scored intermediate on SDM overall or if they scored lower on certain aspects of SDM (specific items on the SDM-Q-9).

We found an response rate of 31.1%. This is a relative low, but still acceptable response rate for online surveys (Meyer et al., 2022; Wu et al., 2022). Most participants that were excluded did not meet the inclusion criteria (30.8%) and 22.1% did not complete the survey. We can only speculate about the reasons for non-completion. Most surveys that were not completed had missing data on the last items suggesting the survey was possibly experienced as too long. Also, it is possible that we mainly included patients who were younger and more digital oriented, although the included asthma-population was slightly older than expected. We speculate that elderly patients had generally more time to complete this relatively lengthy survey. Besides the asthma population being slightly older than expected, note that our population was also quite homogeneous demographically. The study population was mainly Dutch and living in an urban environment. This limits the overall generalizability.

The COVID-19 pandemic may also be of influence on the generalizability of our findings. Although we checked whether SDM was different during COVID-19 compared to before the start of the pandemic, the pandemic could still have had an effect as patients stated they had less contact with their HCP, in line with other research (Rijpkema et al., 2023). Furthermore, the COVID-19 pandemic could have resulted in a selection bias where patients with asthma and COPD who had become more concerned with their health due to the pandemic were more inclined to participate in this study. Patients who are more concerned with their health status or are in poorer health condition are more willing to participate in SDM and are more medication adherent (George et al., 2005; Krauskopf et al., 2015; Plaza et al., 2016; Unni and Shiyanbola, 2016; Alfian et al., 2022). This could have resulted in an inflation of the SDM and medication adherence levels found in this study. Moreover, the pandemic could have affected the view patients had on the healthcare system, HCPs and HCPs' SDM abilities both positively and negatively. During the pandemic, trust in the healthcare system and HCPs declined which could result in participants assessing SDM more negatively (Beller et al., 2022). On the other hand, the importance of the healthcare systems and the HCPs became more evident during the pandemic, which could have resulted in participants assessing SDM more positively (Shan et al., 2022). The possible effects of the pandemic should be taken into consideration when interpreting our study results.

Recommendations

Following the results of this study, a few recommendations can be made.

First, to make SDM more accessible and valuable for research and implementation in daily practice, change in research and policy is needed. In research, we suggest clearer and more detailed description of SDM-interventions—what is the used definition and how is it been put into practice—and the context in which it is performed—who are the patients and what is the setting (Bomhof-Roordink et al., 2019). An opposite direction how to view and use SDM should be considered as well (Montori et al., 2023). With SDM being a highly complex process and therefore also very difficult to relate to patient outcomes such as medication adherence, most importantly SDM is an ethos and mindset in which HCPs want to deliver the best care for each individual patient (Montori et al., 2023). With this in mind, we should move beyond teaching HCPs specific SDM-methods (e.g., three-talk model from Elwyn and others), developing decision aids and new measurement methods (Elwyn et al., 2017). Instead, we should make place for a more human, personal and caring mentality in healthcare education and practice. In continuation of the latter, more patient involvement and the patient perspective is highly recommended in research, training and clinical practice e.g., combining more objective measurements of SDM with measurement methods of SDM from a patient perspective within research (van der Weijden et al., 2022).

Second, it is of utmost importance when interventions intervene in patient behavior or intend to affect patients towards certain behavior, not just the effect of the intervention is to be explored (Stempel et al., 2021; van de Hei et al., 2021). Understanding how an intervention works in its context, makes it possible to generalize it to different populations, settings, and circumstances. Also, this understanding makes it possible to adjust the intervention accordingly for both further research and daily clinical practice. Therefore, more use of social-behavior theories in medical research concerning the relation between SDM and adherence is strongly recommended as well as the use of more qualitative research methods.

Conclusion

To conclude, experienced SDM in daily practice is intermediate while adherence is suboptimal. It remains unclear if and how SDM can contribute to improving medication adherence in patients with COPD and asthma. These results warrant a careful consideration when recommending SDM as intervention in guidelines and more qualitative research is necessary into the relation between SDM and medication adherence. Key in improving medication adherence in

people with COPD and asthma lies in human contact and trying to understand the person in front of you.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation taking the Dutch legal implications regarding data sharing into account.

Ethics statement

The studies involving humans were approved by the Medical Ethics Review Board UMC Groningen (METc UMC Groningen). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

MA: Writing–original draft. PV: Formal Analysis, Methodology, Writing–review and editing. LD: Supervision, Writing–review and editing, Methodology. JB: Supervision, Writing–review and editing, Conceptualization.

Funding

The authors declare that no financial support was received for the research, authorship and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1283135/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 21 November 2023
DOI 10.3389/fphar.2023.1266277

OPEN ACCESS

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RECEIVED 24 July 2023
ACCEPTED 30 October 2023
PUBLISHED 21 November 2023

CITATION
Bell S, Kelly H, Hennessy E, Bermingham M, O'Flynn JR and Sahm LJ (2023), Healthcare professional perspectives on medication challenges in the post-stroke patient.
Front. Pharmacol. 14:1266277.
doi: 10.3389/fphar.2023.1266277

Healthcare professional perspectives on medication challenges in the post-stroke patient

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Background: Medications play an essential role in the management of patients who have experienced a stroke. Despite the recognised importance and widespread availability of secondary prevention guidelines, Irish research has shown a continuous failure to meet secondary prevention targets upon discharge. While complex interventions involving healthcare professionals (HCPs) such as Speech and Language Therapists (SLT), Occupational Therapists (OTs) and Pharmacists have been effective in combatting medication non-adherence, community multidisciplinary teams (MDTs) are not as well defined as in the acute setting, leading to wide variation in patient care. Therefore, this study aims to investigate the knowledge, attitudes, beliefs, and challenges faced by HCPs in the continuity of care post-discharge from a hospital stroke ward, and its impact on medication adherence.

Methods: Semi-structured interviews and one focus group with HCPs were conducted, and data were analysed using Braun & Clarke's reflexive Thematic Analysis.

Results: Fourteen HCPs (6 Pharmacy, 4 SLT, 4 OTs) participated in this study. Participants discussed their views under two main themes 1) continuity of care and 2) medication adherence. Sub-themes observed regarding continuity of care include management and organisation, interpersonal continuity, and informational continuity. Themes generated which impact medication adherence post-discharge include condition-related factors, medication-related factors, systemic and HCP factors, and patient-related factors.

Discussion: Additional resources are required to bring community healthcare in line with the standard of acute care. Increased channels of communication must be established across contexts and disciplines, and may be achieved using interprofessional training through continuous professional development or third-level education, a more clearly defined community team structure, and discharge summaries completed to relevant quality standards. While suboptimal

continuity of care was reported as contributing to medication non-adherence, HCPs also acknowledged the complexities of medication management post-stroke.

KEYWORDS

stroke, medication adherence, continuity of care, healthcare professionals, pharmacy, speech and language therapy, Occupational therapy

1 Introduction

Approximately 7,500 people in Ireland are diagnosed with stroke each year, which has been identified as the leading contributor to adult acquired physical and neurological disabilities (Health Service Executive, 2022). One of the most prominent risk factors for stroke is the presence of previous stroke or transient ischemic attack, where nearly one in four diagnosed cases are classed as a recurrent cerebrovascular accident (CVA) (Tsao et al., 2023). Risk of recurrent stroke has been found to rise to between 30% and 43% within 5 years of the initial cerebrovascular event (Chambers et al., 2010) and incidence of recurrence or death post-stroke rises to 67.7% within 10 years of initial stroke (Flach et al., 2020).

Medications play an essential role in the management and treatment of patients who have experienced a CVA, and substantially decrease the risk of recurrent stroke (Hackam and Spence, 2007). Clinical guidelines recommend several secondary prevention antihypertensive and lipid-lowering medications which should be started immediately and continued indefinitely following the cerebrovascular event (Intercollegiate Stroke Working Party, 2023). While these medications have been specifically prescribed to improve the health and wellbeing of the patient, their positive effects are often hindered by the fact that an estimated 50% of patients are reported not to take medications as directed (Brown and Bussell, 2011). Whether intentional or non-intentional, medication non-adherence is associated with almost 200,000 deaths annually (van Boven et al., 2021). From an economic perspective, non-adherence is responsible for €80–125 billion of potentially preventable direct and indirect costs in the EU (van Boven et al., 2021). The identification of these factors has led to adherence to pharmacotherapy being pinpointed as the most significant long-term target of medical management of stroke (Smith et al., 2012; Dalli et al., 2021).

Despite the recognised importance and widespread availability of secondary prevention guidelines, research conducted on an Irish population has shown a continuous failure to meet secondary prevention targets (Brewer et al., 2015). This is due in part to the fact that in the post-stroke period, patients face a multitude of medication-related challenges. These challenges are poorly characterised in the literature, especially at the transition of care between hospital and home (Andrew et al., 2018). This is particularly true of the experiences of those with more severe stroke-related impairments, who are often excluded from explorations of medication adherence. Though these patients have the capacity to meaningfully participate in healthcare research, their physical, communicative, and cognitive needs often result in their exclusion (De Simoni et al., 2015).

Early, efficient community-based stroke rehabilitation and disability management must be offered to all stroke patients leaving hospitals who require it through a dedicated multidisciplinary team structure (Intercollegiate Stroke Working Party, 2023). Physiotherapy, Occupational Therapy (OT) and Speech and Language Therapy (SLT) are the only disciplines currently reporting into the stroke register regarding access to therapy supports in acute stroke units in Ireland (Health Service Executive, 2022). The majority of these patients have ongoing therapy needs after the acute phase, with the highest demand (52%) being placed on continuing SLT services (Health Service Executive, 2022). However, the broader multidisciplinary team (MDT) structure is ill-defined, with its members dependent on context (e.g. acute care, community care) or purpose (e.g. rehabilitation, palliation). In particular, the concept of MDTs in community settings are not as well defined as they are in the acute setting, leading to wide variation in those involved in the patient's care (Weiss et al., 2014). This is significant as approximately 60% of patients are discharged directly to home following the acute event and rely on community services for their rehabilitation (Health Service Executive, 2022). Depending on stroke severity and availability of resources, patients may also be discharged to complex specialist rehabilitation units, or long-term care facilities (Health Service Executive, 2022). It is widely acknowledged that rehabilitation services are under-developed in Ireland, with the Irish National Stroke Strategy 2022–2027 placing emphasis on the development of organised stroke pathways (Health Service Executive, 2022). Only one-fifth of sites have access to Early Supported Discharge (ESD) teams, a feature of Irish stroke pathways which provide specialist rehabilitation in the community to facilitate an accelerated discharge from the acute setting (Collins et al., 2021). Five of the nine ESD programmes in Ireland are situated in the country's capital with only one hospital serving rural dwellers (Health Service Executive, 2022). These ESD services highlight the importance of team composition and multidisciplinary co-ordination in delivering standard-meeting services (Chouliara et al., 2023), and clearly outline the inclusion of OT, SLT, Physiotherapy, Medical Social Worker, Clinical Nurse Specialist and Therapy Assistant as central roles (Health Service Executive, 2022). However, it is acknowledged that other HCPs also play a key role in providing targeted community rehabilitation for stroke survivors, such as Pharmacy, Dietetics and Psychology (Health Service Executive, 2022).

Continuity of care is considered an important determinant of medication adherence (Yao et al., 2022). While complex interventions involving healthcare professionals have been effective in combatting medication non-adherence (Simoni et al., 2009; Chung et al., 2011) research must be conducted to determine specific roles and tasks within the team for a seamless transition of care (Nieuwlaat et al., 2014). The first step in this process is to establish the current patterns of care from the perspectives of HCPs,

and its perceived shortcomings (Hill et al., 2009). As healthcare systems, procedures, and beliefs vary from country to country, research must reflect the national healthcare landscape (Bauler et al., 2014) and importantly include the perspectives of the HCPs who provide this care. Pharmacists, Speech and Language Therapists and Occupational Therapists all play a role in medication management post-stroke (Health Service Executive, 2022). The Pharmacist is central to all aspects of medication-taking post stroke, most notably dispensing and managing pharmacotherapies (Al-Qahtani et al., 2022). Speech and Language Therapists assess and evaluate the ability of the patient to safely swallow medications (Brown and Bussell, 2011). In addition, they collaborate with the MDT to ensure health information is accessible and appropriate for patients' communicative needs (Brown and Bussell, 2011; Health Service Executive, 2022). The Occupational Therapist is responsible for assisting patients to engage in meaningful and purposeful Activities of Daily Living (Brown and Bussell, 2011). Medication management has been flagged as an ADL essential for allowing an individual to live independently in the community (Allen et al., 2023). Therefore, this study aims to investigate the knowledge, attitudes, beliefs, and challenges faced by HCPs (specifically, Pharmacists, Occupational Therapists and Speech and Language Therapists) in the continuity of care post-discharge from a hospital stroke ward, and its impact on medication adherence.

2 Methods

2.1 Recruitment

This study received ethical approval from the Clinical Research Ethics Sub-committee (CREC) at University College Cork. A purposeful sample of Pharmacists, SLTs and OTs were recruited via email and word-of-mouth. Participants were considered eligible if they were currently practising in the fields of Pharmacy, SLT or OT.

2.2 Data collection

This study had a phenomenological underpinning. Phenomenology is often used in explorations of healthcare professional's perspectives, as it gives a unique insight into the participants lived experience of a phenomenon, while also acknowledging the existing literature. Semi-structured interviews and focus groups with HCPs were conducted by SB, with EH observing and taking field notes. Eleven individual interviews were conducted online. Mean interview time was 25 min 46 s, with a range of 10 min 46 s to 48 min 02 s. In addition, one focus group with three Occupational Therapists was carried out. Focus group time was 49 min 39 s. These semi-structured interviews were conducted in-line with a pre-established topic guide (Supplementary Appendix I), where questions were generated based on the World Health Organisation (WHO) Framework on continuity and coordination of care in integrated people-centred health services (World Health Organization, 2018). Participants were asked to consider each question in terms of medication-related information they and/or the patient may receive. Open-ended questions relating to barriers and facilitators to medication adherence post-stroke were also asked in order to capture salient ideas unrelated to continuity and co-ordination of care (Weller et al., 2018). Interviews were conducted via a closed channel on Microsoft Teams, where each participant was provided with a unique meeting code to ensure data protection. Written informed consent was obtained prior to the meeting and was also recorded verbally at the start of the interview.

2.3 Data analysis

Data analysis was conducted in line with Braun & Clarke's reflexive Thematic Analysis (Braun and Clarke, 2019) as previous research with HCPs has found this appropriate for investigating knowledge, attitudes, and beliefs of participants (Jaam et al., 2018; Kvarnström et al., 2018). Semi-structured questions facilitated inductive generation of themes through the extraction of meaning and identification of trends from data (Galletta, 2013). Themes were not pre-specified prior to analysis. A six-step protocol was followed by SB and EH:

1. Familiarisation with the data: Interview recordings were divided amongst SB and EH for transcription. Both SB and EH engaged in a process of immersion in the data through the thorough examination and re-reading of transcripts. They maintained individual notes on the content and contextual nuances of the data for discussion with the research team.
2. Generating codes: Significant elements of the data were methodically and systematically identified and labelled. SB and EH conducted this step independently. Both researchers then came together to organise these codes into broader categories to represent ideas pertinent to the study issue.
3. Generating themes: SB and EH conducted a systematic exploration of patterns evident in the coded data. This allowed the researchers to generate themes which represent the relationships between several different codes.
4. Reviewing the themes: Critical examination and refinement of the identified themes took place in this stage where SB and EH ensured that the themes were coherent, meaningful, and accurately represented the data.
5. Defining themes: The boundaries and specific characteristics of the themes were clarified, ensuring they accurately captured participants' experiences or perspectives.
6. Write-up: a coherent and comprehensive narrative was composed that presents the research findings based on the identified themes.

3 Results

3.1 Participants

Fourteen HCPs (1 Male: 13 Female), participated in this study (Table 1). Of the 14 participants, six were Pharmacists, four were Speech and Language Therapists, and four were Occupational Therapists. Both junior and senior roles were represented within these professional groups. Median years of practice was 10 years, with an interquartile range of 0.83 years–25 years.

TABLE 1 Participant demographics.

Participant code	Role	Setting	Years of practice
HCPP1	Locum Pharmacist	Community	11
HCPP2	Pharmacist	Community	10
HCPS3	Speech and Language Therapist	Acute/Community	2
HCPP4	Supervising Pharmacist	Community	5
HCPP5	Superintendent Pharmacist	Community	19
HCPP6	Supervising Pharmacist	Community	25
HCPP7	Pharmacist	Community	3
HCPS8	Senior Speech and Language Therapist	Acute	22
HCPS9	Speech and Language Therapist	Community	2
HCPO10	Occupational Therapist	Community	0.83
HCPS11	Senior Speech and Language Therapist	Acute	13
HCPO12	Occupational Therapist	Community	2
HCPO13	Occupational Therapist	Acute	2
HCPO14	Occupational Therapist	Acute	2

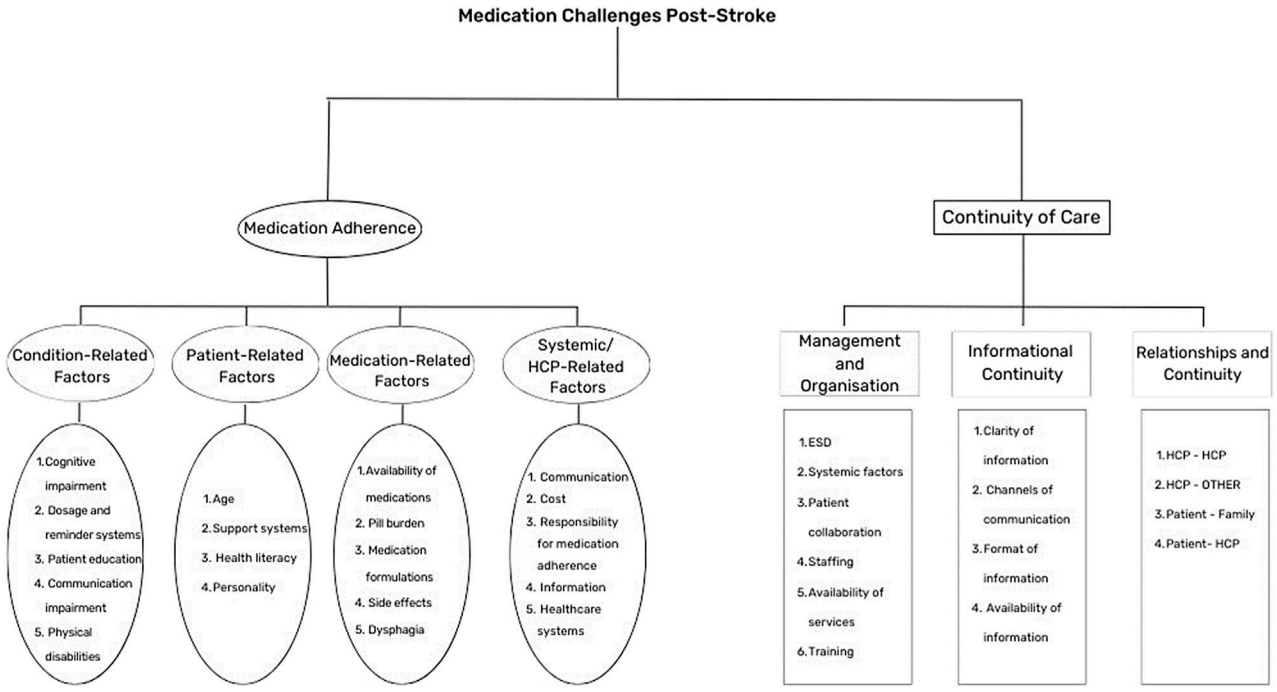

FIGURE 1
Themes and Subthemes identified.

3.2 Themes and Subthemes

The following themes were observed (Figure 1):

(i) Medication Adherence. This theme explored elements which may impact medication taking behaviours of the patient. Four sub-themes were observed: condition-related factors, medication-related factors, systemic factors, and patient-related factors.

(ii) Continuity of Care. This theme focused on the ongoing experience of the patient as they progress through different parts of the service and interact with different members of the

healthcare team. This encompassed three sub-themes: management and organisation, interpersonal continuity, and informational continuity.

3.3 Theme 1: medication adherence

The theme of Medication Adherence encompasses the complex factors influencing an individual's ability and willingness to consistently follow prescribed medication regimens, including challenges and strategies associated with adhering to treatment plans.

3.3.1 Sub-theme: condition-related factors

All participants reported that the occurrence of a stroke could increase medication non-adherence. In particular "if they've got language or cognitive issues, that's going to make it difficult for them to independently manage medication" (HCPS8). Features of cognitive and communicative impairment which participants considered most directly impact medication adherence include "poor recall" (HCPO14), "issues with understanding what their medicines are for and how to take their medicines" (HCPP1), and "fatigue" (HCPS8). Participants stated that the impact of these aspects on medication adherence could be addressed through patient education, though HCPP4 stressed that this should be provided in a manner that doesn't "overload them or overbear them". Participants voiced different views on how this patient education should be provided. Some preferred "more tangible, permanent communication" (HCPS8) such as "a leaflet" (HCPP5), "picture charts . . . having a picture or the actual tablet stuck on" (HCPS8), or a "fact file" with "abbreviations or [drug names]" (HCPS9). HCPP2 indicated a preference for providing information "orally . . . people don't really read stuff . . . and then you can ask them if they have any questions". HCPS8 noted that this may be useful for those with alexia (acquired dyslexia/reading difficulties), though felt that "an overall total communication approach" should be taken so "people can go back to it . . . even if they can understand the verbal speech, if you have emotional or . . . vulnerable factors in it, you're not going to be taking it in".

Eight participants highlighted the benefits of using medication dosage systems to overcome linguistic and cognitive deficits. The systems most mentioned by participants included "dosette boxes" (HCPS11) or "weekly or daily organisers" (HCPP1) and "blister packs" (HCPP5). Participants also found reminder systems to be helpful, such as "reminders on your phone . . . a notebook or the communication diary", "checklists" (HCPS9), "apps" (HCPS3), "[pillboxes] that will alarm" (HCPO10), and "a text message service" (HCPP4). Participants acknowledged that these are not without their drawbacks, with HCPS8 reflecting "you do out like this typed list, and then you know if something changes you have to do a new typed list, then they lose the list". HCPP5 also found that with blister packing "sometimes it only causes more confusion", particularly for those with physical disabilities post-stroke: "the things like dexterity—they might have been able to open blister packs before, they can't afterwards". However, HCPO13 felt that dosette boxes and blister packs might be a facilitator to medication adherence for those with impaired dexterity.

3.3.2 Sub-theme: patient-related factors

The majority of participants highlighted the impact that individual patient factors may have on medication adherence post-discharge. In particular, "the personality of the person, whether they want to take it or not" (HCPS9) was seen as an important predictor of adherence. Participants felt that those with lower health literacy were less likely to adhere to medications as "sometimes people can't follow what you think is a basic instruction, so health literacy [is a barrier]" (HCPP2). While participants acknowledged that "If there's any cognitive impairment or issues with understanding what their medicines are for . . . that would be a barrier [to health literacy]", others found that "they weren't managing their medication before they had their stroke" (HCPO10). HCPP2 stated that some patients have no desire to increase their knowledge: "sometimes they don't want to know . . . sometimes they have no interest. They just are like I was told to take this so I'll take it . . . It's scary how happy they are just to take what's prescribed sometimes" (HCPP2). Participants highlighted that older patients may need more support and education around their medications as "younger patients, they would know and they"d say, "oh, I need my blood thinner" or "I need my blood pressure". Older patients wouldn't and they would maybe go more for "I need the small yellow tablet I've ran out of those" (HCPP4). HCPO10 acknowledged that while many patients dislike taking multiple medications, older patients may be particularly averse to polypharmacy: "They just don't like being on tablets, because it's like, oh, I'm old if I take all these tablets".

One patient-related factor proposed by all participants was the presence of a support system for the patient post-discharge. Carers were seen to be an invaluable asset for medication management: "You're very reliant on family, when it comes to it, so. If somebody can't manage their own medication, and they don't have a reliable family member available, that's really going to impact discharge" (HCPS11). Pharmacists such as HCPP6 stated that "generally it's never the patient I'm dealing with it's a family member. You know, they don't tend to come in. Obviously, there's different stages, there's different disabilities, post stroke . . . But generally speaking, they're so overwhelmed by the change in their life that their input is minimal".

3.3.3 Sub-theme: medication-related factors

Participants considered pill burden, formulation and availability of medication, and side-effects to be the greatest barriers to medication adherence in this cohort. HCPP1 noted that "the fact that some of these patients may have started on no medicines and now they have quite a high pill burden can be a barrier to adherence," while HCPP7 also commented on the "complexity of regimes." HCPO14 saw it as the role of the Occupational Therapist to consider "if they need to take their meds twice a day, and we don't think that's going to happen, have we put in support two times a day?".

Both Pharmacists and Speech and Language Therapists considered the impact of dysphagia (impaired swallow) on medication adherence. Participants felt that "if they have swallow issues, that's going to make things difficult . . . sometimes you have to work around it" (HCPS8). Participants noted that this could be addressed in most cases by "chang [ing] the formulation of their tablets" (HCPP6) or adjusting based on clinical judgements

(HCPS8): "if I'm saying a patient's nil per oral but there's some drugs that they particularly need . . . you have to give it . . . [the] benefit of that outweighs the risk of them aspirating". HCPP6 noted that "We mightn't know that they don't like taking their medication because it's uncomfortable for them to take, or they can't physically take it". HCPS8 noted that while the role of the Speech and Language Therapist is to assess swallow function, "we don't make recommendations as to what form patients should take their medications in . . . there's kind of a standard line on the cover sheet of [the discharge pack] going: "if you have any queries about taking your medications, liaise with your pharmacy . . . if I put the patient on modified diet and fluids and I don't think they can manage their medications whole, I'll send a referral to pharmacy". HCPS3 found that it may be difficult for the patient to advocate for their swallowing needs, as "a patient, if they have a swallowing difficulty and aphasia, they can't necessarily tell you "I"m supposed to be having thickener in my tea". As a Pharmacist, HCPP1 reported that this information was not easily accessible to them, and "the only way sometimes that I can tell . . . they have issues with, say swallowing, for example, is if they were prescribed a thickener. II So it's not always clear that that may be present in a patient". This was not seen as the only barrier to providing alternative drug formulations. HCPP5 described sourcing liquids as being "kind of difficult", as "liquid formulations aren't generally covered on the HSE schemes. So you're looking at crushing tablets, that side of it can be awkward".

Where appropriate medications and formulations have been prescribed, participants found that patients may discontinue medications due to side effects. In HCPS9's experience, "they won't take a certain drug 1 day because they're like, I don't need that one, or I don't like the side effects that one gives me. And I feel like I get I feel more nauseous when I get this one or I feel more down, or I feel more out of sorts, more tired when I take that one". HCPO12 found that the potential to experience drug side effects has led patients to "withdraw from drugs and go into alternative therapies. And then it just cyclical, it just comes back around". The most common side effects mentioned by participants were "dry mouth" (HCPS3), "reflux" (HCPS9), "nausea" and "fatigue" (HCPO10).

3.3.4 Sub-theme: systemic/HCP related factors

The largest systemic contributor to medication non-adherence was, in the words of participants, "breakdown in communication or lack of continuous communication" (HCPP7). HCPP1 stressed the importance of achieving "continuity of medicines, so that the discharge prescription is accurate, that the patient has been started on any medicines that should be newly started, that any medicines that should have been stopped are stopped" to facilitate optimum adherence.

While all participants mentioned that medication non-adherence should be addressed, there was discrepancy among participants regarding which HCPs be involved. Pharmacists were the HCP most commonly associated with medication management, and were seen to have a role in prescribing, patient education, and measuring adherence. GPs were also seen to have a large role in prescribing, counselling, and monitoring medication usage as "their communication of the importance of adherence to the particular meds and stuff like that can be very well received by patients" (HCPP7). Public Health Nurses were recognised as playing an important role in medication adherence, as often "nurses spend more time with the patients" (HCPS3). The role of the Speech and Language Therapist was less recognised, though Pharmacy participants noted their role in "formulations, and what formulations are suitable" (HCPP1), "the thickening agents and such" (HCPP6). Only two participants noted the role of the Occupational Therapist, which would occur if "they can't physically hold something or they need an easier way to manage something" (HCPP6). HCPS9 reported seeing medication management as involving "to an extent, everyone in the MDT including the patient and the family members . . . some roles definitely bigger than others".

Some participants felt that these roles should clearly be addressed in clinician training. HCPS9 observed "could it be promoted to a bigger extent? Yeah, probably. And I think that would also come from probably education and college . . . to clarify what your role is, but also how we all have a role to play on, say, for instance, medication, having that knowledge kind of drilled into every clinician from education up". HCPS3 felt that this lack of training is evident in current practice: "I did a training with some new starter physio and Ots recently . . . their knowledge was really limited and through no fault of their own, but they just hadn't been equipped with those resources". HCPP7 thought that resources in this area should be available to practicing HCPs: "I would probably feel additional resources, support or information would definitely help maximize my input into the patients holistically". HCPS11 felt that current knowledge gap may impact patients' healthcare experiences: "the information that's provided isn't enough, and I don't have the answer for them when they ask". However, some sites are taking their own measures to address staff knowledge gaps: "In my last rotation, we did like a drug of the week. So one person from the team would go pick a drug . . . they'd go off and research it and then just give a few minutes chat through what it is, what it's used for what are the side effects . . . you might not always get the information from the doctors, so it's a good way to go about like getting the knowledge yourself" (HCPO13).

Regardless of the HCP administering medication counselling, all participants regarded patient education as paramount to medication adherence. However, HCPP2 noted that the current healthcare system does not allow the time needed to successfully carry this out: "it's kind of the Pharmacist's job just to try and explain about what the different things are, what they're for, why they're important. But we always don't—we don't always have time to do that because we also have to do 10 other things at the same time". They proposed that "a systematic approach that everybody followed all the time and there was enough people working to be able to do it" would successfully address this gap.

Four participants viewed cost as a barrier to medication adherence. HCPS3 noted that "some people aren't on drugs schemes. A big prescription can cost an awful lot of money". HCPO14 also addressed the fact that "if you're, you're not on a medical card . . . you'd rack up a hefty bill quite quickly". Even for those eligible for drug payment schemes (HSE.ie, 2023), "it's capped at €80 [per month] but it's still a lot of money. That we'd would try and help people to set that up, but it only lasts for 3 months" (HCPP4). In HCPS8's experience "a lot of people here would end up being eligible for the medical card (HSE.ie, 2023) if they have reason.

So I don't think the cost of medication day-to-day necessarily. But like the cost of providing . . . you know, there's very few people probably could pay for private carers for a nurse to come in to actually supervise someone taking their medications". Even for those with the funds to "access home help to supervise medication administration, they're not actually allowed touch the medications . . . if they come to me and I put out two of my tablets instead of one, I don't know what they're actually allowed to do" (HCPS8).

3.4 Theme 2: continuity of care

This theme, encompasses HCP experiences and perceptions of patient access to healthcare services as a whole over time, and relates to acute and community services in both private and public settings. Each participant was asked to provide a definition of their understanding of continuity of care. Most referred to continuity of care being "a good handover of information from one HCP to another" (HCPP2), particularly with regard to "the transition of patients from one section of society to another" (HCPP6). HCPO10 viewed continuity of care as the "gold standard" of hospital discharge, whereas others (HCPO13, HCPO14) indicated that while the principles of continuity of care were familiar to them, they "hadn't really heard of the term before". Five participants discussed the importance of having "the same level of care given all the time" particularly as "people's needs change as they progress" (HCPP4). HCPS9 stressed the importance of recognising the roles of "professionals, family members and the client" in the transition of care.

3.4.1 Sub-theme: management and organisation

Almost half of the participants viewed staffing shortages as a barrier to efficient continuity of care, as "sometimes there just isn't the option to offer that continuing care" (HCPS3). HCPs felt that this impacted their ability to support their patients, as "there's not enough staff trying to do all the jobs that are needed to be done, to make sure that it's done seamlessly" (HCPP2), even though "the people on the ground that are doing it, are really trying their best" (HCPO10). This is particularly true "on discharge day," where HCPP2 felt that more staff was needed in order for them to be "contactable" by community HCPs. HCPP7 compared the staffing levels within the Irish system to the National Health Service (NHS) in the UK and felt that "important steps of discharge can be missed just because of the infrastructure of Irish hospitals". Other participants felt that issue was also prevalent in the community, which is reflected by "the waiting list. They're so long" (HCPO10).

HCPS3 felt that lengthy waiting lists for publicly-funded therapy services reflected the lack of individualised pathways for stroke patients, as HCPs are "dealing with the outpatient community outside of people who went through, say, the stroke pathway", which leads to them "missing out on all that recovery and support, especially within the six first months of all that spontaneous recovery". HCPS11 acknowledged that services were taking steps to address this gap, as "there's people who are developing pathways and that's high on the agenda". Other factors which HCPS3 noted as barriers to service access for patients were their "postcode, funding, and social care".

HCPP6 felt that there was a discrepancy between services available to those in acute pharmacy in contrast with those working in a community setting "In hospital pharmacy, I mean, I'd access to the NEWT guidelines, the handbook of enteral feeding. whereas in community you don't tend to have those same resources. Now I know where to find them but not everybody does, because I've come from that background. But even the information I can find is quite outdated".

One service which participants felt worked well with regard to continuity of care for the stroke patient was the Early Supported Discharge (ESD) team. The core team members of "a speech therapist, a physio, and an OT" (HCPS11) described as providing "intense rehab" for those who are "medically fit and they don't need to be in hospital" (HCPS8). The ESD service is seen to "enable patients to get out of hospital" while providing immediate support (HCPS8). ESD provides patients with "a familiar face . . . someone that knows your history, how you communicate, or what other difficulties you have" (HCPS3). HCPS3 also noted that ESD was not without its flaws, as the criteria can be "quite strict, and very narrow".

3.4.2 Sub-theme: informational continuity

Participants reported different ways of receiving information about the client and their care. Clinical Therapists (SLTs and OTs) report receiving community referrals directly from the hospital therapists: "all the different disciplines like physios, the OTs, SLTs, psychology, all gave a summary of what they did, and the goals that they have set out going forward. And that will be passed on then if they were being referred to community team" (HCPO13). Additional resources are often provided to the patient such as "management booklets" (HCPO13) and "home programmes" (HCPO10). HCPO10 noted that their team acknowledged the importance of making these programmes accessible for patients with communication difficulties by "giving them pictures of the exercises". Clinical Therapists acknowledged the gaps in the information provided to them, such as "the referral onwards is on [the acute] form but it's not always filled out . . . that's inconsistent, but when it is done, it is fantastic". Additionally, HCPO10 disclosed that "I don't think there is a section on it to put down what medications they're on . . . we don't get the hospital notes, then it has to be the patient brings it up".

One of the Pharmacists stated that "the only information I generally get is a prescription is handed to me. I wouldn't get a massive amount of extra information beyond that" (HCPP1). Participants expressed that, given the information provided, it is difficult to discern why they are providing certain medications to the patient: "a lot of the time, we may not even know they've had a stroke . . . It'd be really handy to get even the indication . . . different things can have multiple indications" (HCPP2). HCPP4 considered that this information would be useful to the Pharmacist as "post-stroke they can obviously have the [impaired] swallow", while HCPP5 noted that "there might be all these compliance aids needed". Similar to Clinical Therapists, Pharmacists noted that information "depends on the hospital and how much they fill out on the discharge prescription. Lots of them will have spaces to say "reason for admission" or "the ward that they're on' and at the bottom there'd be "extra notes" or "medication that has been discontinued" and would really depend on the individual doctor

if they actually fill all that out" (HCPP4). HCPP5 acknowledged that "the best-case scenario is you get a phone call from the hospital saying, "look, here"s the prescription, this person, we've been looking after him', but I'd say two out of three times you don't", while HCPP7 also noted that these phone calls "probably happened maybe five times in 18 months". All Pharmacists felt that the patient and their carer were their main source of information about the patient. This might pose additional barriers, as "they don't realise that their medication has been changed or they mightn't bring the letter to the GP so nothing gets updated or else it just gets lost in the administration" (HCPP4).

Both Pharmacists and Clinical Therapists felt that the public showed a misunderstanding of the sharing of information within the healthcare system. HCPS9 noted "once a client says it to one SLT, OT, one professional, they might not say to another person, that might be it. They might just be like sure I've told the SLT about my OT needs and that's that, or I've told this SLT about my SLT needs so of course, the other SLT will have access to it". HCPP5 reported the same experience, saying "A common thing is you'll be told by the patient 'didn't you know? Didn't you know I had a stroke? I thought you were all under one system'. There's this magic system that we're all supposed to be connected to".

HCPS9 reported a reduced flow of information between public and private therapists: "I think for, especially some reports, it wouldn't be encouraged that a client would share it with a private company, because it's a HSE report." Much like Pharmacists, private clinical therapists "get a lot of information from the client as well . . . the facilitator is that the client is knowing what their care was, and where they should be going, or who they are involved with". HCPS8 also reported easier access to information in an acute setting as opposed to a community setting: "we know where to go if we need to find it. Like, you know the kardex is there, you know there's a Pharmacist on the ward. You know you can chat to the nurses or one of the medical team". Participants made suggestions regarding changes to informational continuity that they would like to see from the Irish Healthcare system moving forward. HCPS9 would like to see a "role in hospital for a discharge coordinator and have them be the person to link in with the other professionals as you go on". HCPP7 suggested a "a fixed protocol where you can expect X amount of communication", where "48 h prior to discharge, there's a final assessment, like 36 h prior to discharge, the prescription is finalised and reviewed and disseminated, 24 h prior to discharge the pharmacy is contacted to give the green light that the patient will have access to what they need". In five cases, participants called for "an integrated system" (HCPP4) where patients and providers would have access to the "[acute] care, hospital discharge service and community of care" relevant to the client (HCPS9). HCPs saw this as being "electronic" (HCPS11) or "online" (HCPP4).

3.4.3 Sub-theme: relationships and relational continuity

Relationships were seen to play a central role in continuity of care by all participants. Four central relationships emerged: 1) those between HCPs, 2) those between the HCP and the patient, 3) those between the patient and their support system, and 4) those between the HCP and external organisations.

Participants were asked to describe the disciplinary approach to care post-discharge for a post-stroke patient. The majority of participants stated that the current approach to care is multidisciplinary, where "multiple disciplines [are] acting in their own silos". HCPP7 noted that the lines between multi-, inter-, and transdisciplinary care are unclear, where "the only term that you hear in Irish healthcare is multidisciplinary. it's like a catch all.it's like a movable definition". HCPS8 stated that some aspects of post-stroke care are "uni-to multi-here because [medication management]'s probably mainly resting with the Pharmacist".

Participants acknowledged that the disciplinary approach to care may be differently structured according to the needs of the patient and the context of their care. Many participants, including HCPP7, chose to juxtapose the approach to care in the acute setting with that given in the community setting: "depending on how capable a hospital setting is, they might have interdisciplinary focus especially with stroke . . . In community . . . it definitely would be multidisciplinary and communication would be slim to none. It'll be necessary communication only". HCPS9 felt that public services were more likely to provide multidisciplinary care, whereas private services may operate in a more unidisciplinary manner as communication is less likely to be achieved between different companies and services.

Participants noted that core members of the MDT in community include the Social Worker, OT, SLT, General Practitioner, and Physiotherapist. In particular, "SLTs and OTs work closely together" (HCPS9). Clinical Therapists stated that "the Pharmacist doesn't come to our multidisciplinary team meetings" (HCPS8), while Pharmacists also felt that they operate outside of the MDT: "I have never once had a contact number for a social worker, an Occupational Therapist, or a Speech and Language Therapist that would have been working with or liaising with a patient. Let's say I noticed a problem or something, there's absolutely nothing I can do except ask the patient to reach out to them" (HCPP7). HCPP2 noted "We aren't in that loop of information. We're excluded from it". HCPS9 felt this often resulted in a breakdown of care, as "a lot of clients for me haven't been able to name their SLT or their OT in public. Or I would call a hospital. And I might be like, what's the story now? And they're like, well, they're discharged to community. And I might ask who's community? And they won't know the name".

Pharmacists most often reported liaising with the GP or contacting acute discharge staff and reported difficulty contacting acute prescribers: "[the most difficult thing]'s actually finding the same person. And secondly, is finding the relevant information. It's very, very hard. There's no central team, you ring. Even finding the prescribers or their team can be extremely difficult. I've even had instances where I phoned about something and they've never phoned me back. Did they just forget about it? Or is it too complicated? It's very frustrating" (HCPP6).

HCPS3 emphasised the benefit of professional relationships between healthcare providers and social supports in the community, with reference to the Stroke Association (Stroke.org.uk, 2023), Aphasia Café (UCC.ie, 2023) and communication groups. They noted that this is particularly important for "patients who say they don't have very severe difficulties, but there's still something going on . . . sometimes having peer support and attending group sessions . . . can be just as beneficial, if not more beneficial sometimes to patients".

HCPS9 considered that this benefit came in the form of "hearing information from peers . . . to also link in with and contact and offer to keep up that continuity of care".

While the relationship between the patient and the healthcare provider was viewed as an important component of continuity of care, participants found this to be the most open to communicative breakdowns. Participants attributed this mostly to the inconsistency of HCPs involved in the patient's care: "I think it can change a lot. I think that can be really confusing" (HCPO10). HCPS9 encountered patients who "often say that, 'oh, another person's changed. It's another person, it's another person the whole time' and that does impact the therapeutic relationship". HCPS9 attributed this to "a mix of things in terms of the workers themselves wanting to move places, they could feel burnt out, the resources there, but it's also the lack of permanent positions they might be able to get", while HCPO10 regarded this as a more systemic issue "they'll have an OT in the hospital, then they'll have an OT in ESD, let's say they have a primary care need, that will be a separate person. And then if they come to community rehab, OT rehab, that will be another person again". HCPO14 relayed the story of a patient who felt that "every time I go in, it's a different one and I end up telling the story all over again and they don't know me and they don't really care about me because I'm just in there for 15-min appointments". HCPO12 felt "that the client can't build a relationship with their doctor, and then they're not inclined to kind of tell them what's really going on". However, HCPS8 felt that "people should be able to move around easier in their employment . . . the methodology is described and the pathway is there. So I wouldn't be too concerned about [staff rotating], I think it's a healthy thing". HCPS3 and HCPS9 both felt that an outreach service would address this inconsistency, "so they get picked up quickly and they're seeing a familiar face".

Participants reported that the relationship between the patient and their individual support systems were great facilitators to continuity of care. Participants described these systems as including family and friends, carers, and home help. HCPP6 noted that "The carers are usually very good . . . [patients] just want to get on with things and just somebody to look after them". Participants saw the carer as playing a prominent role in helping to manage medications, organise appointments, and to advocate for the patient post-stroke. Pharmacists saw carers as an important point of contact between them and the other members of the MDT. HCPO13 spoke of the importance of providing carers with exercises between blocks of care and "setting them up with [a handover], having the information concise for their carers or family that are continuing the patient's care when they go home".

4 Discussion

Several existing studies have examined the relationship between continuity of care and medication adherence in patients with chronic diseases (Kerse et al., 2004; Robles and Anderson, 2011; Chen et al., 2013). However, a majority of this research examines the relationship quantitatively (Warren et al., 2015; Dossa et al., 2017). Participants recognised the importance of continuous care for the patient post-discharge, and acknowledged the central role that this may play in medication non-adherence. However, it was observed that HCPs view medication adherence as a multifactorial issue, of which continuity of care is only one aspect. This reflects findings from qualitative studies of HCPs conducted by Kvarnström et al. (Kvarnström et al., 2018) and Jaam et al., (Jaam et al., 2018).

The factors influencing medication adherence as identified by participants in this study broadly correspond with the WHO's Multidimensional Adherence Model (AlGhurair et al., 2012). This ecological model considers intra- and interpersonal, systemic, regulatory, and community barriers to medication adherence (AlGhurair et al., 2012). The results of this study show that the boundaries between these influencing factors are not always clear. Often patient-related and illness- or condition-related factors were found to overlap, with broad terms such as "understanding" used in relation to both. This may reflect not only the complexity of influencing factors for medication adherence, but a lack of separation found between the patient and their condition (Karnilowicz, 2011). Stroke survivors often feel a loss of identity following their CVA, as stroke may impair not only their abilities, but their resources to scaffold their recovery. Healthcare providers highlighted a lack of patient desire to increase knowledge as a patient-related factor impacting medication adherence—however, linguistic, or cognitive deficits may be a barrier to the knowledge needed to understand their medication regimen properly. The unification of these factors may lead to inadequate interventions which do not fully address the root of the issue. A study by Alfian et al., 2020 found that sociodemographic and clinical factors were not associated with non-adherence to antihypertensive drugs, while higher necessity beliefs were associated with less non-adherence. Al-Lawati, 2014 showed that regular interactions between patients and their healthcare providers result in higher adherence rates for all patients. Therefore, patient education programmes designed to convey the importance of treatment may be highly effective, particularly when delivered routinely, and with consistency across members of the multidisciplinary team.

Patient education programmes tend to be more successful when the preventative counselling is interactive and the HCP has appropriate access to resources (e.g., time available to HCPs, suitable counselling materials, knowledge, and skills). This underscores the need for training for healthcare staff to ensure high-quality counselling and patients' adherence to secondary preventative behaviours (Oikarinen et al., 2017). HCPs involved in this study expressed a desire for this training to have an interprofessional focus, whether this be conducted during third-level education or continuous professional development. While participants in this study indicate a knowledge of the importance of consistent patient counselling and display a willingness to conduct these sessions, constraints on time, knowledge of interdisciplinary roles, and access to resources impede their ability to do so.

Participants have shown a desire for the appointment of a Stroke Key Worker, whose role would be to provide specific support and advice to stroke patients and their families, and to assist with the transition of care from hospital to home. The Irish National Stroke Strategy 2022–2027 (Health Service Executive, 2022) has outlined its intention to appoint one such Key Worker in each community

health organisation, with the role being piloted in a single site in 2023. While current research has shown the benefit of stroke co-ordinators (Fisher et al., 2021; Hitch et al., 2020; von Koch et al., 2000), future research should aim to evaluate the effectiveness of this role within an Irish context.

The Irish National Stroke Strategy also outlines its intent to increase ESD sites. HCPs in this study criticised the narrow inclusion criteria of these ESD services, which was highlighted in a recent Cochrane review that revealed a median of only 33% of patients met the inclusion criteria for ESD programmes (Langhorne et al., 2017). However, the Irish government aims to increase the number of ESD sites from the current nine to twenty-one by the end of 2025 (Health Service Executive, 2022). This increase in sites may allow the service to work under less narrow criteria. Participants in this study praised the ESD service for its contributions to continuity of care and patient re-integration in the community.

One benefit of ESD in comparison to usual stroke care is the inclusion of a well-defined team structure. Participants in this study reported difficulties in identifying, knowing the roles of, and establishing lines of communication with community HCPs. Pharmacists reported feeling more separated from other members of the MDT than SLT or OT. This aligns with findings from a study by Weiss et al., 2014 who found that 22% of Pharmacists did not consider themselves to be part of a multidisciplinary team. This same study found that only 1% of Pharmacists reported working with SLTs on a regular basis, while 3% of Pharmacists reported working with OTs on a regular basis. Regular communication and a positive working relationship with the multidisciplinary team are considered crucial for increasing medication adherence for those with chronic conditions (Herrerias et al., 2022).

Written communication was noted as an important method of communication between HCPs and patients in this study. The Irish National Stroke Strategy (Health Service Executive, 2022) proposes the introduction of a stroke passport, in addition to the current discharge report. This stroke passport will allow the patient to maintain accurate and timely records of their care and assistance throughout their rehabilitation. Participants report using similar, informal strategies in their current practice, however noted that current discharge reports are often not completed to the highest standard. It is fair to assume that the addition of a further discharge document will increase workload and therefore also may not be completed satisfactorily. Though the Health Research and Quality Authority (HIQA) have published a National Standard for Patient Discharge Summary Information (Health Research and Quality Authority, 2013), it was found in 2019 that the standard of discharge summaries from secondary care still fell short of accepted standards (O'Connor et al., 2019). Future research should examine whether the suggested interventions have been successful at improving discharge report standards and determine the persistent areas of concern in order to best facilitate informational continuity.

5 Limitations

A greater number of Pharmacists participated in the study than SLTs or OTs, which may have influenced the findings. However, this may simply be reflective of HCPs' views of the more prominent role that the Pharmacist plays in the management of medication adherence post-stroke. Similarly, thirteen of the fourteen participants in this study were female. However, this reflects the current gender imbalance among HCPs in Ireland, particularly in the fields of SLT and OT.

As participant recruitment was carried out through word-of-mouth, this may have introduced sampling bias by limiting the reach of the project. This may also have limited the diversity of the participant pool.

6 Conclusion

This study explored the knowledge, attitudes, and beliefs of HCPs regarding continuity of care post discharge from stroke wards in Ireland, and its impact on medication adherence post-stroke. HCP participants reported that additional resources must be provided in order to bring community healthcare to the same standard currently provided by acute care. Increased channels of communication must be established across contexts and disciplines. While suboptimal continuity of care was reported as contributing to medication non-adherence, HCPs also acknowledged the complexities of medication management for the patient post-stroke.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

SB: Data curation, Formal Analysis, Methodology, Writing–original draft, Writing–review and editing. HK: Supervision, Writing–review and editing. EH: Data curation, Formal Analysis, Methodology, Writing–review and editing. MB: Conceptualization, Writing–review and editing. JF: Conceptualization, Writing–review and editing. LS: Conceptualization, Supervision, Writing–review and editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1266277/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 11 December 2023
DOI 10.3389/fphar.2023.1285383

OPEN ACCESS

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RECEIVED 29 August 2023
ACCEPTED 20 November 2023
PUBLISHED 11 December 2023

CITATION
Sampogna G, Luciano M, Di Vincenzo M, Toni C, D'Ambrosio E, Rampino A, Rossi A, Rossi R, Amore M, Calcagno P, Siracusano A, Niolu C, Dell'Osso L, Carpita B, LIFESTYLE Working Group and Fiorillo A (2023), Physical activity influences adherence to pharmacological treatments in patients with severe mental disorders: results from the multicentric, randomized controlled LIFESTYLE trial.
Front. Pharmacol. 14:1285383
doi: 10.3389/fphar.2023.1285383

Physical activity influences adherence to pharmacological treatments in patients with severe mental disorders: results from the multicentric, randomized controlled LIFESTYLE trial

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Introduction: Poor adherence to pharmacological treatment is frequent in people with severe mental disorders and it often causes lack of effectiveness of many psychotropic drugs. Thus, efforts should be made to improve adherence to pharmacological treatments in patients with these disorders.

Methods: In this paper, based on the LIFESTYLE randomized, controlled multicentric trial, we aim to: 1) assess the level of adherence in a real-world sample of patients with severe mental disorders; 2) evaluate differences in treatment adherence according to patients' socio-demographic and clinical characteristics; 3) evaluate the impact of an innovative psychosocial intervention, on patients' adherence to treatments. The Lifestyle Psychosocial Group Intervention consists of group sessions, focused on different lifestyle behaviours, including healthy diet; physical activity; smoking habits; medication adherence; risky behaviours; and regular circadian rhythms. At end of each session a 20-min moderate physical activity is performed by the whole group.

Results: The sample consists of 402 patients, mainly female (57.1%, N = 229), with a mean age of 45.6 years (±11.8). Less than 40% of patients reported a good adherence to pharmacological treatments. Adherence to treatments was not influenced by gender, age, diagnosis and duration of illness. At the end of the intervention, patients receiving the experimental intervention reported a significant improvement in the levels of adherence to treatments (T0: 35.8% vs. T3: 47.6%, $p < 0.005$). Patients practicing moderate physical activity reported a two-point improvement in the levels of adherence [odds ratio (OR): 1,542; 95% confidence intervals (CI): 1,157–2,055; $p < 0.001$], even after controlling for several confounding factors.

Discussion: The experimental lifestyle intervention, which can be easily implemented in the routine clinical practice of mental health centres, was effective in improving adherence to pharmacological treatments.

KEYWORDS

adherence, physical activity, severe mental disorder, lifestyle, personalization

Background

Adherence to treatment or medication compliance, defined as intake of medications according to the prescribed dosage provided by referring clinician and with persistence over time (World Health Organization, 2003). A different concept is that of medication persistence, referring to the act of continuing the treatment for the prescribed duration (Cramer et al, 2008). Medication adherence is fundamental to prevent relapses, improve long-term clinical and functional outcome, and reduce healthcare costs in people suffering from chronic physical or mental disorders (Davidson and Tondora, 2022; McIntyre et al., 2022). People suffering from severe mental disorders often report non-adherence to prescribed medications, ranging from 28%–52% in people suffering from major depression to 70% in patients with schizophrenia (Baylé et al., 2015). About 40% of patients stop taking their medication within a year, and up to 75% up to 2 years (Semahegn et al., 2020). Poor adherence to pharmacological treatment is also common in people suffering from other chronic diseases, such as diabetes, cardiovascular diseases or chronic obstructive pulmonary disease (COPD) (Vetrano et al., 2017; Marrie and Bernstein et al., 2021), with approximately 50% of patients not taking properly the drugs prescribed for long-term therapies (Brown and Bussell, 2011; Kim et al., 2021; Fusar-Poli et al., 2022; Mirhaj Mohammadabadi et al., 2022; Ostuzzi et al., 2022).

Lack of adherence is one of the causes for low efficacy of many pharmacological treatments and should be carefully evaluated in clinical practice. In fact, the WHO has defined an "invisible epidemic" the poor or lack of adherence to treatments, which should be tackled with any possible effective initiative (WHO, 2003).

Nonadherence to pharmacological and non-pharmacological interventions is considered a multifactorial phenomenon, including causes related to the patient, the healthcare system and the clinician (Lam and Fresco, 2015; Caqueo-Urízar et al., 2021). Patients' adherence to medications is significantly reduced by lack of insight (Novick et al., 2015), negative beliefs about the efficacy of the medications, concerns about side effects, costs of medications, low educational level, and belonging to ethnic minority (Lemay et al., 2018). In particular, several studies have highlighted that lower insight is associated with lower adherence and a worse therapeutic relationship (Novick et al., 2015; Elowe et al., 2022; Okobi et al., 2022). Healthcare system factors mainly include polypharmacy (particularly in older adults) and care fragmentation provided by different healthcare professionals (Aggarwal et al., 2020). Clinician-related factors include excessive workload, lack of time for patient's education about treatments, poor adoption of the shared decision-making approach (Dell'Osso et al., 2020; Caqueo-Urízar et al., 2021). Because these factors usually interact and potentiate each other, multilevel and integrated strategies are required to efficiently address poor adherence to medications.

Available interventions for improving treatment adherence have been grouped into four categories: educational, behavioural, cognitive-behavioural, and multicomponent approaches (Torres-Robles et al., 2018; Cuijpers et al., 2021; Leichsenring et al., 2022). The most frequently adopted interventions are psychoeducation (Killaspy et al., 2022; Harmancı and Yıldız, 2023), problem-solving strategies (Chatoo and Lee, 2022), and programmes aiming to promote the adoption of a shared decision-making clinical style (Fiorillo et al., 2020; Fulford and Handa, 2021; Roe et al., 2022). Despite this, adherence rates to treatments remain incredibly low, highlighting the need to develop and implement innovative and effective strategies. One of these innovative strategies is represented by the promotion of healthy lifestyle behaviours, including regular physical activity. A recent study carried out in a cardiology unit involving patients suffering from hypertension has shown the positive effect of regular physical activity on adherence to medications (Fragoulis et al., 2023) after a behavioral activation intervention. Thus, the authors concluded that there is the need for innovative research in this field for further confirmation of the positive relationship between treatments' adherence and physical activity. Indeed, physical activity defined as any planned, systematic, and repetitive physical exercise that enhances athletic performance by improving body composition, fitness, and motor abilities (Mahindru et al., 2023), is considered a complementary treatment modality in the management and control of non-communicable diseases, including severe mental disorders, and is associated with the reduction of cardiovascular risk, morbidity and mortality (Theofilou and Saborit, 2013; Saqib et al., 2020; Arango et al., 2021; Baron and Noordsy, 2021; Suokas et al., 2022). People with severe mental disorders too often have a sedentary lifestyle and do not perform any kind of physical activity (Sampogna et al., 2022a; Sampogna et al., 2022b; Correll et al., 2022; Højlund et al., 2022). Several psychosocial interventions with a specific focus on physical activity and other healthy lifestyle behaviours—such as quit smoking and balanced diet—have been recently developed for people with severe mental disorders (Masa-Font et al., 2015; Speyer et al., 2016; De Rosa et al., 2017; Swift et al., 2021). These interventions showed promising results in terms of reduction of the long-term morbidity and mortality, but a few data are available on their efficacy on adherence to treatments. Indeed, an emerging body of research has linked both the onset and symptoms of various mental disorders to "lifestyle factors", a term referring to health behaviors such as physical activity, diet, tobacco smoking and sleep and therefore the innovative field of lifestyle psychiatry is nowadays very active and expanding quickly (Firth et al., 2020).

The present research project entitled "LIFESTYLE trial" is a multicentric, randomized controlled study aiming to test the efficacy of an innovative psychosocial intervention on several lifestyle behavioural domains (Sampogna et al., 2018). This paper aims to: 1) assess the level of adherence in a real-world sample of patients with severe mental disorders; 2) evaluate differences in

adherence to pharmacological treatments according to patients' socio-demographic and clinical characteristics; 3) evaluate the impact of an innovative psychosocial intervention on patients' adherence to treatments.

Methods

The LIFESTYLE trial was coordinated by the University of Campania "Luigi Vanvitelli" in Naples and carried out in the mental health units of the Universities of Bari, Genova, L'Aquila, Pisa, and Rome-Tor Vergata (Sampogna et al., 2018; Luciano et al., 2022).

The full methodology of the study is available in Sampogna et al. (2018). Patients were included if they met the following criteria: 1) age between 18 and 65 years; 2) diagnosis of schizophrenia, schizoaffective disorder, delusional disorder, other psychotic disorder, major depressive disorder, or bipolar disorder, according to the DSM-5 criteria and confirmed by the Structured Clinical Interview for DSM-5 (SCID-5); 3) ability to provide written informed consent; 4) BMI ≥ 25; 5) in charge at the local mental health unit for at least 3 months before recruitment. Exclusion criteria were: inability to perform moderate physical activity (i.e., walking at least 150 min per week, or 75 min of vigorous activity twice a week, according to the guidelines of the Italian Ministry of Health); pregnancy or breast-feeding; intellectual disability or severe cognitive impairment; hospital admission in the previous 3 months.

The main outcome measure considered for the present analyses is a change of global score at the Morisky Medication Adherence Scale (MMAS) (Morisky et al., 1986), which evaluates the levels of adherence to pharmacological treatments. The MMAS-4 uses a scoring scheme of "Yes" = 0 and "No" = 1. Therefore, the items were summed up to obtain scores ranging from 0 to 4 (e.g., a score of 0 was considered poor; while a score of 4 was considered complete adherence).

Besides the MMAS, all recruited patients were assessed through the following tests: a) the International Physical Activity Questionnaire (IPAQ)—short form (Craig et al., 2003); b) the Food Frequency Questionnaire—short version (Marventano et al., 2016); c) the 24-item Questionnaire on lifestyle behaviours, developed by the Italian National Institute of Health (ISS, 2010); d) the Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al., 1991); e) the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989); f) the Leeds Dependence Questionnaire (LDQ) (Raistrick et al., 1994); g) the Recovery Style Questionnaire (RSQ) (Drayton et al., 1998); h) the Cumulative Illness Rating Scale (CIRS) (Linn et al., 1968); i) the Manchester Short Assessment of Quality of Life (Priebe et al., 1999); j) the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB)—brief version (Kern et al., 2008); k) the Internalized Stigma of Mental Illness (ISMI) (Ritsher et al., 2003); l) an *ad hoc* questionnaire on sexual health; m) the Pattern of Care Schedule (PCS)—modified version (Morosini et al., 2000); n) the 24-item Brief Psychiatric Rating Scale (BPRS) (Lukoff et al., 1986); o) the Personal and Social Performance Scale (Morosini et al., 2000).

Information on weight, height, BMI, waist circumference, blood pressure, resting heart rate, HDL, LDL and overall levels of cholesterol, blood glucose, triglycerides, and blood insulin were collected by researchers with an Anthropometric schedule.

All patients have been assessed at the baseline (T0); 2 months post-randomization (T1); 4 months post-randomization (T2); 6 months post-randomization (T3); 12 months post-randomization (T4); and 24 months post-randomization (T5). T1 and T2 assessments include only anthropometric tests. For the scope of the present study, only data collected at baseline and 6 monts post-randomization have been considered.

Patients were randomly allocated to receive the Lifestyle Psychosocial Group Intervention (experimental group) or a Brief Psychoeducational Group Intervention (control group).

The Lifestyle Psychosocial Group Intervention consists of group sessions, delivered every 7–10 days for about 6 months, focused on different lifestyle behaviours, including healthy diet; physical activity; smoking habits; medication adherence; risky behaviours; and regular circadian rhythms. At end of each session a 20-min moderate physical activity is performed by the whole group.

The control Brief Psychoeducational Group Intervention consists of group sessions, delivered every 7 days for about 2 months and focusing on healthy lifestyle; early detection of clinical relapses; effects of pharmacological treatment and management of side effects; stress management techniques; and problem-solving techniques. The interventions were delivered by trained psychiatrists, attending an *ad hoc* brief course on the main characteristics of the interventions. All characteristics of the two interventions are reported in Sampogna et al. (2018).

This study was conducted in accordance with globally accepted standards of good practice, in agreement with the Declaration of Helsinki and with local regulations. The study protocol was formally approved by the Ethics Committee of the Coordinating Center in January 2017 (approval number: 64). Trial registration number is 2015C7374S.

Statistical analyses

Statistical analyses were conducted according to the "Intention To Treat" principle. Missing data were handled using the Last Observation Carried Forward. Descriptive statistics and frequency tables were used to assess patients' socio-demographic and clinical characteristics. Chi-square with multiple comparisons and ANOVA with Bonferroni corrections were adopted to detect differences in the levels of adherence to treatments. Bivariate analyses were performed in order to evaluate the association between levels of adherence and severity of clinical symptoms. Descriptive statistics (frequency table, means and standard deviation) were calculated for both experimental and control groups at baseline and at the end of the intervention. Differences in sociodemographic and clinical characteristics among the two groups at baseline and at the end of the intervention were tested using χ^2 or t-test for independent samples, as appropriate.

Generalized estimating equation (GEE) models were used for evaluating the impact of the experimental intervention on the primary outcome. GEE models allow estimation of population-averaged models in repeated-measures data. Control vs. intervention interaction terms assessed changes between groups over time; Wald tests determined whether joint effects of time-by-group equalled zero. Age and center were included as time-invariant covariates; time-varying covariates included medications,

TABLE 1 Patients' socio-demographic and clinical characteristics.

	Global sample (N = 401)	Experimental group (N = 206)	Control Group (N = 195)
Gender, female, % (N)	57 (227)	55.3 (114)	59.0 (115)
Age, M (sd)	45.8 (11.8)	45.9 (11.6)	45.3 (12.1)
Living situation, % (N)	71.4 (287)	26.3 (54)	31.3 (61)
Single			
Married/with partner	28.6 (115)		
Years of education, M (sd)	11.7 (2.9)	11.8 (2.7)	11.5 (2.9)
Employed, yes, % (N)	35.7 (143)	37.6 (77)	33.8 (66)
Diagnosis, % (N)	43.3 (174)	43.2 (89)	43.6 (85)
Bipolar disorder			
Schizophrenia and other psychotic disorders	29.6 (120)	32.0 (66)	27.2 (53)
Major Depression	27.1 (108)	24.8 (51)	29.2 (57)
Years in charge to the mental health service, M (sd)	5.9 (6.9)	6.6 (8.1)	7.4 (8.3)
Duration of illness, M (sd)	15.6 (11.3)	16.2 (11.7)	16.4 (22.3)
Number of hospitalizations, M (sd)	2.8 (5.1)	2.1 (4.1)	2.4 (4.3)
Suicide attempts, M (sd)	1.8 (1.6)	1.7 (3.1)	1.8 (3.0)
BPRS, Positive symptoms, M (sd)	5.4 (2.1)	5.5 (3.1)	5.3 (2.1)
BPRS, Negative symptoms, M (sd)	7.7 (3.1)	7.7 (3.0)	7.6 (2.9)
BPRS, Depressive/anxiety symptoms, M (sd)	8.8 (3.1)	8.6 (3.0)	8.7 (3.1)
BPRS, Manic/hostility symptoms, M (sd)	4.7 (1.9)	4.7 (1.9)	4.7 (1.9)
MANSA, Total score, M (sd)	4.1 (1.0)	4.0 (1.1)	4.2 (1.0)
MMAS, total score, M (sd)	1.06 (1.1)	1.1 (1.2)	1.2 (1.1)
B-MCCB, Symbol coding, M (sd)	36.9 (50.3)	34.5 (14.1)	39.4 (70.5)
B-MCCB, Animal naming, M (sd)	20.3 (49.3)	18.2 (51.7)	22.5 (70.4)
B-MCCB Trial making test A, M (sd)	69.1 (127.9)	69.1 (127.9)	69.1 (127.9)
PSP, Total score, M (sd)	65.5 (15.1)	64.5 (14.1)	65.5 (16.2)
Typical Antipsychotics, yes % (N)	22.5 (90)	22.3 (46)	20 (39)
Atypical Antipsychotics, yes % (N)	59 (236)	61.7 (127)	57.4 (112)
First generation antidepressants, yes % (N)	5.7 (23)	6.3 (13)	5.1 (10)
Second generation antidepressants, yes, % (N)	51.5 (205)	45.6 (94)	47.2 (92)
Benzodiazepine, yes % (N)	47.1 (189)	47.1 (97)	46.2 (90)
Mood stabilizers, yes %(N)	65.8 (264)	55.3 (114)	54.4 (103)

cognitive functioning, age, gender, and diagnosis of mental disorder. GEE models with a normal distribution and identity link were used. Covariate-adjusted results using robust estimates of standard errors are reported. All models were adjusted for diagnosis, pharmacological treatments, duration of illness, and educational level. Pharmacological treatments (i.e., mood stabilizers, tricyclic antidepressants, new-generation antidepressants, first- and second-generation antipsychotics) and psychiatric diagnoses (i.e., depressive disorder, bipolar disorders, psychosis) were included in the regression models as dummy variables.

The level of statistical significance was set at $p < 0.05$ and statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 26.0, and STATA, version 15.

Results

The sample consists of 401 patients, with a mean age of 45.6 years (±11.8), mainly female (57%, N = 227), single (71.4%, N = 287), and unemployed (64.3%, N = 258). The mean duration of illness was 16.3 (±17.8) years, with a median value of 15 years, Inter Quartile Range, INR: 6;23; patients were in charge at the local mental health centre for 5.9 (±6.9) years, with a median value of 3 years (IQR: 1; 9), with a diagnosis of bipolar disorder (43.4%; N = 174), psychotic spectrum disorders (29.6%; N = 120) and major depressive disorder (27.1%; N = 108) (Table 1).

The levels of anxiety/depressive symptoms were moderate (8.8 ± 3.1) as well as the level of personal functioning (65.5 ± 15.1 at the PSP scale). All patients were receiving a pharmacological drug treatment;

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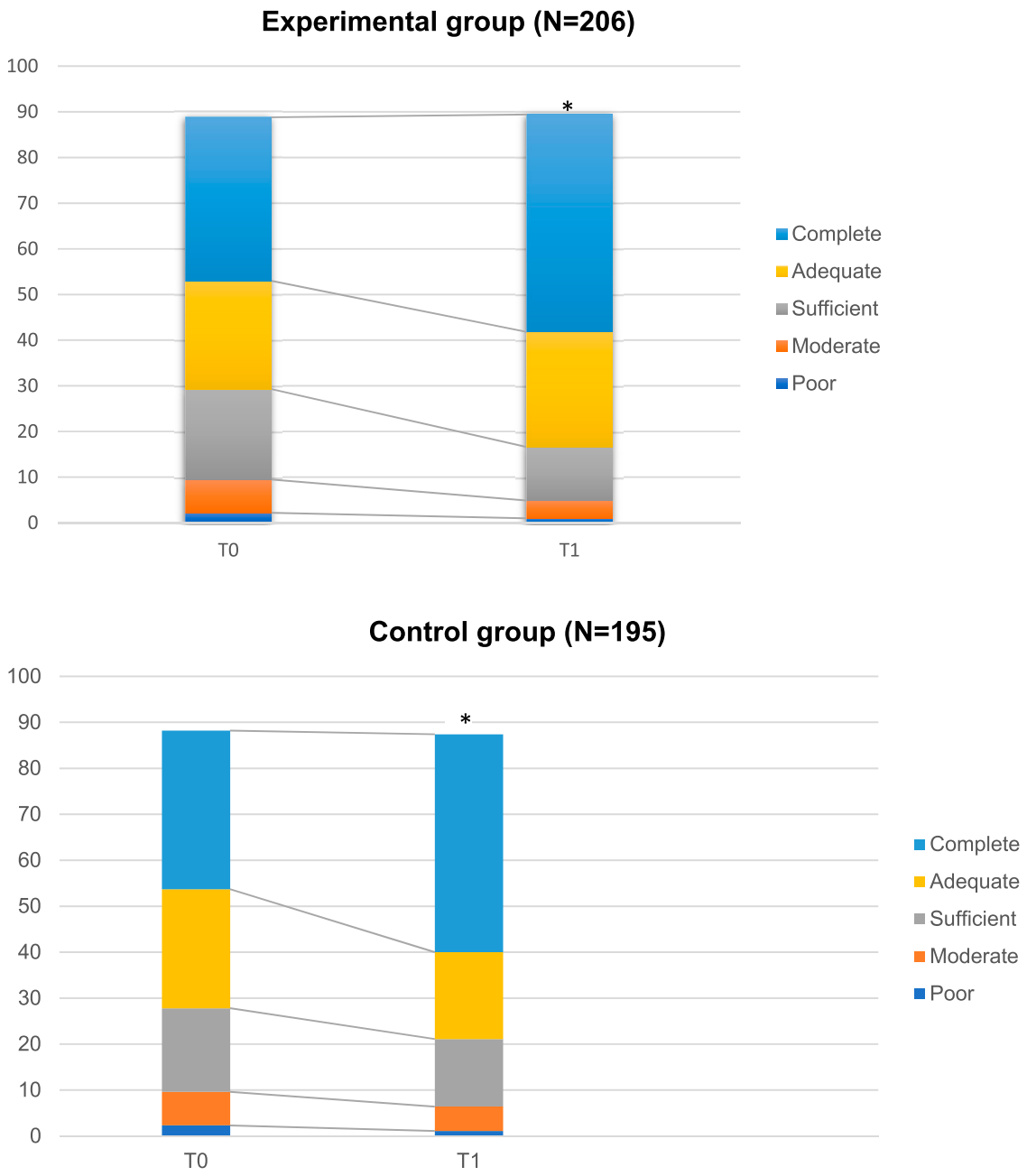

FIGURE 1
Levels of adherence to pharmacological treatments in the study sample. The weight of the different bars corresponds to the frequency of responses in the different categories of adherence, as evaluated at the Morisky scale. In particular, poor category indicates a condition where all items were scored as "yes", while "complete adherence", indicates a condition where all items were scored as "no" *$p < 0.005$.

in particular, 59% (N = 236) were treated with a second-generation antipsychotic and 65.8% (N = 264) with a mood stabilizer.

39.8% of patients reported a good adherence to the prescribed pharmacological treatments (Figure 1). At bivariate analyses, age, gender, duration of illness and type of the disorder did not influence patients' adherence to medications. A significant inverse correlation was found between adherence and quality of life (Rho di Person: −0.140, p <.005).

The majority of patients were obese (63.1%, N = 253), with a mean BMI of 32.2 (0.2); 53.4% of them were suffering from the metabolic syndrome. All metabolic parameters have been reported in Table 2. Although 29.4% of patients (N = 118) declared to perform physical activity, only 16.1% were found to be very physically active at the IPAQ scale. The most frequently practiced sport activities were walking (52.1%, N = 62), going to the gym (21.8%, N = 26) and playing football (7.5%, N = 9).

TABLE 2 Metabolic parameters.

	Global sample	Baseline				End of intervention			
		Experimental		Control		Experimental		Control	
Abd. Circum., M (SD)	108.3 (0.5)	108.64	14.370	109.8	13.65	107.8	12.79	109.5	13.97
BMI, M (SD)	**32.2 (0.2)**	**32.2**	**0.36**	**32.9**	**0.41**	**31.60**	**0.46**	**32.83**	**0.67**
Glycemia, M (SD)	94.5 (1.1)	95.32	20.90	95.56	32.30	96.04	25.93	99.13	42.21
Insuline levels, M (SD)	16.76 (0.7)	16.90	19.32	17.78	17.2	16.45	16.63	23.82	30.77
Trygliceric levels, M (SD)	165.6 (5.0)	180.86	159.16	161.0	87.72	172.7	129.9	154.4	81.18
Colesterol levels, M (SD)	190.5 (1.7)	192.7	42.0	186.86	39.62	188.2	36.00	187.3	41.90
LDL levels, M (SD)	121.2 (1.9)	120.98	36,095	117.4	33.68	126.8	101.9	121.4	41.15
HDL levels, M (SD)	46.4 (0.5)	46.16	14.55	45.87	14.74	46.46	14.17	46.11	14.98
Systolic pressure, M (SD)	124.7 (0.5)	125.58	13,638	125.6	13.4	124.2	11.79	124.7	11.93
Dyastolic pressure, M (SD)	80.1 (0.3)	81.14	9,329	80.34	8.60	79.9	7,472	78.8	11.59
Inactive <700 MET	56.7	55.9		58.2		50.6		54.7	
Active 701-2519 MET	27.2	29.1		24.7		29.9		28.4	
Very active > 2520 MET	16.0	15.1		17.1		19.5		16.8	

Bold characters indicate significant differences ($p < 0.05$).

34.5% of patients (N = 138) reported a frequent use of alcohol; 41% of them (N = 163) declared to smoking and 36.3% of them never tried to quit smoking.

There were no significant differences between the experimental (N = 206) and the control (N = 195) groups in any of the considered domains. Further data are available in Supplementary Table S1.

Longitudinal evaluation of levels of physical activity and adherence to treatments

Hundred and three patients from the experimental group and 95 patients from the control group were re-assessed at 6 months, with an attrition rate of 49.4%. Drop-outs were due to lack of time, reduced interest in the intervention, other personal commitments, and clinical relapses.

At 6 months, the levels of adherence to pharmacological treatment changed from 35.8% at baseline to 47.6% at the end of the intervention (p <.005) in the experimental group, while the levels of physical activity did not change between baseline (T0: 6.3%) and 6- month (T1: 9.7%), although a reduction of BMI, weight and other metabolic parameters was found.

The GEE model showed a significant effect of physical activity on adherence to treatments. In particular, at the end of the intervention, patients performing moderate physical activity reported a two-point improvement of adherence to pharmacological treatments (odds ratio [OR]: 1,542; 95% confidence intervals [CI]: 1,157–2,055; $p < 0.001$). Other factors positively influencing adherence were having a diagnosis of major depression ($p < 0.001$), a better cognitive functioning ($p < 0.001$) and quality of life ($p < 0.05$), a shorter duration of illness ($p < 0.001$) and time in contact with the local mental health centre ($p < 0.001$). Surprisingly, treatment adherence was not influenced by symptom severity and type of pharmacological treatment (Table 3).

Discussion

Patients' adherence to treatments is a complex phenomenon posing a significant burden on health professionals, users and carers, and on the healthcare system in general (Atreja et al., 2005).

Lack of adherence is associated with negative consequences on patients' outcomes, including lack of efficacy of treatments, poor clinical outcome, and worsening of patient health status. This clinical worsening usually requires the subsequent prescription of more drugs, increasing dosages of current drugs, cross-titration of more drugs and other add-on or replacement strategies, which can lead to increased healthcare costs, more frequent consultations, higher rates of emergency services and of hospitalization rates (Semahegn et al., 2020; Gosh et al., 2022; McCutcheon et al., 2022).

Several strategies have been developed in recent years to enhance patient adherence, although the target of "complete adherence" to treatments has not been reached yet (Loots et al., 2021).

In our study on real-world patients suffering from severe mental disorders, 40% of participants reported a good adherence to pharmacological treatments. This finding is slightly lower compared to that reported by the WHO in developed countries, who found that "adherence among patients suffering from chronic diseases averages 50%" (WHO, 2003). However, both our and WHO findings highlight the need to improve medication adherence among patients with chronic physical and mental illnesses (Fernandez-Lazaro et al., 2019; Laranjeira et al., 2023). The lower adherence rates found in people with severe mental disorders compared to those reported by people suffering from other chronic conditions can be due to the presence of specific symptoms, such as cognitive impairment in schizophrenia (El-Missiry et al., 2015; Mendes et al., 2019; Senner et al., 2023); inflated mood in bipolar disorder or hopelessness in major depressive disorder (Chauhan et al., 2021). Indeed, in our sample having a psychiatric diagnosis of schizophrenia and/or bipolar disorder did not influence

TABLE 3 GEE model for adherence to treatments.

	Sign	OR	95% confidence interval	
			Lower bound	Upper bound
Experimental treatment	**0.008**	**1.035**	**0.870**	**1.232**
Moderate Physical activity	**0.003**	**1.542**	**1.157**	**2.055**
Gender, ref. female	0.529	0.958	0.838	1.095
Diagnosis, ref. bipolar		1		
Psychosis spectrum	0.867	0.988	0.859	1.136
Depression	**<0.001**	**1.426**	**1.188**	**1.712**
Patient's age	0.551	0.997	0.987	1.007
brief assessment of cognition	0.039	0.998	0.997	1.000
Category fluency: animal naming	**<0.001**	**1.001**	**1.001**	**1.001**
Trail making test	0.691	1.000	0.999	1.002
Personal functioning	0.625	1.000	0.999	1.001
Typical antipsychotic	0.669	0.973	0.860	1.102
Atypical antipsychotic	0.524	0.893	0.629	1.266
Mood stabilizer	0.749	0.968	0.793	1.182
Tryciclic antidepressant	**0.036**	**0.703**	**0.506**	**0.978**
II generation antidepressant	0.189	0.920	0.811	1.042
BPRS global score	0.008	1.137	1.033	1.251
Comorbidity index_CIRS	0.005	0.925	0.875	0.977
Quality of life	**<0.001**	**0.898**	**0.858**	**0.940**
Sleep disturbances	0.431	1.010	0.986	1.034
Duration of the illness	**0.042**	**0.997**	**0.994**	**1.000**
Time in charge to the mental health service	**0.045**	**0.999**	**0.998**	**1.000**
Number of voluntary admissions	**0.479**	**0.993**	**0.974**	**1.012**
Number of involuntary admissions	**0.011**	**0.962**	**0.933**	**0.991**
Intercept	0.020	2.893	1.185	7.064

Bold characters indicate significant variables associated with the outcome measure considered.

patients' adherence to treatments, which is partially in line with findings from Ghosh et al. (2022). This would imply that all psychiatric symptoms have the same weight on adherence rates, and that other causes common to all mental disorders can play a role, such as stigma, prejudices and misconceptions against psychiatric treatments (Kamaradova et al., 2016). Informative campaigns should be carried out at the population level in order to reduce such misconceptions, helping people who take these medications not to feel stigmatized (Corrigan, 2022; Sum et al., 2022).

No significant association was found between illness severity and medication non-adherence. However, lack or poor adherence to medications usually worsens illness severity which, in turn, reduces insight into the illness and has significant adverse clinical outcomes (Wu and Moser, 2018).

Moreover, several socio-demographic variables, including patient's age and gender, as well as levels of personal functioning and presence of any physical comorbidities did not have any specific impact in modifying the levels of medication adherence. In particular, studies evaluating gender-based difference in medication adherence have highlighted that women are consistently less likely than men to be adherent with their diabetes and cardiovascular medications (Venditti et al., 2023). Some authors argued that this difference may be explained by the fact that women experience more drug side effects than men, while others pointed out that differences in medication adherence are largely due to the type of disorders considered. It should be that the core psychopathological features of different mental disorders play a crucial role in modifying medication adherence, more than socio-demographic features (Semahegn et al., 2020).

At the end of the psychosocial intervention, patients showing a significant improvement in treatments' adherence also reported increased moderate physical activity. This association can be explained considering the multiple components of our experimental

intervention, that include specific sessions dedicated to treatment adherence and to physical activity, with a synergic positive effect of both sessions. Several studies showed that patient's knowledge about treatments is the strongest predictor of adherence (Jankowska-Polańska et al., 2016; López-Pintor et al., 2021; Kanyongo and Ezugwu, 2023), particularly in patients with severe mental disorders, who can have more difficulties than other patients in understanding the need for taking pharmacological drugs. It can be that the improved adherence found in our sample at the end of the intervention is due to the inclusion of psychoeducational components, motivational interview and cognitive-behavioral techniques (Vieta, 2005; Depp et al., 2008; Okazaki et al., 2023). However, this finding deserves confirmation in long-term studies with larger samples.

The positive association between improved adherence and higher levels of moderate physical activity highlights that physical activity improves global health and functional status. Moreover, it also shows that exercise/physical activity training shall be included in the multilevel personalized treatment for people with severe mental disorders, as already happens in other chronic conditions, such as cardiovascular disease and diabetes mellitus. As recently pointed out by the European Association for Sport and Mental Health (EASMH), the dissemination of sport-based psychosocial interventions for people with severe mental disorders in routine clinical practice is still very low, although considerable evidence is accumulating regarding their efficacy (Sampogna et al., 2022c).

The present study has some limitations, which should be acknowledged. First, the inclusion of patients in a stable phase of the disorder might have biased the results, since they may not be the patients usually seen in routine clinical practice. However, this potential bias has been managed by adopting the GEE model for evaluating the effect of the interventions on the primary outcome (i.e., medication adherence); moreover, all statistical analyses have been controlled for confounding variables, such as type of pharmacological treatment and severity of clinical symptoms. Second, adherence to pharmacological treatments has been evaluated only through a self-reported questionnaire, without other objective measures, which might have led to a potential recall bias. However, introducing more sophisticated biological and clinical evaluations might have hampered the conduction of the study, also because the experimental intervention was developed with the aim to be easily used in routine clinical practice, without a sophisticated training for mental health professionals and high costs. A final limitation is the high drop-out of almost 50%. Reasons for such a high attrition rate vary including the duration of the interventions (which are considered too long by many patients), too structured and manualized approaches (which are considered difficult to follow by many patients), difficulties to travel to the place where the intervention is provided or clinical relapses. In particular, the high attrition should have biased towards those patients more prone to follow recommendations regarding medications as well as practicing physical activity. However, the attrition rate found in our study is similar to that found in other studies on psychosocial interventions. Moreover, the sample size was adequate according to the power analysis, which supports the evidence that the moderate physical activity can improve the levels of adherence.

Thus, future approaches should consider to have a lower total number of sessions, a less structured approach, and the inclusion of online sessions to reduce the need to travel biweekly.

Conclusion

The poor rate of adherence to treatment reported by patients affected from chronic mental and physical disorders is considered by the WHO an "invisible epidemic". Poor adherence to treatments is one of the most important—yet modifiable—causes of low efficacy of medications, treatment failure, re-hospitalization, delayed remission and recovery. Therefore, the identification of innovative, multilevel, integrated strategies is essential for overcoming this public health emergency (Kestel, 2022). The promotion of moderate physical activity, which was integrated in our experimental intervention, can represent a valid approach to improve treatment adherence in patients with severe mental disorders. Physical activity exercises, which can be easily implemented in routine clinical practice, are associated with improved outcome. Further studies are needed in larger samples and in acutely severe patients with mental disorders.

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Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethical review Board University of Campania Vanvitelli. The studies were conducted in accordance with the local legislation and institutional

requirements. The participants provided their written informed consent to participate in this study.

Author contributions

GS: Conceptualization, Formal Analysis, Methodology, Writing–original draft. ML: Writing–review and editing. MDV: Data curation, Writing–review and editing. CT: Methodology, Writing–review and editing. ED: Writing–review and editing, Validation. AnR: Investigation, Writing–review and editing. AlR: Writing–review and editing. RR: Writing–review and editing. MA: Writing–review and editing. PC: Writing–review and editing. AS: Writing–review and editing. CN: Writing–review and editing. LD: Writing–review and editing. BC: Writing–review and editing. LG: Writing–review and editing. AF: Writing–review and editing, Conceptualization, Investigation, Writing–original draft.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1285383/full#supplementary-material

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frontiers | Frontiers in Public Health

TYPE Brief Research Report
PUBLISHED 11 January 2024
DOI 10.3389/fpubh.2023.1296073

OPEN ACCESS

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RECEIVED 03 October 2023
ACCEPTED 29 December 2023
PUBLISHED 11 January 2024

CITATION
Sakai C, Iguchi K, Tachi T, Noguchi Y, Hisamatsu A, Katsuno S and Teramachi H (2024) Effectiveness of distributing pocket cards in improving the behavior, attitude, and knowledge regarding proper medication use among junior high school students in Japan.
Front. Public Health 11:1296073.
doi: 10.3389/fpubh.2023.1296073

Effectiveness of distributing pocket cards in improving the behavior, attitude, and knowledge regarding proper medication use among junior high school students in Japan

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Objective: This study aimed to explore the effectiveness of distributing pocket cards with summaries of key information on appropriate medication usage after the implementation of a structured school-based medication education program for junior high school students in Japan.

Methods: A total of 227 3rd-grade high school students participated in the intervention. Students who received the program without the provision of pocket cards in 2022 were included in the comparison group, and students who took the program with the provision of pocket cards in 2023 were included in the intervention group. After propensity score matching, the final sample of $N = 116$ comprised $n = 58$ comparison group participants and $n = 58$ intervention group participants. Questionnaires were administered at baseline, end-of-class, and 3-month follow-up to assess the changes in behavior, attitude, and knowledge scores.

Results: The matched intervention group showed significantly lower scores at the 3-month follow-up than the matched comparison group. The results of the multiple linear regression analysis showed that for both groups, only the attitude scores were significantly correlated with the behavior scores. In addition, regardless of the baseline scores, the matched intervention group demonstrated smaller or negative changes in scores at the 3-month follow-up.

Conclusion: Overall, the results of this study did not support the effectiveness of distributing pocket cards after in-class intervention. However, the usefulness of medication education intervention was confirmed. These results emphasize the need to explore other supplemental teaching tools to further enhance the impact of structured medication education programs.

KEYWORDS

self-medication, education, junior high school, school-based intervention, Japan

1 Introduction

According to the World Health Organization, self-medication, as an element of self-care, is defined as "the selection and use of medicines (including herbal and traditional products) by individuals to treat self-recognized illnesses or symptoms" (1). In recent years, medication literacy has gained global attention as a key factor in proper medication use-associated behavior (2, 3). For example, among adolescents, junior high school students with lower medication literacy are significantly more likely to engage in inappropriate self-medication practices (4). In addition, lower medication literacy has been associated with longer-term usage of medications such as painkillers and antacids (5).

Previous studies have shown that adolescents begin to self-administer medications at junior high school age. For instance, in a survey conducted in Canada, 75.9% of 651 junior high school students (including students from the 7th, 8th, and 9th grades) reported that they had taken medication independently (6). In Japan, among 348 3rd-graders from five public junior high schools, 32.3% of the male and 33.7% of the female students reported that they had taken medication without speaking to an adult, and the rates increased to 37.1 and 42.2% for the male and female students, respectively, of a total of 1,420 first-graders at seven public high schools (7). Therefore, improving the medication literacy is necessary, particularly among adolescents.

In Japan, which is one of the world's oldest societies, a variety of national-level cost-containment measures have been implemented in response to the increase in national medical expenses. One of the primary measures is the promotion of self-medication. Specifically, the government introduced a new over-the-counter medication retail system and self-medication tax deduction in 2006 and 2017, respectively, to advance the use of over-the-counter medications for non-severe symptoms with the intention of reducing patients' hospital visits (8, 9). In response to the need for acquiring the knowledge and skills to administer safe self-medication because of the expanding use of over-the-counter medication, Japan's Ministry of Education, Culture, Sports, Science and Technology revised the national education guidelines for junior high school and high school students, adding new content to teach the proper use of medicines in the health and physical education fields (10). In accordance with the revision of the national education guidelines, all junior high school students aged 14 or 15 and all high school students aged 17 or 18 were required to acquire basic knowledge of medication and self-medication, including the role of medication in treatment, dose–response relationship, and importance of following drug fact labels.

Considering all these contexts, the authors of this study conducted multiple surveys using both regional- and national-level samples to collect information on the behavior, attitude, and knowledge regarding medication use among elementary, junior high, and high school students in Japan (11, 12). Based on the results of these studies, the authors developed a structured school-based medication education program aimed at promoting students' behavioral and attitudinal changes as well as improving their basic medication literacy in collaboration with physical education teachers and school nurses (13). However, the results of a large-scale cross-sectional study conducted by the authors revealed the possibility of insufficient effectiveness of classes provided at schools attended by survey participants (14). Another study conducted by the authors, in which Bayesian network analysis for causal inference was adopted, suggested that an improvement in knowledge of appropriate medicine use might lead to the acquisition of favorable attitudes, which could result in positive behavioral changes (14).

Based on the findings of the previous studies (11, 13), the authors developed a school-based medication education program for junior high school students. The program has been provided to junior high school students, and its effectiveness in changing participant behaviors, attitudes, and knowledge has been confirmed (15). Therefore, the present study examined whether distributing pocket cards with basic information on proper medication use after carrying out a medication education program would further promote behavioral and attitudinal changes and knowledge acquisition. To investigate this, the authors compared a group of students who were provided only the program with another group of students who were provided both the program and pocket cards.

The present study examined the following three hypotheses:

> *H1*: Compared to the students not provided with pocket cards, the students provided with pocket cards show higher behavior, attitude, terminology, and understanding scores at the 3-month follow-up.
>
> *H2*: The effect of scores on terminology and understanding on the behavior score at the 3-month follow-up is greater among the students provided with pocket cards than among the students not provided with pocket cards.
>
> *H3*: Regardless of the behavior, attitude, terminology, and understanding scores at baseline, the students provided with pocket cards show a greater increase in scores at the 3-month follow-up than those of the students not provided with pocket cards.

2 Methods

2.1 Participants and setting

The 50-min medication education program developed by the authors was delivered to all 3rd-grade students aged 14 or 15 in a public junior high school in Seki City in 2022 and 2023. The pocket cards with the key points of the program were provided to the students who received the program in 2023, and they were asked to carry the cards with them. The group of students who received the program in 2022 without pocket card provision was enrolled as the comparison group, whereas the group of students who received the program in 2023 with pocket card provision was enrolled as the intervention group.

The contents of the program were structured to align with the Course of Study for Junior High School Students (10), and the following contents were taught in the class: the role of natural healing power and medication; classification of medication, including the difference between prescribed and over-the-counter medication; rules for medication use, including dosage and administration; how to read labels of over-the-counter medication; dose–response relationship and mechanism of how medications work in the body. To facilitate students' understanding, a variety of visual materials and experimental demonstrations were presented in class.

To evaluate the changes in students' behavior, attitude, and knowledge, three types of in-person anonymous surveys were administered by homeroom teachers in classrooms to all the participants who were included in the program. The surveys were conducted at baseline, end-of-class, and 3-month follow-up. In total, 114 and 94 students responded to the surveys in 2022 and 2023, respectively, among which the numbers of valid responses were 113 and 94 (99.1 and 100.0%), respectively.

2.2 Instruments

The questions asked in the survey had been used in our previous studies (11, 12, 14) and had been assessed by school teachers to determine whether the terms used were understandable enough for junior high school students. The term "medication" was clearly defined and indicated at the beginning of the survey as follows: "Please tell me what you think about medication. 'Medication' used in this questionnaire refers to the medication you are given at the hospital or buy at a community pharmacy or a drug store. It includes not only medication for internal use but also compresses, external medicines, and disinfectants used for injuries and other occasions. It also includes household medication, eye drops, troches, and inhalants. However, it does not include nutritional supplements or energy drinks."

The questionnaire comprised 13 single-and multiple-choice questions. Questions regarding general healthcare and medication use included the following: (1) What do you do when you are in poor physical condition? (i.e., go to sleep early, take medicine at home, consult with families, consult with a teacher, see a doctor, consult a pharmacy, other); (2) For what purpose do you use medication? (i.e., stomachache, headache, cold, fever, toothache, allergies, car sickness, other); (3) Who do you consult when you use medication? (i.e., parents/grandparents, brothers/sisters, friend, doctor/dentist, pharmacist, schoolteacher, I have medication that I take regularly, there is no medicine I take regularly, other); and (4) Have you ever done the following: purchased medication on your own judgment, received medication from a friend, gave medication to a friend? Questions regarding behavior, attitude towards, and knowledge of medication use included the following: (1) When you use medication, what kinds of things are you careful about? (i.e., read the description, check the dosage, check the dosage time, check that I had a meal, take medication with water, ensure the medication is suitable to my constitution, I do not care, other); (2) When you use medication, what do you think is important to be careful of? (i.e., read the description, check the dosage, check the dosage time, check that I had a meal, take medication with water, ensure the medication is suitable to my constitution, other); (3) What terminology do you know? (i.e., over-the-counter medicine, prescribed medicine, generic medicine, family pharmacy, medication notebooks, doping, and school pharmacist); and (4) Which items related to a medicine's proper use do you know? (i.e., do not take medication with milk or juice; do not bite tablets or disassemble capsules; between meals is not the same as during meals; take medication for the indicated number of days; most medication has some side effects; do not overdose even if the medication does not work soon; do not double the dosage, even if you forget to take it once; cold over-the-counter medicine is symptomatic treatment). The baseline and 3-month follow-up surveys included questions on behavior, attitude, and knowledge, and the end-of-class survey included only questions regarding attitude. The respondents were asked to select "yes" for all choices that applied to them on each list.

2.3 Statistical analysis

Questions regarding the behaviors, attitudes, terminology, and knowledge of proper medication use were scored for each item, and the total scores for each domain were calculated, with the answer "Yes" counting as one point (14). According to this calculation method, the behavior scores ranged from 0 to 6. Similarly, the attitude, terminology, and knowledge scores ranged from 0 to 6, 0 to 7, and 0 to 8, respectively.

As the groups with and without the provision of pocket cards differed in group-level characteristics, propensity score matching was used to ensure that the intervention and comparison groups were as similar as possible. Propensity score matching is a method used to adjust for selection bias in non-randomized studies of causal effects (16). It is designed to improve the match between individuals in the intervention group and those in the comparison group using demographic or other characteristics. In this study, a propensity score for the participating students was created based on sex and total scores for behavior, attitude, and knowledge at baseline. For each intervention group participant, one control participant with the closest propensity score was selected as the matched participant.

Different statistical methods were used to test each hypothesis. For Hypothesis 1, an independent sample *t*-test was used to compare the scores on the four domains between the two groups. For Hypothesis 2, multiple linear regression was adopted to assess the strength of the relationship between the behavior and the variables that could affect it, namely attitude, terminology, and understanding, at the 3-month follow-up. For Hypothesis 3, the students in both the intervention and comparison groups were divided into two groups, namely students with lower scores at baseline and those with higher scores at baseline, utilizing the mean scores of each domain as cut-off scores. Then, the difference in scores on the four domains between the baseline and 3-month follow-up surveys (the score in the 3-month survey subtracted from the score in the pre-survey) was calculated for each participant in each group. For within-subgroup comparisons, differences between the intervention and comparison groups were tested. For between-subgroup comparisons, differences between the subgroups were tested. All analyses were performed using SPSS version 27.

3 Results

After nearest-neighbor propensity score matching, the final sample of $N = 116$ comprised $n = 58$ comparison participants and $n = 58$ intervention participants; unmatched participants were excluded from the analysis. The results suggested that propensity score matching reduced the differences in the percentages of male and female students as well as the differences in the baseline scores on the four domains between the matched comparison and matched intervention groups (Table 1).

TABLE 1 Participant characteristics and scores at baseline before and after propensity score matching.

	Comparison group		Intervention group	
	Unmatched (n = 113)	Matched (n = 58)	Unmatched (n = 94)	Matched (n = 58)
Demographic				
Female (%)	44.7	50.0	56.1	50.0
Scores at baseline (score (SD))				
Behavior	3.16	3.33	3.76	3.47
Attitude	3.70	3.98	4.75	4.16
Terminology	4.31	4.69	4.89	4.67
Understanding	4.34	5.34	6.27	5.31

TABLE 2 Comparison of scores in post- and 3-month surveys.

	Matched comparison group (n = 58)	Matched intervention group (n = 58)		
	M of score (SD)	M of score (SD)	Cohen's d and 95% C.I.	t-test
Post-test				
Attitude	5.10 (1.25)	4.77 (1.49)	0.24 (−0.18, 0.84)	1.293
3-month follow-up				
Behavior	4.38 (1.28)	3.64 (1.37)	0.56 (0.24, 1.24)	2.927**
Attitude	5.21 (1.31)	4.60 (1.47)	0.43 (0.080, 1.13)	2.286*
Terminology	5.31 (1.52)	5.23 (1.64)	0.053 (−0.51, 0.68)	0.279
Understanding	6.68 (1.98)	5.77 (1.93)	0.47 (0.17, 1.66)	2.434*

* and ** indicate significance at the 95 and 99% levels, respectively.

3.1 Test of hypothesis 1

Compared to the 58 participants included in the matched comparison group, the 58 participants included in the matched intervention group demonstrated significantly lower behavior, attitude, and understanding scores at the 3-month follow-up (behavior: t (109) = 2.927, p = 0.004; attitude: t (109) = 2.286, p = 0.024; understanding: t (107) = 2.439, p = 0.016) (Table 2).

3.2 Test of hypothesis 2

In Models 1 and 2, multiple linear regressions were fitted to explain the scores of changes in behavior based on the scores of changes in attitude, terminology, and understanding. Overall, Models 1 and 2 explained 47.2 and 46.6% of the variations, respectively, and were significantly useful in explaining the behavior score at the 3-month follow-up (Model 1: F (3, 49) = 14.604, p < 0.001; Model 2: F (3, 52) = 15.148, p < 0.001).

For Models 1 and 2, with a one-unit increase in the attitude scores, the behavior scores increased by 0.519 and 0.590, respectively, and these changes were significant (Model 1: t (49) =5.085, p < 0.001; Model 2: t (52) =4.460, p < 0.001) (Table 3). With a one-unit increase in the terminology scores, the behavior scores for Models 1 and 2 increased by 0.113 and 0.140, respectively; however, these changes were not significant (Model 1: t (49) = 0.113, p = 0.294; Model 2: t (52) =1.026, p = 0.310). With a one-unit increase in the understanding scores, the behavior scores for Models 1 and 2 increased by 0.028 and 0.148, respectively; these changes were also not significant (Model 1: t (49) = 0.396, p = 0.694; Model 2: t (52) =1.089, p = 0.281).

TABLE 3 Multiple-linear regression models predicting the behavior scores at the 3-month follow-up.

	Model 1 Matched comparison group	Model 2 Matched intervention group
Constant	0.837	−0.746
Attitude	0.519**	0.590**
Terminology	0.113	0.140
Understanding	0.028	0.148
R square	0.472	0.466

* and ** indicate significance at the 95 and 99% levels, respectively.
Model 1: F (3, 49) = 14.604, p < 0.001.
Model 2: F (3, 52) = 15.148, p < 0.001.

3.3 Test of hypothesis 3

For the within-subgroup analysis of participants with lower behavior, attitude, terminology, and understanding scores at baseline, the matched intervention group showed smaller changes in scores than those of the matched comparison group, and changes in the behavior and attitude scores were statistically significant (behavior: t (49) = 2.240, p = 0.030; attitude: t (60) = 2.268, p = 0.013) (Table 4).

10.3389/fpubh.2023.1296073

TABLE 4 Subgroup analysis of the degree of changes in scores between the baseline and 3-month follow-up.

		Students with lower scores at baseline				Students with higher scores at baseline				(In the matched comparison group)[a]		(In the matched intervention group)[b]	
		Matched comparison group	Matched intervention group	Within-subgroup		Matched comparison group	Matched intervention group	Within-subgroup		Between-subgroup		Between-subgroup	
	M of scores at baseline	M (SD) (*n*)	M (SD) (*n*)	Cohen's d (95% C.I.)	*t*-test	M (SD) (*n*)	M (SD) (*n*)	Cohen's d 95% C.I.	*t*-test	Cohen's d 95% C.I.	*t*-test	Cohen's d 95% C.I.	*t*-test
Behavior	3.40	1.68 (1.36) (*n* = 28)	0.87 (1.18) (*n* = 23)	0.63 (0.083, 1.53)	2.24*	0.47 (0.94) (*n* = 30)	−0.40 (1.30) (*n* = 30)	0.76 (0.28, 1.45)	2.96**	1.04 (0.60, 1.82)	3.97**	1.02 (0.57, 1.97)	3.66**
Attitude	4.07	2.12 (1.67) (*n* = 34)	1.25 (1.27) (*n* = 28)	0.58 (0.10, 1.63)	2.27*	−0.042 (1.20) (*n* = 24)	−0.52 (1.64) (*n* = 25)	0.33 (−0.35, 1.31)	1.16	1.44 (1.36, 2.96)	5.43**	1.22 (0.97, 2.57)	4.43**
Terminology	4.68	1.29 (1.68) (*n* = 24)	0.87 (1.22) (*n* = 23)	0.29 (−0.44, 1.29)	0.98	,15 (1.31) (*n* = 34)	0.30 (1.49) (*n* = 30)	−0.11 (−0.85, 0.55)	−0.44	0.78 (0.36, 1.93)	2.92**	0.41 (−0.20, 1.34)	1.49
Understanding	5.33	2.04 (2.39) (*n* = 25)	1.14 (1.82) (*n* = 28)	0.43 (−0.27, 2.06)	1.55	0.78 (1.58) (*n* = 32)	−0.21 (1.77) (*n* = 24)	0.60 (0.089, 1.89)	2.20*	0.64 (0.20, 2.31)	2.39*	0.75 (0.35, 2.35)	2.70**

[a]Comparison between students with lower scores and those with higher scores at baseline in the matched comparison group.
[b]Comparison between students with lower scores and those higher scores at baseline in the matched intervention group.

On the other hand, among the students whose behavior, attitude, terminology, and understanding scores at baseline were higher than average, the matched intervention group showed negative changes, and the behavior and understanding scores at the 3-month follow-up were lower than those at baseline, with statistical significance for behavior and understanding (behavior: t (58) = 2.958, p = 0.004; understanding: t (54) = 2.203, p = 0.032).

For the between-subgroup analysis, in the matched comparison group, the students with lower scores at baseline showed greater positive changes in their scores for all four domains (behavior: t (56) = 3.970, $p < 0.001$; attitude: t (56) = 5.432, $p < 0.001$; terminology: t (56) = 2.918, p = 0.005; understanding: t (55) = 2.388, p = 0.020). Similarly, in the matched intervention group, the students with lower scores at baseline had greater positive improvements in the scores for all four domains, and changes in the behavior, attitude, and understanding scores were statistically significant (behavior: t (51) = 3.662, $p < 0.001$; attitude: t (51) = 4.431, $p < 0.001$; understanding: (50) = 2.704, p = 0.009).

4 Discussion

The present study examined the effectiveness of distributing pocket cards after providing a school-based medication education program developed by the authors, in comparison with providing the program alone, for improving the behavior, attitude, and knowledge regarding medication use among junior high school students.

Overall, the examination of the three hypotheses yielded unexpected results. While both the matched intervention and matched comparison groups showed an increase in the scores at the 3-month follow-up, which can be seen by comparing the results in Tables 1, 2, the results of testing Hypothesis 1 demonstrated that the matched intervention group had lower behavior, attitude, and understanding scores than those of the matched comparison group at the 3-month follow-up. The analysis of Hypothesis 2 revealed that only the attitude score had a significant effect on the behavior score, not only in the matched control group, but also in the matched intervention group. In our previous study utilizing Bayesian inference, we reported a causal relationship among the four domains in that acquiring the knowledge on approprate medication use leads to the acquisition of favorable attitudes, which may result in behavioral changes (14). The results of this study and the authors' previous study (14) were consistent in terms of the implication that attitude could be the most influential factor affecting behavior. Therefore, attitude changes might be the key to promoting behavioral changes.

This study also posited that regardless of the scores for the four domains at baseline, pocket cards would be useful for all participants to achieve a substantial increase in scores at the 3-month follow-up, which was tested through Hypothesis 3. However, the within-subgroup comparison showed an overall smaller positive change in scores in the matched intervention group than in the matched comparison group. In addition, in the between-subgroup comparison, compared to the students with lower scores at baseline, the students with higher scores at baseline tended to show significantly smaller or negative changes, indicating a decline in the scores after the

intervention. This may be explained by the fact that participants with relatively high baseline scores could easily reach the highest level and had difficulty demonstrating further improvement. In contrast, participants with relatively low baseline scores may have more room for improvement.

Given that the examination of all three hypotheses showed unexpected results, while both groups received exactly the same medication education class, it is possible that they were not similar, even though propensity score matching was carried out. This implied that matching based only on sex and scores for the four domains at baseline might have been insufficient and that other variables such as those regarding the participants' other characteristics should have been included in the matching. This study adopted pocket cards as supplemental teaching material to further enhance the impact of the medication education program on the participants; however, the results of this study did not demonstrate their usefulness. Thus, while pocket cards are a relatively low-cost supplemental teaching material, the impact of pocket cards on behavioral and attitudinal changes remains controversial. On one hand, Shearer et al. (17) reported that distributing pocket cards or stickers contributed to promoting adult participants' desired behavior, stressing their convenience and feasibility. On the other hand, another study reported the insufficiency of a simple traditional tool that included the provision of a virtual educational program and pocket cards to improve malnutrition or nutritional treatment awareness (18). Given that there are reports that support their effectiveness and ineffectiveness in promoting behavioral and attitudinal changes, it may be necessary to explore the factors attributing to these disparitiess. In addition, exploring other forms of supplemental educational material that could help reinforce the impact of in-class program may be important.

The limitations of this study include its focus on a single junior high school with a small sample size, limited demographic variables used in group matching, and inability to confirm the effectiveness of pocket cards. In particular, despite that it is generally uncommon in Japan to ask socio-economic status-related questions in surveys for children and adolescents and to use student academic performance-related variables in social science studies, appending the demographic factors that could have an association with medication use in propensity score matching may be of use in such a study. Nonetheless, this study is the first to examine whether pocket cards can be used as supplementary educational material for teaching proper medication use and enhancing medication literacy in a junior high school setting. Furthermore, the results of this study implied that the medication education program itself had a positive impact on increasing the scores, suggesting that it promotes favorable changes in behavior, attitude, and knowledge among junior high school students. Therefore, further exploration of evidence-based supplementary teaching tools with promising effects may be needed to increase the effectiveness of medication education programs.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Gifu Pharmaceutical University. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because The purpose of the survey was explained to the principals of the participating schools, and written consent was obtained. At the beginning of the questionnaire, it was noted that the questionnaire was not a requirement, and a student could stop at any time. Completion of the questionnaire was treated as consent for participation.

Author contributions

CS: Formal analysis, Writing – original draft. KI: Formal analysis, Writing – review & editing. TT: Formal analysis, Writing – review & editing. YN: Formal analysis, Writing – review & editing. AH: Writing – review & editing. SK: Writing – review & editing, Conceptualization, Data curation, Project administration. HT: Conceptualization, Data curation, Funding acquisition, Project administration, Supervision, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was funded by the Japan Society for the Promotion of Science (Grant no. 20K02831).

Conflict of interest

TT is currently an Associate Editor.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1296073/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 16 January 2024
DOI 10.3389/fphar.2023.1257353

OPEN ACCESS

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RECEIVED 12 July 2023
ACCEPTED 29 December 2023
PUBLISHED 16 January 2024

CITATION
Rianto L, Agustina I, Alfian SD, Iskandarsyah A, Pradipta IS and Abdulah R (2024), Development and validation of a structured questionnaire for assessing risk factors of medication non-adherence among pulmonary tuberculosis patients in Indonesia.
Front. Pharmacol. 14:1257353.
doi: 10.3389/fphar.2023.1257353

Development and validation of a structured questionnaire for assessing risk factors of medication non-adherence among pulmonary tuberculosis patients in Indonesia

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Background: Medication non-adherence is a significant concern in tuberculosis (TB) treatment, requiring a precise understanding of the associated risk factors. However, there is a lack of appropriate means to assess the risk factors among TB patients in Indonesia, leading to the development and validation of a structured questionnaire for this purpose.

Method: This study unfolded in two distinct phases, namely, the first included questionnaire construction through framework development, item generation, item screening, and pretesting (in 50 patients). The second comprised questionnaire validation with 346 participants using confirmatory factor analysis (CFA) and structural equation modeling-partial least squares (SEM-PLS). Additionally, reliability testing was conducted using Cronbach's alpha and composite reliability statistical techniques.

Results: In the development phase, 168 items were defined, consisting of sociodemographic characteristics (8 items) and risk factors for medication non-adherence (160 items). Expert evaluation reduced the number of items to 60, which decreased to 22 after performing a pilot study. Subsequent SEM-PLS modeling resulted in the identification of 14 valid items, representing five major risk factors, namely, socioeconomics (4 items), healthcare team (4 items), condition (3 items), therapy (2 items), and patient (1 item). Only condition-related factors were found to influence non-adherence, and all constructs showed good reliability based on Cronbach's alpha (>0.6) and composite reliability (0.7) values.

Conclusion: The final 22 items that emerged from this rigorous process indicated a valid and robust questionnaire for assessing risk factors of medication non-adherence among pulmonary tuberculosis patients in Indonesia. The developed

questionnaire was positioned to be a valuable tool for healthcare professionals, policymakers, and scientists in creating patient-centered strategies and interventions to address non-adherence.

KEYWORDS

tuberculosis, non-adherence, questionnaire development, questionnaire validation, SEM-PLS, prediction

1 Background

Tuberculosis (TB) is a significant public health concern, particularly in regions such as Asia and Africa, with the highest fatality rates emanating from infectious diseases worldwide (Zhu et al., 2022). In 2018, TB initiated greater mortality accounting for 1.5 million deaths, compared to HIV/AIDS (Harding, 2020). The complex, prolonged, and often poorly tolerated regimens for both drug-susceptible and resistant TB pose substantial challenges to treatment adherence (Alipanah et al., 2018; Pradipta et al., 2021; Pradipta et al., 2022a). Moreover, non-adherence to necessary medications increases the risk of negative outcomes, including treatment failure, elevated TB transmission, relapse, drug resistance emergence, as well as higher morbidity and mortality (Fang et al., 2019; Saha et al., 2022). Many patients fail to complete the full 6-month course of anti-TB medications, jeopardizing their health and contributing to the development of multidrug-resistant and extensively resistant. According to the World Health Organization (WHO), TB therapy adherence means the extent to which the prescribed pharmaceutical regimen is being followed. Several quantitative studies (El Sahly et al., 2004; Munro et al., 2007; Shargie and Lindtjørn, 2007) investigated risk variables linked to suboptimal treatment adherence, but only a few explored the relationship shared with socioeconomic factors. These sources showed that low education level, place of residence, financial constraints, comorbid chronic diseases, medication discontinuation, and anti-TB treatment frequency influence non-adherence (Alipanah et al., 2018; Zhu et al., 2022).

In the study conducted in rural and urban districts of the Democratic Republic of Timor-Leste, it was found that information about TB, its treatment, and the availability of incentives, such as transportation cost reimbursement or food support, positively influenced adherence (Ruru et al., 2018a). Four key determinants contribute to non-adherence, namely, structural (e.g., poverty and gender discrimination), social, and health service-related factors, as well as individual considerations (World Health Organization, 2003; Munro et al., 2007). An Indonesian study revealed that the most common reasons for non-adherence included patients feeling better, economic issues, and side effects of therapy. Other reasons were bad perceptions about the healthcare staff, treatment, and medication quality (Widjanarko et al., 2009). Recent investigations indicate the significance of socioeconomic challenges and the lack of adequate patient support in contributing to high rates of treatment discontinuation in Indonesia (Global, 2021). Effective adherence relies on social support, which may include the presence of a treatment observer and health education (Widjanarko et al., 2009; Ruru et al., 2018a; Pradipta et al., 2022b). Additional barriers to this consist of a preference for traditional medicine and economic and geographical problems (Ruru et al., 2018a; Pradipta et al., 2023).

Several existing questionnaires, such as the Morisky Medication 8-item Adherence Scale (MMAS-8) and MARS-5 Medication Adherence Report Scale-5 items (MARS-5) have been widely used to assess patient adherence to ongoing treatment (Lee et al., 2013; Rosyida, 2015; Naafi et al., 2016; Pradipta et al., 2020; Iranpour et al., 2022). However, their suitability for measuring non-adherence levels remains uncertain. There is no universally accepted gold standard questionnaire for evaluating non-adherence, specifically within the scope of TB. To address this gap, structural equation modeling-partial least squares (SEM-PLS) analysis was applied to develop a questionnaire that can be used to create a predictive model. The SEM-PLS approach comprised two distinct phases, i.e., the evaluation of measurement and structural models (Kono and Sato, 2022; Kori and Azmi, 2022).

Tuberculosis still poses a significant health challenge in Indonesia, necessitating interventions tailored to the diverse settings of the country (World Health Organization, 2003; Lestari et al., 2023). Therefore, this study presents a meticulously designed questionnaire for assessing the factors contributing to medication non-adherence among TB patients. Drawing inspiration from the five-dimensional framework established by WHO, the questionnaire was developed based on comprehensive systematic reviews and prior qualitative studies (DiMatteo, 2004; Munro et al., 2007). Importantly, before pilot testing, the initial development phase did not include direct patient input, instead, the primary focus was placed on capturing expert perspectives to refine item selection (World Health Organization, 2003). While the questionnaire yields statistically robust insights, its true value lies in practical applications. Considering the vast geographical and sociocultural differences in Indonesia, this tool is designed for flexible integration into various local contexts, facilitated through collaborations with local health entities (Lutge et al., 2014; Jimmy and Jose, 2011). Additionally, it is intended for use among TB patients in the early stages of treatment, capturing critical insights during this crucial period. The results can aid healthcare professionals in refining treatment adherence strategies and serve as a foundation for policymakers aiming to enhance TB management on a national scale (Stirratt et al., 2015).

2 Methods

2.1 Ethics approval

This study obtained approval from the ethics committees of Universitas Padjadjaran (No: 086/UN6. KEP/EC/2021), private hospitals (No: 1212/XIII/12/2020), and public hospitals (No: 13/

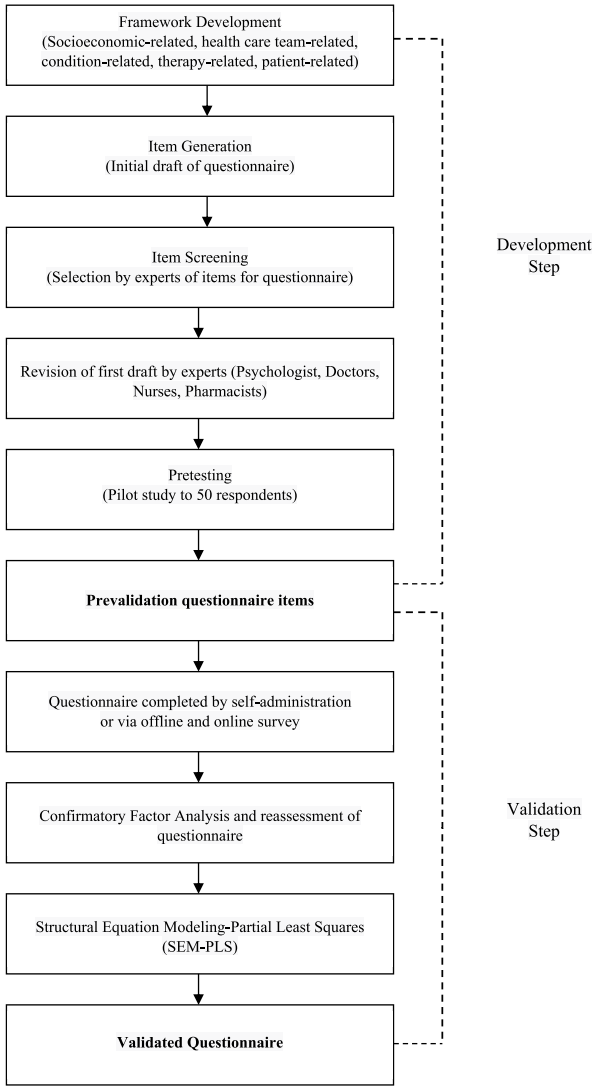

FIGURE 1
Flowchart of questionnaire development and validation.

KEPK-RSUPP/02/2021). Additionally, it was conducted in accordance with the Helsinki Declaration, and all participants provided informed consent.

2.2 Study design and sample size

The initial phase of questionnaire development constituted the engagement of a cohort of 50 patients, each with an extensive TB treatment regimen spanning a minimum of 6 months. This collective cohort participated in an inaugural assessment aimed at quantifying the efficacy of the measuring instrument in capturing the underlying construct. The construct validity assessment primarily focused on evaluating the ability of the questionnaire to measure the intended variables. Subsequently, a purposive sampling strategy was applied in the validation phase, targeting patients with a shorter TB treatment duration, ranging from one to 2 months.

For the validation phase, a representative sample was selected from the cohort of newly diagnosed patients in the Jakarta area between 2020 and 2021. Based on the Indonesian Health Profile report, published by the Ministry of Health, it was determined that Jakarta discovered a total of 28,125 cases in 2021 compared to the 24,274 recorded in 2020. This signified a discernible increment of 3,851 cases, which constituted the entire patient population scrutinized in this study.

The following two distinct methods were used to determine the optimal sample size: 1) The Krejcie and Morgan table in conjunction with the population parameters was deployed to obtain an optimal sample size ranging from 346 to 351 patients; 2) Alternatively, the Slovin formula, a well-established mathematical construct was applied for calculating sample size, with an error margin (e) of 5% (0.05). This included using the formula $n = N/(1 + Ne^2)$, yielding a minimum sample size of 362 patients.

In summary, the methodological framework determined a required sample size ranging from 346 to 362. Consequently, the comprehensive patient cohort for this study comprised 396 individuals, out of which 50 were actively engaged in the developmental phase and the remaining 346 were allocated to the validation stage. A flow diagram indicating the development and validation of the questionnaire is presented in Figure 1.

2.3 Development of questionnaire items

2.3.1 Framework development

A systematic review and a qualitative study were initially conducted to identify relevant factors used to construct a questionnaire for predicting TB patient non-adherence. Subsequently, a framework that described the five factors influencing long-term medication adherence, namely, socioeconomic status, healthcare team, medical conditions, therapy, and patients, was adopted from the WHO (World Health Organization, 2003).

2.3.2 Item generation

Building upon the previously established framework, questionnaire items representing each dimension or variable to be measured were developed. Although the framework primarily pertained to adherence, this study adapted all the obtained dimensions to the context of non-adherence. Five items created for each indicator in the variable were assessed by TB treatment experts and analyzed by psychologists.

2.3.3 Item screening

A panel of experts, including a psychologist, three pulmonary specialists, two nurses, and three pharmacists, assessed the level of difficulty and adequacy of the questionnaire. This evaluation was based on qualitative study activities conducted before the questionnaire development. The experts participated in focus group discussions (FGD) regarding the factors influencing non-adherence and were selected according to the possession of at least 1 year of experience in TB medication. Specifically, psychologists were engaged in assessing the readability and comprehensibility of the items before the pretesting stage. Following this process, the initial selection of items was refined based on assigned the median

total score. Items that received higher scores, as indicated by multiple experts, proceeded to the next stage.

2.3.4 Pretesting (pilot study)

After the panel of experts conducted a content validity assessment, a pilot questionnaire was pretested on 50 respondents in December 2021, as recommended by healthcare professionals. Criteria for participant selection included a history of medication non-adherence, age 18 years or older, a minimum of high school education, and willingness to provide informed consent. Respondents were recruited during hospital visits, and each completed a paper copy of the questionnaire. Trained assistants reviewed the self-administered questionnaires on-site before being delivered to the study team.

2.4 Validation of questionnaire items

The pilot study produced prevalidated questionnaire items that showed statistical validity and could be applied in a comprehensive validation process using SEM-PLS. The entire validation phase was conducted from January to March 2022 and respondents were selected through a purposive sampling technique. Selection criteria included sensitive TB patients recently placed on medication (1–2 months), aged 18 years or older, with a minimum of high school education, and willing to sign an informed consent. Questionnaires were distributed in one public and six private hospitals, as well as nine community health centers in Jakarta. An online Google survey was used for remote respondents registered as patients at the designated study location.

2.4.1 Confirmatory factor analysis (CFA)

Confirmatory factor analysis (CFA) is an integral component of SEM, valuable for the appropriateness of variable measurements concerning the number of factors. In CFA, factors can be considered as constructs, and this analysis represents an interdependence technique for determining the underlying structure in construct variables. High partial correlation in factor analysis holds practical and statistical significance, with the general rule of thumb suggesting values above 0.70 as conceptually valid (Lance and Vandenberg, 2002; Harrington, 2009; Brown and Moore, 2012). However, the Bartlett roundness test at a level of >0.05 indicates a sufficient correlation between construct variables for a single-factor analysis (Suhr, 2006; Hair et al., 2014a; Gatignon and Gatignon, 2014; Brown, 2015).

2.4.2 Structural equation modeling-partial least squares (SEM-PLS)

SEM is a statistical model that describes the relationships among several variables (Hair et al., 2014b). During the calculation process, SEM simultaneously examines the structural relationships expressed through a series of equations resembling multiple regression equations. These equations elucidate all the interconnections between analyzed constructs, comprising both dependent and independent variables. Constructs are unobservable and cannot be represented by numerous variables compared to those representing factors in CFA. Moreover, PLS-SEM is a causal-predictive method of SEM that stresses prediction in estimating statistical models aimed at providing causal explanations (Hair et al., 2019). In this study, each item used an ordinal Likert scale for measurement, with five potential response levels. Indicators with ordinal responses from at least four categories may be interpreted as intervals, or at the very least, as continuous variables. No two indicators for a construct must have the same scale type, and scale values need not be normalized (Hair et al., 2014b). The utility of a questionnaire as a study instrument is evaluated using the validity and reliability method. Validity refers to the extent to which observations accurately record the examined variables. Meanwhile, reliability relates to the consistency of observations, often determined by whether two (or more) observers or the same observers, monitoring the same event on successive occasions, reach similar conclusions (Sekaran and Bougie, 2016).

2.5 Statistical analysis

Data analysis was performed using SPSS Statistics for Windows (version 24.0) and SMART-PLS software (version 3.0) in an SEM-PLS environment. In the pretesting phase, bivariate Pearson correlation statistical analysis was applied to determine the validity of the items sorted by experts. Pearson correlation measures the relationship between observations from a population with two variants (bivariate), normally distributed. With the participation of 50 patients, items indicating a Pearson correlation value exceeding 0.278 proceeded to the validation phase, which used SEM. Besides, SEM-PLS incorporates a measurement model that evaluates the relationship between indicators and their latent variables, automatically presenting the factor load as an indicator of the validity of a factor or latent variable (Ghozali, 2014). Regarding the validity limits, indicators with factor loadings between 0.40 and 0.70 are considered for removal only when the scenario tends to enhance the composite reliability score. However, content validity factors must be considered during the elimination of these indicators. Indicators with factor loading values below 0.40 should be removed, and those between 0.40 and 0.70 may be retained supposing their presence does not adversely affect the average variance extracted (AVE) gain or composite reliability. In this study, the validity limit value used was 0.40, considering the applicable terms and conditions, as well as the significance of the coefficient at a 5% level (Hair et al., 2021). Composite reliability and Cronbach's alpha were applied to assess the reliability of the study instruments. While these two methods use distinct calculation methodologies, both reveal the level of reliability for each latent or constructed variable. The minimum value required for optimal reliability is 0.60, with higher values indicating greater reliability (Hair et al., 2021). Computation analysis and validity-reliability testing were performed using SEM-PLS and SmartPLS 3 software (Hair et al., 2019). The value of composite reliability was assessed to test the reliability of each indicator on a variable, and >0.70 was considered the benchmark for high reliability. Specifically, reliability is essential for ensuring the precision and accuracy of measurements. Reliability testing was conducted by examining the value of Cronbach's alpha to determine whether the data obtained from the instrument showed adequate internal

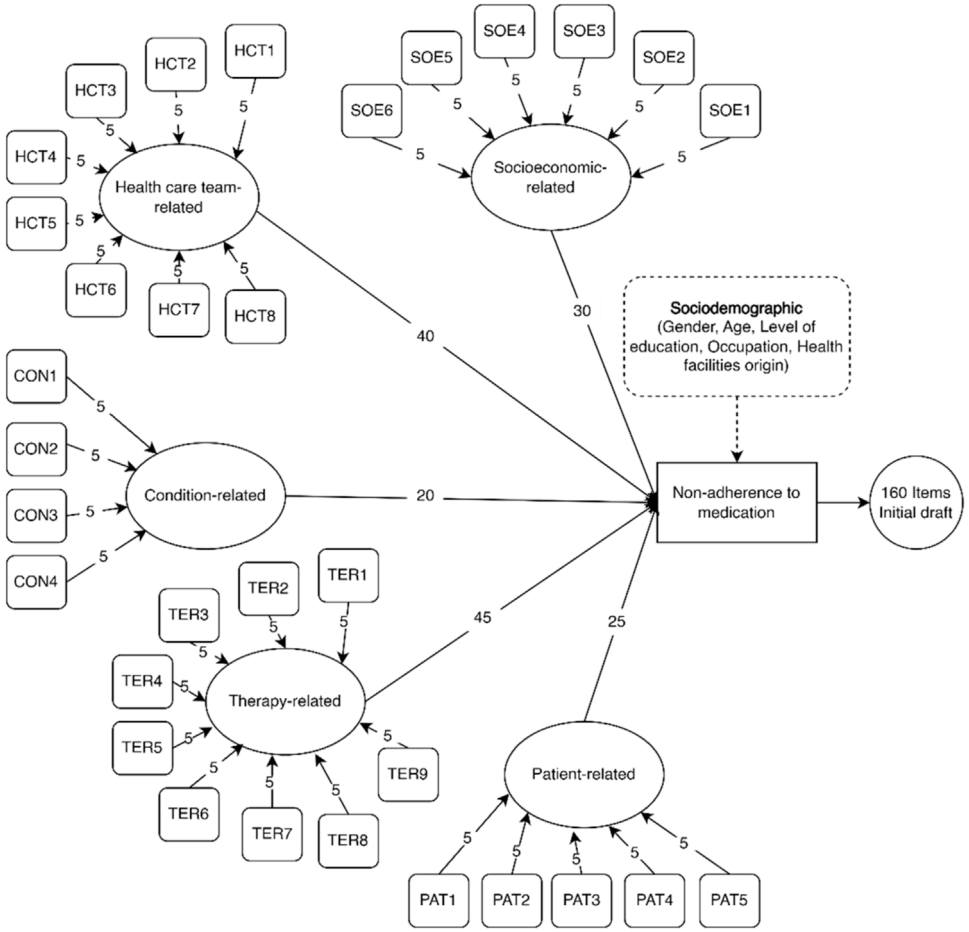

FIGURE 2
Framework development for questionnaire items.

consistency. Note that a study instrument is considered reliable once the Cronbach's alpha value is >0.60 (Chin, 1998; Hair et al., 2014a; Ghozali, 2016).

3 Results

3.1 Development of questionnaire items

3.1.1 Framework development

The five-dimensional framework of WHO for adherence was adapted into the concept of non-adherence in this study. These five dimensions comprised the various causes and risk factors associated with non-adherence, based on the results of systematic reviews and qualitative studies conducted previously. Each dimension had specific indicators used for measuring its impact on medication non-adherence. A total of 32 indicators were successfully generated, with each contributing five items. As shown in Figure 2, the dimensions were as follows: socioeconomic (6 indicators; 30 items), healthcare team (8 indicators; 40 items), conditions (4 indicators; 20 items), therapy (9 indicators; 45 items), and patients (5 indicators; 25 items). This resulted in the generation of a total of 160 items in the subsequent stage.

3.1.2 Item generation

The items generated for the questionnaire were adapted to local settings and divided into six main sections, as presented in Table 1. These included Demographic factors (5 items) which examined demographic and socioeconomic characteristics. Socioeconomic-related factors (30 items) constituting considerations such as economic priorities. In developing countries, patients with low socioeconomic status often face the challenge of balancing competing priorities. These competing priorities might require allocating limited resources to meet the needs of other family members, such as the children or parents catered for (Killewo, 2002; World Health Organization, 2003; Diniawati and Wibowo, 2018; Mahara et al., 2018). Healthcare team-related factors (40 items) explored the effects of the patient-provider relationship, and more investigations are needed concerning the impact of the healthcare team and system-related factors on non-adherence. While an excellent patient-provider relationship can increase adherence several factors have a negative effect. These are comprised of underdeveloped healthcare services, inadequate or nonexistent reimbursement by health insurance plans, poor drug distribution systems, and a lack of knowledge and training among healthcare providers in managing chronic diseases (World Health Organization, 2003; Do Peterson et al., 2012; Gugssa Boru et al., 2017). Condition-related factors (20 items) included demands, symptoms, and disease-specific issues targeted by

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TABLE 1 Details of questionnaire sections on sociodemographic and all factors.

Section	No. of items	Concept measured	Response options
Sociodemographic	5	1) Gender	Closed-ended, multiple-choice
		2) Age	
		3) Education level	
		4) Occupation	
		5) Health facilities origin	
Socioeconomic-related	30	1) Availability of social support from fellow patients	1 = Strongly disagree 2 = Disagree
		2) Bad perception of disease (Communities)	3 = Not sure
		3) Environmental support	4 = Agree
		4) Fear of infecting families	5 = Strongly Agree
		5) Getting financial and logistical assistance	
		6) Social and family support	
Healthcare team-related	40	1) Availability of disease education by health workers	1 = Strongly disagree 2 = Disagree
		2) Availability of information and education	3 = Not sure
		3) Communication effectiveness	4 = Agree
		4) Lack of health facility services	5 = Strongly Agree
		5) Limitations of treatment services	
		6) Limited and inaccurate information	
		7) Negative prognosis of health professionals	
		8) Quality of service from healthcare professionals	
Condition-related	20	1) Availability of facilities and affordable health facilities	1 = Strongly disagree 2 = Disagree
		2) Dirty and unhealthy work environment	3 = Not sure
		3) Long distance to health facilities	4 = Agree
		4) Deteriorating and uncontrolled patient conditions	5 = Strongly Agree
Therapy-related	45	1) Comorbidity	1 = Strongly disagree
		2) Drug resistance	2 = Disagree
		3) Impact of treatment on activities	3 = Not sure
		4) Impact of treatment on health conditions	4 = Agree
		5) Lower pill burden	5 = Strongly Agree
		6) More efficient drug preparations	
		7) Relapse/retreatment	
		8) Supporting therapy	
		9) Treatment side effects	
Patient-related	25	1) Stigma against disease (Patient)	1 = Strongly disagree
		2) Motivation to live	2 = Disagree
		3) Motivation for adhering to treatment	3 = Not sure
		4) Negative perceptions of disease and treatment	4 = Agree
		5) Self-vulnerability	5 = Strongly Agree

TABLE 2 The results of questionnaire validation through expert review and statistical analysis.

No.	Items	Expert choice	Pearson correlation	Sig. (2-Tailed)	N
1	SCA11	3	0.015	0.916	50
2	SCA12	5	0.081	0.575	50
3	**SCA21**	**9**	**0.614****	**0**	**50**
4	**SCA23**	**9**	**0.519****	**0**	**50**
5	**SCA24**	**3**	**0.701****	**0**	**50**
6	SCA31	3	0.156	0.278	50
7	SVA13	3	0.09	0.532	50
8	SVA14	3	−0.024	0.869	50
9	SVA22	5	0.194	0.177	50
10	SVA23	3	−0.099	0.495	50
11	SVA31	6	0.008	0.957	50
12	SVA34	3	0.031	0.832	50
13	**SVA41**	**8**	**0.552****	**0**	**50**
14	SVA44	3	−0.1	0.49	50
15	SVA51	3	−0.122	0.397	50
16	BNA11	6	0.112	0.439	50
17	BNA14	3	−0.164	0.255	50
18	BNA21	4	0.215	0.134	50
19	**BNA31**	**6**	**0.370****	**0.008**	**50**
20	**BNA34**	**5**	**0.633****	**0**	**50**
21	BNA41	4	−0.013	0.93	50
22	BNA43	3	0.114	0.432	50
23	BNA51	3	0.109	0.449	50
24	BNA52	3	0.215	0.134	50
25	BNA61	4	0.029	0.844	50
26	BNA63	4	0.048	0.74	50
27	BRA14	4	0.171	0.235	50
28	**BRA21**	**6**	**0.586****	**0**	**50**
29	BRA33	3	−0.033	0.821	50
30	BRA35	4	0.089	0.54	50
31	BRA41	4	0.097	0.503	50
32	BRA44	3	−0.129	0.371	50
33	BRA51	3	0.148	0.305	50
34	BRA55	4	0.073	0.612	50
35	BRA65	4	0.15	0.299	50
36	**SEA11**	**8**	**0.501****	**0**	**50**
37	**SEA15**	**7**	**0.554****	**0**	**50**
38	**SEA23**	**9**	**0.464****	**0.001**	**50**

(Continued on following page)

TABLE 2 (*Continued*) The results of questionnaire validation through expert review and statistical analysis.

No.	Items	Expert choice	Pearson correlation	Sig. (2-Tailed)	N
39	SEA31	4	0.064	0.661	50
40	SEA33	3	−0.107	0.461	50
41	SEA45	4	0.159	0.271	50
42	**CAA11**	**7**	**0.597****	**0**	**50**
43	**CAA12**	**5**	**0.690****	**0**	**50**
44	**CAA13**	**7**	**0.579****	**0**	**50**
45	**CAA14**	**4**	**0.750****	**0**	**50**
46	**CAA15**	**4**	**0.406****	**0.003**	**50**
47	CAA22	4	0.072	0.617	50
48	CAA23	4	−0.133	0.357	50
49	CAA33	6	−0.097	0.502	50
50	CAA35	3	0.118	0.416	50
51	**CAA41**	**5**	**0.721****	**0**	**50**
52	**CAA42**	**5**	**0.590****	**0**	**50**
53	**CAA43**	**6**	**0.702****	**0**	**50**
54	**CAA44**	**6**	**0.648****	**0**	**50**
55	**CAA45**	**4**	**0.506****	**0**	**50**
56	CAA51	4	0.202	0.16	50
57	CAA61	7	−0.027	0.854	50
58	CAA65	4	0.071	0.625	50
59	**CAA71**	**7**	**0.567****	**0**	**50**
60	**CAA72**	**6**	**0.434****	**0.002**	**50**

The bold values in Table 2 serve as highlights to indicate items with significance levels above 1% and above 5%, helping to differentiate which items are considered valid and can be progressed to the next stage.
Specifically, ** represents significance above 1%, while * represents significance above 5%. In this context, the value 0.278, marked with a *, signifies a significance level of 5%, indicating that this item is valid for further consideration. Conversely, the value 0.354, marked with **, signifies a significance level of 1%, further emphasizing its validity for progression to the next stage.

healthcare professionals. Several conditional factors, such as patient geography and health status, influenced their willingness to complete medication (World Health Organization, 2003; Shargie and Lindtjørn, 2007; Tadesse et al., 2013; Woimo et al., 2017; Ruru et al., 2018b). Therapy-related factors (45 items) consisted of the main barriers to adherence found in intervention studies, such as dosing frequency and side effects. Collaboration between pharmaceutical companies, health professionals, and researchers is essential to address this issue. Health systems play an essential role in minimizing the impact of side effects (World Health Organization, 2003; Do Peterson et al., 2012; Gugssa Boru et al., 2017; Heuvelings et al., 2017). Patient-related factors (25 items) examined the primary barriers to compliance as described in the reviewed literature, namely, a lack of information and self-management skills, difficulties with motivation and self-efficacy, and inadequate support for behavioral change (Morisky et al., 1990; Chambers et al., 2010; Gugssa Boru et al., 2017). These barriers are specifically relevant for interventions aimed at changing habits and lifestyles, as well as influencing drug use. The WHO recognizes the need to support patient self-management efforts, and many researchers are working to develop, enhance, and disseminate self-management guidelines (World Health Organization, 2003; Gough and Kaufman, 2011; Van Den Boogaard et al., 2012; Chowdhury et al., 2015; Sahile et al., 2018).

This section consisted of choices on a scale from one to five, with response categories ranging from "strongly disagree" to "strongly agree" for each question. Following the results of the item selection by experts, a total of 60 questionnaire items were used in the pilot study. At this stage, the expectation was to obtain a questionnaire containing a more streamlined set of items to facilitate measurement with fewer items during validation.

3.1.3 Item screening

In this phase, the initial selection of 160 items was reduced to 60, based on a median total score of 2.0 for each. Items selected by more than two experts proceeded to the next stage.

3.1.4 Pretesting (pilot study)

The results of face validity obtained during the pilot study featuring 50 respondents reduced the number of questionnaire items from 60 to 22. The response rate was 100% (50/50 participants), with respondents

TABLE 3 Twenty two-item and theme validation study.

Factor	No.	ID	Theme
Socioeconomic-related	1	SCA21	Families understand TB disease suffered
	2	SCA23	Cutlery/drinks are separated from those of family members
	3	SCA24	Cutlery, clothes, and items are washed separately
	4	SEA23	Financial and moral support needed from the family
	5	CAA45	Talks to the family about medical conditions and the burden
Healthcare team-related	1	SVA41	Takes medication before the test results come out
	2	CAA41	Undergoes treatment after receiving an explanation of the procedure
	3	CAA42	Knows the side effects and therapy of drugs
	4	CAA43	The team of health workers continues to communicate during treatment
	5	CAA44	Speaks with the doctor/nurse because the information is not understood
Condition-related	1	CAA11	Takes alternative medicine to aid healing
	2	CAA12	Takes other drugs to relieve side effects of treatment
	3	CAA13	Does light exercise regularly
	4	CAA14	Maintains the diet
	5	CAA15	Consumes herbs to promote breathing
Therapy-related	1	BNA31	The amount of medication taken has decreased with the start of treatment
	2	BNA34	No more injections when coming to health facilities
	3	CAA71	Excited to undergo treatment once the number of drugs is reduced
	4	CAA72	It feels better to take medicine than to have an injection
Patient-related	1	BRA21	Side effects decrease after a long course of treatment
	2	SEA11	Needs support to recover and undergo treatment
	3	SEA15	Needs information and education for treatment

requiring an average of 15 min to complete the questionnaire. The validity of each item is presented in the Pearson correlation column in Table 2. Considering the 50 respondents (N) and a significance level of 0.05, the minimum Pearson correlation value was 0.278. Therefore, 22 items exhibited Pearson correlation values exceeding 0.2732, denoted by * or ** in the Pearson correlation column of the output table. As a result, 38 items were considered invalid, while 22 were validated.

3.1.5 Prevalidated questionnaire items

The 22 questionnaire items identified during the face validity assessment were administered to a total of 346 sensitive TB patients as respondents. None of the patients from the pilot study were included in the validation phase. Table 3 presents an overview of selected items and themes that successfully passed face validity.

Overall, the results of the questionnaire development phase can be seen in Figure 3.

3.2 Validation of questionnaire items

3.2.1 Sociodemographic details of respondents

Table 4 presents the demographic characteristics of the 346 respondents who participated in this study. The most common age range found was 20–29 years (24.28%), with a mean of 39.71 (±10.71) years. Most of the respondents were male (54.91%). The educational background was predominantly high school (82.37%), while some (17.34%) completed tertiary education. A significant proportion was unemployed (39.30%) and a small percentage was health workers (0.76%). A substantial number came from private hospitals (38.15%), which was justifiable because these hospitals served as referral centers for pulmonary diseases in Jakarta.

3.2.2 Confirmatory factor analysis (CFA)

Table 5 shows the results for each measured factor, as each item in all the factors was tested for factor loading to identify the influence of each item.

Standardized factor loadings were expected to exceed 0.70, but factor loadings in the 0.40–0.70 range could be evaluated. The evaluation conducted featured content validity by considering the impact exerted on the AVE gain and composite reliability. A higher factor loading value signified greater validity of the construct measurement (Hair et al., 2014b). Factor loadings must be statistically significant, with t values exceeding 1.96 for a 5% significance level (Hair et al., 2014b). To measure convergent validity, the AVE was used, with a threshold value of 0.50. A higher AVE value indicated more information obtained from the latent and reflected similarity in the latent construct (Hair et al., 2014b).

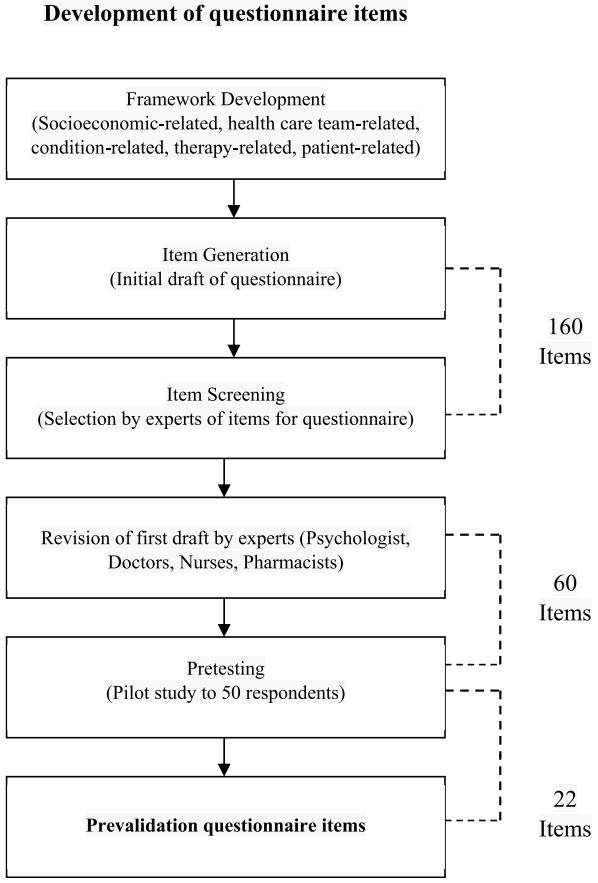

FIGURE 3
Process and results of questionnaire development.

TABLE 4 Sociodemographic characteristics of respondents.

Sociodemographic characteristic	n (%)
Gender	
Male	190 (54.91%)
Female	155 (44.80%)
Rather not to say	1 (0.29%)
Age (years)	
<20	23 (6.65%)
20–29	84 (24.28%)
30–39	75 (21.68%)
40–49	64 (18.50%)
50–59	53 (15.32%)
>60	47 (13.58%)
Level of Education	
Highschool	285 (82.37%)
Undergraduate	59 (17.05%)
Postgraduate	1 (0.29%)
Rather not to say	1 (0.29%)
Occupation	
Employed	124 (35.84%)
Enterpreneur	84 (24.28%)
Unemployed	136 (39.30%)
Rather not to say	2 (0.58%)
Health Facilities Origin	
Community Health Center	104 (30.06%)
Private Hospital	132 (38.15%)
Public Hospital	110 (31.79%)
Medication Status	
Complete	255 (73.70%)
Incomplete	91 (26.30%)
Reasons for Incomplete Medication	
Not Evaluated/Moved	75 (82.42%)
Failed/Not Completed	16 (17.58%)

Composite reliability and Cronbach's alpha ought to have a value of at least 0.70, although a minimum of 0.60 is acceptable for exploratory studies (Hair et al., 2014b). Regarding cross-loading, each indicator should exhibit a stronger correlation with its construct than other constructs, indicating discriminant validity. This empirical standard ensures that a measured construct is distinct from other constructs (Hair et al., 2014b).

3.2.2.1 Socioeconomic-related factors

The composite reliability value for socioeconomic-related factors was >0.7, confirming the suitability of the data for factor analysis. Based on commonality, one item (SEA23) had a very low factor loading and was excluded from further analysis, as it would not correlate with other items representing socioeconomic-related factors. Additionally, one item (SCA21) had the lowest factor loading (0.52) but was retained in the analysis because a factor loading >0.4 was considered the minimum acceptable value. The other three items (SCA23, SCA24, CAA45) met the criteria for reliability and were retained. In summary, only SEA23 was excluded and four items (SCA23, SCA24, SEA23, and CAA45) were considered reliable for socioeconomic-related factors (Table 6).

3.2.2.2 Healthcare team-related factors

The composite reliability value for healthcare team-related factors also exceeded 0.7, indicating data suitability for factor analysis. One item (SVA41) showed a very low factor loading and was excluded from further analysis, as it would not correlate with others representing healthcare team-related factors. Additionally, two items (CAA41 and CAA42) had relatively low factor loadings but were maintained in the analysis due to their factor loadings exceeding the minimum acceptable value of 0.4. The other two items (CAA43 and CAA44) met the reliability criteria and were retained. In summary, only SVA41 was excluded and CAA41, CAA42, CAA43, and CAA44 were considered reliable for healthcare team-related factors (Table 6).

3.2.2.3 Condition-related factors

The composite reliability value for condition-related factors was >0.7, indicating data suitability for factor analysis. No item had low factor loading, consequently all were included in further analysis. One item (CAA14) had a low factor loading of 0.48 but was maintained in the analysis due to being greater than the minimum acceptable value of 0.4. The remaining four items (CAA11, CAA12, CAA13, and CAA15) met the reliability criteria and were retained. In summary, all five items were considered reliable for condition-related factors (Table 6).

TABLE 5 Analysis of all factors.

Factor	Cronbach's alpha	Composite reliability	AVE
Socioeconomic-related	0.29	0.60**	0.43
Healthcare Team-related	0.47	0.67**	0.40
Condition-related	0.70**	0.80**	0.46
Therapy-related	0.66**	0.80**	0.50**
Patient-related	−1.09	0.26**	0.60**

The asterisk (*) in Cronbach's Alpha and Composite Reliability signifies a high level of statistical significance or strong validity. In simpler terms, it indicates that the measurements or constructs being assessed are reliable and consistent for the analysis or research being conducted.

TABLE 6 Factor loading of 22-items.

Factor	Items	Factor loading
Socioeconomic-related	SCA21	0.52*
	SCA23	0.75**
	SCA24	0.75**
	SEA23	−0.58
	CAA45	0.62*
Healthcare team-related factors	SVA41	−0.26
	CAA41	0.65*
	CAA42	0.63*
	CAA43	0.72**
	CAA44	0.76**
Condition-related factors	CAA11	0.78**
	CAA12	0.67*
	CAA13	0.62*
	CAA14	0.48*
	CAA15	0.78**
Therapy-related factors	BNA31	0.72**
	BNA34	0.55*
	CAA71	0.79**
	CAA72	0.74**
Patient-related factors	BRA21	0.71**
	SEA11	−0.84
	SEA15	0.77**

In the context of loading factors in Structural Equation Modeling (SEM), the asterisk (*) typically indicates that the loading factor has achieved a high level of statistical significance or strong validity. In simpler terms, it suggests that the measurement variable has a strong influence on the factor or construct being measured in the SEM model.

3.2.2.4 Therapy-related factors

The composite reliability value for therapy-related factors was >0.7, indicating that the data were suitable for factor analysis. No item had low factor loading, consequently all were included in further analysis. One item (BNA34) showed the lowest factor loading (0.55) but was retained, as it exceeded the minimum acceptable value of 0.4. The other three items (BNA31, CAA71, and CAA72) met the reliability criteria and were retained. All four items were considered reliable for therapy-related factors (Table 6).

3.2.2.5 Patient-related factors

The composite reliability for patient-related factors was >0.7, indicating data suitability for factor analysis. One item (SEA11) had a very low factor loading and was excluded from further analysis, as it would not correlate with other items representing patient-related factors. The remaining two items (BRA21 and SEA15) were deemed acceptable and retained patient-related factors (Table 6), hence only SEA11 was excluded.

3.2.3 Structural equation modeling-partial least square (SEM-PLS)

The results of the questionnaires at the validation stage determined the items that proceeded to the SEM-PLS modeling stage (Figure 4). Upon model simulation, differences emerged between valid items in factor loadings at the analysis stage and factor loadings on SEM. In the analysis stage, SEA23, SVA41, and SEA11 were deemed invalid. In the simulated SEM-PLS model, SEA23, SVA41, CAA13, CAA14, BNA34, CAA72, SEA11, and SEA15 were excluded. The three items, including SEA23, SVA41, and SEA11, remained invalid in both factor analysis and SEM despite sharing similarities. CAA13, CAA14, BNA34, CAA72, and SEA15 which were valid in the factor analysis became invalid in SEM. This showed that SEM examined the effect of each item on the factor measured, and the influence of the factor on non-adherence. Consequently, SEM yielded more invalid items compared to factor analysis.

In the simulated SEM-PLS model, only one factor, namely, condition, significantly influenced non-adherence. This indicated why all condition-related factor items remained entirely valid at the analysis stage. However, the therapy-related factors had no impact on non-adherence in the SEM-PLS model. In comparison to the other four, condition-related factors significantly influenced patient non-adherence to medication.

Following the SEM-PLS modeling process, 14 valid items remained across the five factors, including those related to socioeconomics (4 items; SCA21, SCA23, SCA24, CAA45), healthcare team (4 items; CAA41, CAA42, CAA43, CAA44), medical condition (3 items; CAA11, CAA12, CAA15), therapy (2 items; BNA31, CAA71), and patients (1 item; BRA21). Only

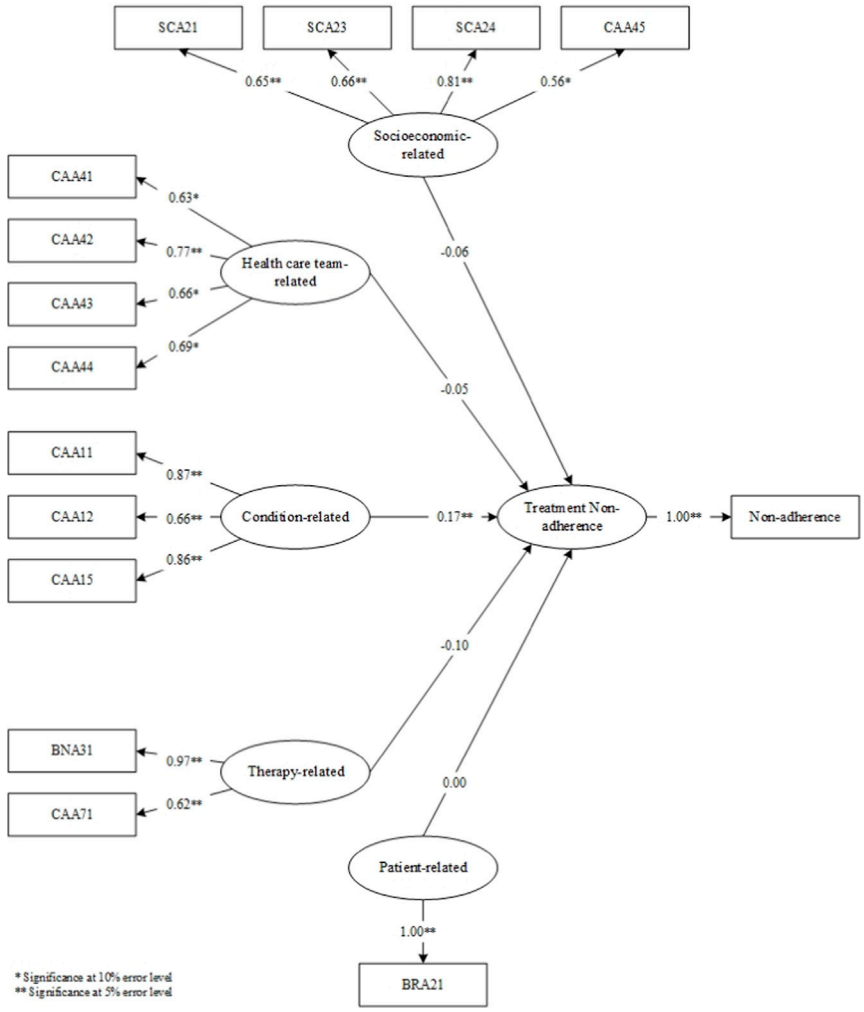

FIGURE 4
SEM-PLS modeling.

TABLE 7 Analysis of all factors after SEM-PLS modeling.

Factor	Cronbach's alpha	Composite reliability	AVE
Socioeconomic-related	0.62**	0.77**	0.46
Healthcare Team-related	0.65**	0.78**	0.48
Condition-related	0.72**	0.84**	0.64**
Therapy-related	0.60**	0.79**	0.66**
Patient-related	1.00**	1.00**	1.00**

The asterisk (*) in Cronbach's Alpha and Composite Reliability signifies a high level of statistical significance or strong validity. In simpler terms, it indicates that the measurements or constructs being assessed are reliable and consistent for the analysis or research being conducted.

condition-related factors significantly influenced non-adherence, and as indicated in Table 7, the constructs developed were reliable. The reliability test conducted in PLS applied Cronbach's alpha and composite reliability techniques. Cronbach's alpha measures the lower limit of the reliability value of a construct, while composite reliability estimates the actual value. Composite reliability is considered better at estimating the internal consistency of a construct. Moreover, the rule of thumb used for the composite reliability value indicated >0.7, and the obtained Cronbach's alpha value exceeded 0.6 (Chin, 1998; Ghozali, 2016), signifying that all constructs had good reliability.

Overall, the results of the questionnaire validation phase can be seen in Figure 5.

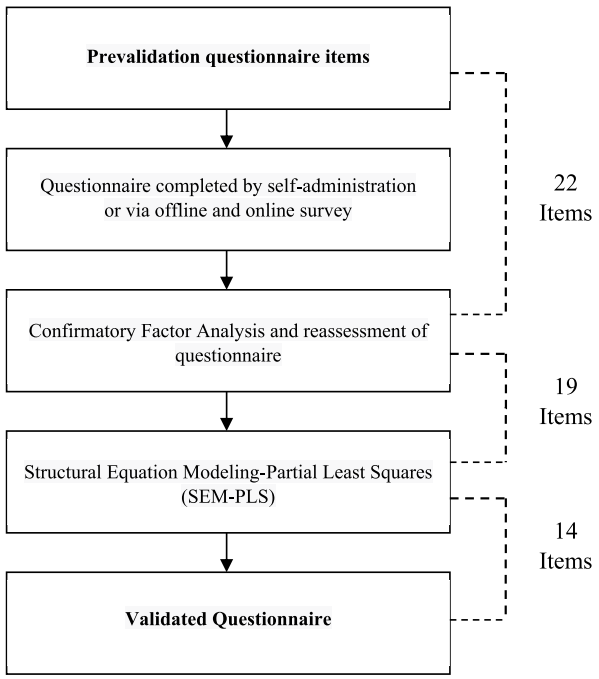

FIGURE 5
Process and results of questionnaire development.

4 Discussion

Following a rigorous validation process featuring nine experts, including a psychologist, three pulmonary specialists, two nurses, and three pharmacists, as well as 50 patients from two health facilities, 22 items were obtained for the final draft of the questionnaire. The questionnaire was tested using 346 TB patients who had only been on medication for 1–2 months. Additionally, it was distributed offline and online in accordance with ethical research agreements. The results of this study showed the influence of each item on the factors examined.

The questionnaire was suitably developed to address the complexities of the diverse regions in Indonesia and the unique healthcare challenges encountered. Indonesia has been reported to show significant regional disparities in healthcare infrastructure, patient attitudes, and socioeconomic influences (Erawati and Andriany, 2022; Siswantining et al., 2020; Pratiwi et al., 2020). Considering these disparities, the questionnaire was designed to be adaptable and relevant across different areas of the country, but some regional customization was required before the broad implementation (Mahmudiono and Laksono, 2021). In the initial phase of item development, the questionnaire was created based on evidence gathered from systematic reviews and qualitative studies rather than direct patient engagement (Bowden and Fox-Rushby, 2003). This choice was influenced by studies suggesting that expert-driven item generation often provides a more structured foundation for pilot testing (Collins, 2003). The questionnaire was designed to assess medication non-adherence factors in TB patients and intended for use across public and private healthcare settings in Indonesia, providing actionable insights for healthcare professionals. The insights provided by this questionnaire (Mekonnen and Azagew, 2018; Vaughan et al., 2019) were expected to assist policymakers, medical practitioners, and scientists in enhancing healthcare delivery and patient adherence to improve treatment outcomes (DiMatteo, 2004; Departemen Kesehatan, 2018; Kemenkes, 2020).

This study identified socioeconomic, healthcare team, condition, therapy, and patient-related issues as the five main factors contributing to medication non-adherence in TB patients. One item in each of the socioeconomic, healthcare team, and patient-related factors did not exert statistically significant effects, while all items in both condition and therapy were found to have significant impacts. Additionally, the factor loading value considered for each item was ≥0.40. The influence of each factor on the possibility of patient non-adherence was examined as presented in Figure 4. The analysis results showed that only condition-related factors significantly influenced medication non-adherence.

This study applied methods similar to those used in previous investigations conducted in Sabah, Malaysia (Guad et al., 2021). While several methods were replicated, the primary difference could be found in the analytical method. This study combined CFA with SEM-PLS, but other sources commonly used a single method, such as CFA or Exploratory Factor Analysis (EFA) (Deng et al., 2017; Soh et al., 2018; Gunawan et al., 2021). EFA is mostly used in cases where initial information is lacking or when hypotheses must be derived from a set of indicators, leading to the creation of variables from these indicators (Gorsuch, 1988; Fabrigar et al., 1999; Cudeck, 2000; Suhr, 2006; Fabrigar and Wegener, 2011; Hooper, 2012). During the analytical process, CFA was conducted because the indicators and variables were known. Besides, SEM-PLS is a relatively less utilized method for developing questionnaires, primarily due to its prevalence in investigations focused on predictive modeling (Brown, 2015). The combination of CFA and SEM-PLS was deployed to elucidate the capability of the developed and validated questionnaire to measure the impact of indicators on variables or dimensions and the effect of each variable on non-adherence (Brown and Moore, 2012; Hair et al., 2019; Kono and Sato, 2022). Through SEM-PLS analysis, this questionnaire was used to construct a predictive model for predicting TB patient non-adherence at the onset of treatment.

In the aspect of statistical analysis, this study applied robust methodological tools, specifically CFA and SEM-PLS, to examine the empirical results (Hair et al., 2019; Erawati and Andriany, 2022). This methodological choice was based on the predictive potential of the carefully developed and validated questionnaire. The CFA and SEM-PLS techniques not only clarified the complex causal pathways underlying the observed phenomena but could also forecast future trends (Luies et al., 2017). These methodologies synergistically facilitated a comprehensive examination of the relationships within the model, enabling predictions and enhancing the understanding of variable interactions (Collins et al., 2015; Dessalegn et al., 2016).

The applied methodologies were intentionally selected due to certain considerations. Despite other approaches, such as the regression technique, being valid and widely utilized, the

distinctive focus of this study necessitated a non-traditional approach (Zhu et al., 2022; Do Peterson et al., 2012; Chowdhury et al., 2015; Erawati and Andriany, 2022). The adopted approach created a distinct path suitably tailored to the inherent intricacies and nuances of the study question. In summary, the utilization of CFA and SEM-PLS represented a streamlined approach. Additionally, the predictive potential of the model constructed from the questionnaire resonated strongly with the applied methods. These statistical tools impart explanatory power and the invaluable ability to predict future trends.

The questionnaire served as a foundation for constructing a predictive model for non-adherence. Furthermore, the score of each item in it offered valuable insights into the influence exerted on non-adherence. Theoretically, this study provided an overview of the steps and procedures for developing and validating questionnaires used to assess non-adherence in TB patients as well as those suffering from other diseases. The questionnaire could be practically tested in various provinces across Indonesia or Southeast Asia, supporting healthcare providers in delivering appropriate services to patients at risk of non-adherence. However, this study is currently limited to measuring non-adherence in TB patients due to the unique demographic conditions in Indonesia.

5 Conclusion

A structured questionnaire was successfully developed to assess medication non-adherence among TB patients in Indonesia. The final 22 items that emerged from this rigorous process indicated a valid and robust questionnaire for assessing risk factors of medication non-adherence among pulmonary tuberculosis patients in Indonesia. The developed questionnaire was positioned to be a valuable tool for healthcare professionals, policymakers, and scientists in creating patient-centered strategies and interventions to address non-adherence.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

This study obtained approval from the ethics committees of Universitas Padjadjaran (No: 086/UN6. KEP/EC/2021), private hospitals (No: 1212/XIII/12/2020), and public hospitals (No: 13/KEPK-RSUPP/02/2021). Additionally, it was conducted in accordance with the Helsinki Declaration, and all participants provided informed consent.

Author contributions

LR: Data curation, Investigation, Writing–original draft. IA: Data curation, Writing–original draft. SA: Validation, Writing–review and editing. AI: Supervision, Writing–review and editing. IP: Supervision, Writing–review and editing. RA: Supervision, Writing–review and editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was funded by the Indonesian Ministry of Education, Culture, Research, and Technology through the BPPDN scholarship for LR. The funding source had no engagement in the design, collection, analysis, and interpretation of data, as well as in the manuscript writing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Pharmacology

TYPE Systematic Review
PUBLISHED 22 January 2024
DOI 10.3389/fphar.2024.1327155

OPEN ACCESS

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RECEIVED 24 October 2023
ACCEPTED 03 January 2024
PUBLISHED 22 January 2024

CITATION
Del Pino-Sedeño T, Infante-Ventura D, Hernández-González D, González-Hernández Y, González de León B, Rivero-Santana A, Hurtado I and Acosta Artiles FJ (2024), Sociodemographic and clinical predictors of adherence to antidepressants in depressive disorders: a systematic review with a meta-analysis. *Front. Pharmacol.* 15:1327155. doi: 10.3389/fphar.2024.1327155

Sociodemographic and clinical predictors of adherence to antidepressants in depressive disorders: a systematic review with a meta-analysis

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Introduction: Current evidence reveals concerning rates of non-adherence to antidepressant treatment, possibly influenced by various relevant determinants such as sociodemographic factors or those related to the health system and their professionals. The aim of this paper is to review the scientific evidence on sociodemographic and clinical predictors of adherence to pharmacological treatment in patients diagnosed with a depressive disorder.

Methods: a systematic review (SR) was conducted. The search for a previous SR was updated and *de novo* searches were performed in Medline, EMBASE, Web of Science (WoS) and PsycInfo (last 10 years). The risk of bias was assessed using the Cochrane tool for non-randomized studies—of Exposure (ROBINS-E). Meta-analyses were conducted.

Results: Thirty-nine studies (n = 2,778,313) were included, 24 of them in the meta-analyses. In the initiation phase, no association of adherence was found with any of the predictors studied. In the implementation and discontinuation phases, middle-aged and older patients had better adherence rates and lower discontinuation rates than younger ones. White patients adhered to treatment better than African-American patients.

Discussion: Age and ethnicity are presented as the predictive factors of pharmacological adherence. However, more research is needed in this field to obtain more conclusive results on other possible factors.

Systematic Review Registration: [https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023414059], identifier [CRD42023414059]

KEYWORDS

adherence, antidepressants, depression, depressive disorder, sociodemographic predictors, clinical predictors, systematic review, meta-analysis

1 Introduction

Mood disorders have become a central axis of public health policies due to both their high prevalence and the consequences that this group of disorders have in patients (GBD, 2019 Mental Disorders Collaborator, 2022).

Depressive disorders are a common mental health condition that can have a significant impact on an individual's overall well-being and daily functioning (World Health Organization, 2017; GBD, 2019 Mental Disorders Collaborator, 2022). This condition results in a reduction in the average life expectancy of 15 years with respect to the population that does not suffer from it (Rivera et al., 2019). In 2019, around 3.9% of the global population suffered from some type of depressive disorder, which translates into a figure of more than 279 million people (Santomauro et al., 2021). On the other hand, persistent depressive disorder, due to the long-lasting manifestation of symptoms, is related to higher rates of comorbidity and a considerable reduction in wellbeing and health-related quality of life (HRQoL) (Nübel et al., 2020).

There is a wide variability of therapeutic options available for the management of depressive disorders. Psychotherapy is indicated for mild to moderate depression, due to its proven effectiveness (NICE, 2022), its long-term superiority, as well as lower dropout rates and lower relapse rates than pharmacological treatments with tricyclic and second generation antidepressants (ADs) (selective serotonin reuptake inhibitors -SSRIs) (Cano-Vindel et al., 2012). However, for the approach and treatment of moderate to severe depressive disorders (Kok and Reynolds, 2017), pharmacological treatment with AD medications, accompanied by a relevant high-intensity psychological intervention is the recommended therapeutic choice (NICE, 2022). Therefore, pharmacological treatment is also among the treatments with proven effectiveness for the management of depression (NICE, 2022). The most recommended current pharmacological regimen, due to its benefit-risk balance, is monotherapy with second-generation ADs, such as SSRIs, among others. Therefore, it should be mentioned that the most recent generations of therapeutic agents have been shown to have higher adherence rates (Sheehan et al., 2008). Nevertheless, most patients do not achieve remission of their symptoms, which is why clinical practice guidelines recommend different second-order options, such as changing monotherapy or combined treatment with two types of ADs (Wolff et al., 2021). However, the effectiveness of a treatment depends on both the efficacy of a medication and patient adherence to the therapeutic regimen (Jimmy and Jose, 2011).

As stated by the World Health Organization (WHO) (World Health Organization, 2004), adherence is defined as the degree to which the person's behavior-taking medication, following a diet and executing lifestyle changes-corresponds to the agreed recommendations from a healthcare provider. The pharmacological adherence process consists of three phases (Vrijens et al., 2012): initiation, when the patient takes the first dose of a prescribed drug; implementation, defined as the extent to which a patient's actual dose corresponds to the dose of the prescribed regimen, and discontinuation, when the patient stops the medication on their own initiative, taking no doses thereafter.

Adherence to treatment with ADs significantly impacts the clinical outcomes of the recovery process, with non-adherent patients showing higher rates of relapse, hospitalizations, and visits to the emergency room for events related to depression. This increased need for ongoing medical care imposes a significant burden and economic impact on any healthcare system (Ho et al., 2016), especially considering that, 3 months after starting treatment, the percentage of non-adherent patients ranges from 30% to 70% (Párraga Martínez et al., 2014).

In this context, numerous studies have been carried out to determine the degree of adherence to psychopharmacological treatment with ADs and to analyze its correlates and predictors (Rivero-Santana et al., 2013; Párraga Martínez et al., 2014). The WHO identifies five groups of factors that influence, to a certain extent, the lack of adherence to drug treatment: social and economic factors, therapy-related factors, disease-related factors, patient-related factors, and healthcare system-related factors (Pagès-Puigdemont and Valverde-Merino, 2018). However, current evidence is not consistent regarding the factors relevant to predicting good adherence.

Lack of adherence has serious consequences for patients. Therefore, it is essential to identify the factors that influence the decision-making process regarding the initiation, continuation, or discontinuation of treatment. This information will help enhance current theoretical models and develop more precise and effective interventions tailored to diverse subgroups within the population (Saldaña et al., 2019) at a higher risk of non-adherence (Akincigil et al., 2007). However, the last systematic review (SR) published in this field was conducted 10 years ago (Rivero-Santana et al., 2013), and, thus, updating the available evidence is necessary.

The objective of this systematic review (SR) is to identify, critically evaluate and synthesize the new evidence available in the scientific literature on the sociodemographic and clinical predictive factors influencing adherence to drug treatment in adult patients diagnosed with a depressive disorder.

2 Methods

A systematic review (SR) was conducted by updating the search of a previous SR (Rivero-Santana et al., 2013), following the methodology of the Cochrane Collaboration, according to the MECIR (Methodological Expectations of Cochrane Intervention Reviews) standards (Higgins et al., 2016). The information related to this SR is presented following the guidelines of the PRISMA statement (Page et al., 2021). The SR protocol was registered in PROSPERO (registration number: CRD42023414059).

2.1 Selection criteria

Studies that evaluated sociodemographic and clinical factors predictive of adherence to AD treatment in patients diagnosed with depressive disorders and which met the selection criteria described below were selected.

Observational studies of prospective and retrospective cohorts were included for the study design. Randomized clinical trials, non-randomized clinical trials, experimental studies with a before-after design, case-control studies, cross-sectional studies, case series and isolated cases, animal studies, and *in vitro* studies were excluded.

The patients included were those over the age of 18 diagnosed with a depressive disorder (ICD-10: F32, depressive episodes; F33, recurrent depressive disorder; F34.1, dysthymia; DSM-V: 296.33, major depressive disorder; 300.4, persistent depressive disorder) by a healthcare provider or by the study investigator. Studies with patients with a manic episode and bipolar affective disorder (ICD-10: F-30-31), schizophrenia, schizotypal, and delusional disorders (ICD-10: F20-29), as well as patients receiving AD treatment without reported diagnosis, were excluded.

The following sociodemographic and clinical variables were considered as predictive factors: age, sex, ethnicity, education, marital status, income, employment status, diagnostic subtype, severity of depression, previous episodes, psychiatric and medical comorbidities, cognitive impairment, and self-perceived health or HRQoL.

Adherence (initiation, implementation and discontinuation) of the pharmacological prescriptions were included as result measures.

Regarding language, only studies published in English and/or Spanish were considered.

As for the type of publication, complete original papers and those published in scientific journals were considered. Conference papers, editorials, conference abstracts, letters to the editor, and opinions were excluded.

2.2 Bibliographic search

The search for relevant studies was performed following a search strategy around the terms depressive disorders, antidepressants and adherence in Medline (Ovid platform), EMBASE (Elsevier interface), Web of Science (WoS) (Clarivate Analytics) and PsycInfo (11/09/2022) (see Supplementary Table S1). The search was restricted to studies published in English or Spanish in the last 10 years, the date of the search for the previous SR (Rivero-Santana et al., 2013). The search for published studies was completed with the review of the bibliography lists of the relevant publications retrieved from the electronic databases and with verification in Google Scholar of the studies citing the selected studies.

2.3 Study selection processes

The bibliographic references recovered from the different databases were imported into the RAYYAN platform (Ouzzani et al., 2016) where duplicates were eliminated to subsequently select the pertinent studies.

Five reviewers performed the pairwise selection process independently and in parallel. The studies were selected in two phases, a first phase when the studies were selected based on the information provided in the title and abstract; and a second phase when the full texts of the studies selected as relevant in the first phase were analyzed and classified as included or excluded according to the specified selection criteria.

2.4 Data extraction processes

Data extraction from the studies was performed using data extraction sheets in Excel format designed *ad hoc*. A pilot test was conducted with two of the studies, independently by the all reviewers, with the aim of unifying extraction criteria. The rest of the extraction from each study was carried out in duplicate.

2.5 Data list

Data related to the identification of the article (authors, date of publication, country where the study was conducted, funding, etc.), the design and methodology (objective, design and duration of the study, characteristics and sociodemographic and clinical variables of participants and measure of adherence), as well as predictive factors and adherence, were extracted.

2.6 Assessment of risk of bias

The methodological quality of the included studies was assessed independently and in parallel by all reviewers using the Cochrane tool for non-randomized studies - of Exposure, ROBINS-E (ROBINS-E Development Group et al., 2023). Following the guidelines of the ROBINS-E tool, some specific characteristics of the study led directly to the result having a very high risk of bias since the control of confounders did not match the study's objective. In this SR, this minimal set of confounders include age, sex, and the level of depression.

The graphs for the summary of the risk of bias assessments were drawn with the Rovbis web app (McGuinness and Higgins, 2020).

Disagreements in the selection, extraction and risk of bias assessment phases were resolved after discussion and, if consensus was not reached, a third reviewer was consulted. The discussions and agreements were documented.

2.7 Synthesis of the evidence

The information collected was synthesized narratively with tabulation of the results from each included study. A quantitative synthesis using meta-analyses (MA) was performed when the reported data were combinable and the studies were homogeneous in their methodology (population, predictive factors, etc.). To estimate adherence rates (implementation and discontinuation), MA was conducted using the metaprop command (Nyaga et al., 2014) in the STATA software version

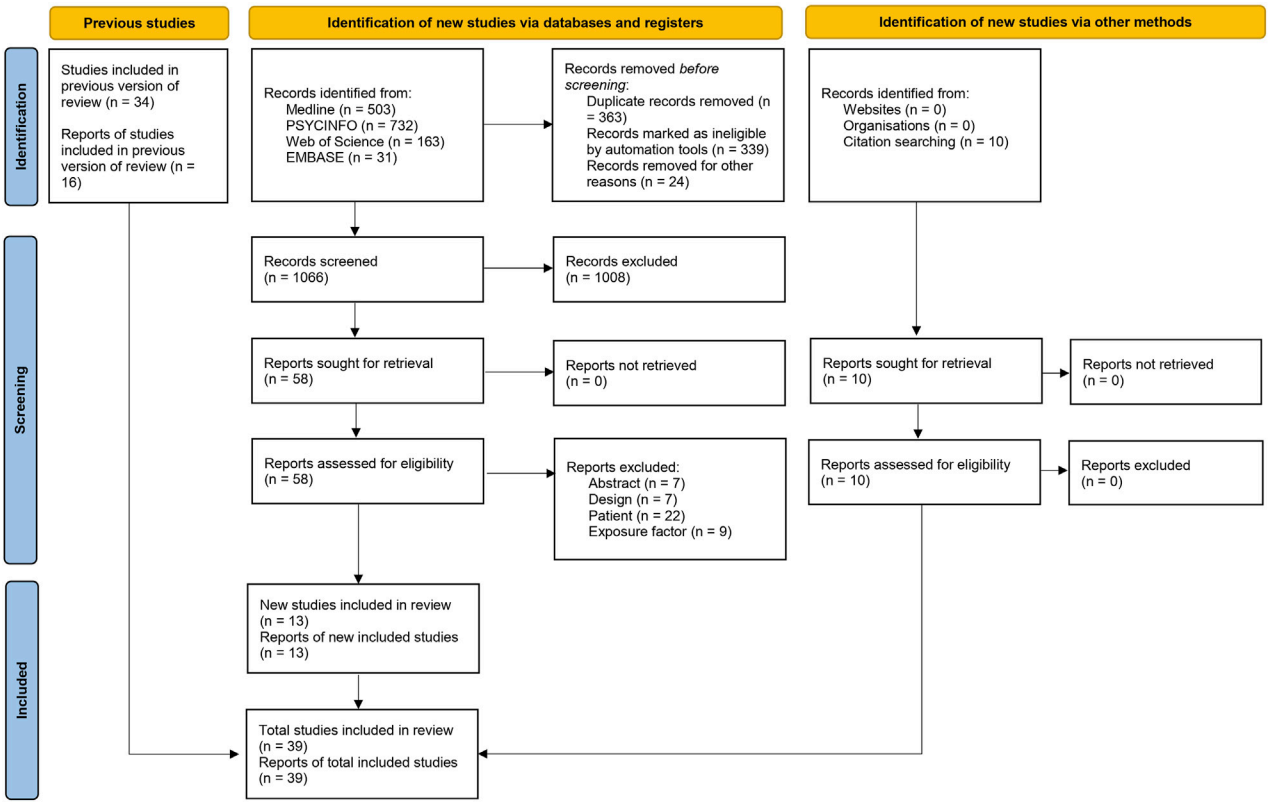

FIGURE 1
Flow diagram of the selection process of studies.

17 for Windows (Stata Corp LLC, College Station, TX, United States). To synthesize the predictors of adherence, taking into account the weeks of follow-up, odds ratio (OR) or hazard ratio (HR) and their 95% confidence intervals were synthesized using the generic inverse variance method with the Review Manager software for Windows (RevMan, version 5.4.1., 2020; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). MA were performed using univariate estimates only, multivariate estimates only, and preferably univariate or multivariate estimates for each predictor. MA were performed for each predictive factor using both univariate and/or multivariate estimates. An MA was performed exclusively using the respective data type in scenarios where only univariate or multivariate data were available. Conversely, when both univariate and multivariate data were present, preference was given to conducting multivariate estimates. If multivariate data were not available, univariate estimates were preferably used as an alternative. The I^2 was used to assess statistical heterogeneity. Even so, a random effects model was used to address the inherent variability between studies. In the case of psychiatric comorbidities, the analysis was performed both globally (having a psychiatric comorbidity or not), and separately for different psychiatric comorbidities (sleep disorders vs. alcohol-related disorders vs. substance-related disorders). It was not possible to perform meta-regression or publication bias analyses due to the small number of studies included in each MA.

3 Results

The number of references identified during the bibliographic search, once the duplicates were eliminated, came to 1,066. After the title and abstract screening, 58 publications were retrieved for full-text evaluation. After applying the pre-established selection criteria, 45 were excluded. On the other hand, the review of the studies included in the previous SR according to the current selection criteria resulted in 16 additionally included studies. Finally, by hand-examining the bibliography listings of the selected studies, as well as by checking Google Scholar for studies citing the selected studies, an additional 10 studies were located.

Thus, 39 studies were included in the final selection (Lin et al., 1995; Lin et al., 2011; Keeley et al., 2000; Keeley et al., 2007; Demyttenaere et al., 2001; Sirey et al., 2001; Cohen et al., 2004; Donohue et al., 2004; Olfson et al., 2006; Akincigil et al., 2007; Goethe et al., 2007; McLaughlin et al., 2007; Stang et al., 2007; ten Doesschate et al., 2009; Yen et al., 2009; Chen et al., 2010; Ereshefsky et al., 2010; Holma et al., 2010; Liu et al., 2010; Liu et al., 2011; Milea et al., 2010; Woolley et al., 2010; Hung et al., 2011; Vlahiotis et al., 2011; Merrick et al., 2012; Wu et al., 2012; Wu et al., 2013; Kales et al., 2013; Kales et al., 2016; Wu and Davis-Ajami (2014); Yau et al., 2014; Kogut et al., 2016; Gerlach et al., 2017; Gerlach et al., 2019; Holvast et al., 2019; Bhattacharjee et al., 2020; Nam-Ju and Yeon-Pyo, 2020; Noh et al., 2020; Noh et al., 2022; Shin et al., 2022) (See Figure 1).

10.3389/fphar.2024.1327155

TABLE 1 General characteristics of the included studies.

Study	Country	Setting	Funding	Design	No of cohorts	Follow-up (weeks)
Akincigil et al. (2007)	United States	Database	No	RCS	1	33
Bhattacharjee et al. (2020)	United States	Database	No	RCS	1	52
Chen et al. (2010)	United States	Database	NR	RCS	1	39
Cohen et al. (2004)	Canada	Psychiatric center	Yes	RCS	1	14
Demyttenaere et al. (2001)	Belgium	Primary care	Yes	RCS	1	24
Donohue et al. (2004)	United States	Database	No	RCS	1	26
Ereshefsky et al. (2010)	United States	Database	Yes	RCS	1	26
Gerlach et al. (2017)	United States	Primary care and veteran center	No	PCS	1	16
Gerlach et al. (2019)	United States	Veterans center	No	RCS	1	52
Goethe et al. (2007)	United States	Database	Yes	PCS	1	12
Holma et al. (2010)	Finland	Psychiatric center	No	PCS	1	260
Holvast et al. (2019)	Netherlands	Database	No	RCS	1	42
Hung et al. (2011)	Taiwan	Hospital	No	PCS	1	24
Kales et al. (2013)	United States	Primary care	No	PCS	2	16
Kales et al. (2016)	United States	Veterans center	No	PCS	1	16
Keeley et al. (2000)	United States	Primary care	NI	RCS	1	14
Keeley et al. (2007)	United States	Primary care	No	PCS	1	12
Kogut et al. (2016)	United States	Database	No	RCS	1	12
Lin et al. (1995)	United States	Primary care	No	RCS	1	16
Lin et al., 2011	United States	Database	NI	RCS	1	52
Liu et al. (2010)	United States	Database	Yes	RCS	3	52
Liu et al. (2011)	United States	Database	Yes	RCS	1	52
McLaughlin et al. (2007)	United States	Database	Yes	RCS	1	39
Merrick et al. (2012)	United States	Database	No	RCS	1	16
Milea et al. (2010)	France	Database	NR	RCS	1	52
Nam-Ju and yeon-pyo (2020)	South Korea	Database	No	RCS	1	26
Noh et al. (2022)	South Korea	Database	No	RCS	1	26
Olfson et al. (2006)	United States	Database	No	RCS	1	12
Shin et al. (2022)	South Korea	Database	No	RCS	2	26
Sirey et al. (2001)	United States	Outpatient clinic	No	RCS	1	12
Stang et al. (2007)	United Kingdom	Database	Yes	RCS	2	39
ten Doesschate et al. (2009)	Netherlands	Psychiatric center	No	PCS	1	104
Vlahiotis et al. (2011)	United States	Database	No	RCS	1	26
Woolley et al. (2010)	United States	Hospital	Yes	PCS	1	12
Wu et al. (2012)	United States	Database	No	RCS	1	52
Wu et al. (2013)	Taiwan	Database	No	RCS	1	26
Wu and Davis-Ajami, 2014	United States	Database	No	RCS	1	26
Yau et al. (2014)	China	Hospital	No	RCS	1	52
Yen et al. (2009)	Taiwan	Database	NR	PCS	1	52

Note: Funding: industry funding; N: number; NR: NR: not reported; PCS: prospective cohort study; RCS: retrospective cohort study.

Although many of these articles were excluded because they did not meet more than one selection criteria, Supplementary Table S2 shows the main reason for their exclusion.

3.1 Characteristics of included studies

The characteristics of the studies, participants, predictive factors and adherence can be seen in more detail in Tables 1, 2, 3; however, a description of the main characteristics is provided below.

All included studies were published in English between the years 1995 and 2022. The countries where such studies were published were: United States (25 studies), South Korea (3 studies); Taiwan (3 studies), the Netherlands (2 studies), Belgium (1 study), Canada (1 study), China (1 study), Finland (1 study), France (1 study) and the United Kingdom (1 study).

In terms of design, 12 were prospective observational cohort studies (Demyttenaere et al., 2001; Cohen et al., 2004; Goethe et al., 2007; Keeley et al., 2007; ten Doesschate et al., 2009; Yen et al., 2009; Holma et al., 2010; Woolley et al., 2010; Hung et al., 2011; Kales et al., 2013; Kales et al., 2016; Gerlach et al., 2017) and the remaining 27 were retrospective observational cohort studies.

Of all the selected studies, the majority, 35 (89.7%), included one cohort, three studies (7.69%) included two cohorts (Stang et al., 2007; Kales et al., 2013; Shin et al., 2022) and one study included three cohorts (Liu et al., 2010). Multiple cohort studies were compared based on characteristics such as the dose or type of medication, ethnicity, and the healthcare insurance coverage (e.g., uninsured, partially or fully insured).

The studies were carried out in psychiatric settings (Cohen et al., 2004; ten Doesschate et al., 2009; Holma et al., 2010), primary care centers (Lin et al., 1995; Keeley et al., 2000; Keeley et al., 2007; Demyttenaere et al., 2001; Kales et al., 2013; Gerlach et al., 2017), hospitals (Woolley et al., 2010; Hung et al., 2011; Yau et al., 2014), veterans clinics (Kales et al., 2016; Gerlach et al., 2017; Gerlach et al., 2019), outpatient clinics (Sirey et al., 2001), while the rest were conducted with database records.

Of the studies selected for this review, 23.08% received industry funding (Demyttenaere et al., 2001; Cohen et al., 2004; Goethe et al., 2007; McLaughlin et al., 2007; Stang et al., 2007; Ereshefsky et al., 2010; Liu et al., 2010; Liu et al., 2011; Woolley et al., 2010), 64.10% did not receive funding from industry and the source of their funding is unknown in 12.82% of the studies.

Follow-up periods were variable, with the closest follow-up being 12 weeks after starting treatment (Sirey et al., 2001; Olfson et al., 2006; Goethe et al., 2007; Keeley et al., 2007; Woolley et al., 2010; Kogut et al., 2016) and the longest period was 260 weeks (Holma et al., 2010). The information regarding the characteristics of the studies can be seen below in Table 1.

Regarding the predictive factors, more specifically the sociodemographic ones, of the 39 studies selected for this SR, 34 analyzed the effect of age on adherence to treatment, 28 the effect of sex, 13 studies analyzed ethnicity, six studies explored the influence of educational level, five of marital status, and five studies of employment status.

Regarding clinical factors, of the 39 studies, 13 analyzed the relationship of psychiatric comorbidities on adherence to treatment, 16 medical comorbidities, five the severity of depression, two the relationship of previous episodes, three the subtype of diagnosis and one perceived health on adherence.

In relation to the phases of adherence, of all the selected studies, only one studied the adherence initiation phase (Holvast et al., 2019), 29 studied the implementation phase and 16 the discontinuation phase.

The selected studies used different tools to measure adherence in the implementation phase. By using the Medication Possession Ratio (MPR), nine studies established a threshold of 80%, one study a threshold of 75% and another one a threshold of 70%; two studies used the Brief Medication Questionnaire; one study used the Medication Adherence Behavior Scale; one the Medication Event Monitoring System - Pill Count; one the Medication Adherence Questionnaire (MAQ); three used self-reports developed *ad hoc* and eight used prescription records.

The information described above is shown in more detail in Table 3 below.

3.2 Risk of bias assessment

In general, the risk of bias was considered very high in 20 of the studies in this SR due to the lack of control over significant confounding variables such as age, sex, and the severity of depression. In the rest of the fully evaluated articles, the risk of bias was high in four studies, low in 13 studies, while only one study presented unclear risk of bias.

Detailed judgments for each of the risk of bias domain criteria are shown in Figures 2, 3.

3.3 Evidence synthesis

The evidence tables included in Supplementary Tables S3–S6 show the main findings obtained in the included studies.

Of the total number of included studies, 24 could be included in the MA (Donohue et al., 2004; Olfson et al., 2006; Akincigil et al., 2007; Goethe et al., 2007; Stang et al., 2007; ten Doesschate et al., 2009; Yen et al., 2009; Chen et al., 2010; Ereshefsky et al., 2010; Liu et al., 2010; Liu et al., 2011; Milea et al., 2010; Woolley et al., 2010; Vlahiotis et al., 2011; Merrick et al., 2012; Wu et al., 2012; Wu et al., 2013; Kales et al., 2013; Kales et al., 2016; Yau et al., 2014; Kogut et al., 2016; Gerlach et al., 2019; Holvast et al., 2019; Noh et al., 2022). Tables 4, 5 show the results of the estimation of the global effect size for the outcome measures that could be meta-analyzed (see forest plots in Supplementary Figures S1–S13).

3.3.1 Adherence rates

In relation to the initiation rates, 36.04% of the patients who were prescribed an AD treatment did not start it (Holvast et al., 2019).

Regarding the implementation phase, only 14% of the patients complied with the pharmacological treatment for up to 3 months, a similar percentage of the patients complied between months three and six (13%). In addition, a slight increase to 29% was observed between months six and nine and this increased to 57% between months nine and twelve, with this being the moment of greatest

TABLE 2 Main demographic and baseline clinical characteristics of the participants in the included studies.

Study	Diagnosis of depression	Population subgroup	Inclusion criteria	Exclusion criteria	N	N loss	N women (%)	Mean (SD) range
Akincigil et al. (2007)	MDE	Adults	1. ≥ 18 years	NR	4312	0	2907 (67.42)	NR
			2. New MDE					
			3. New indication AD.					
Bhattacharjee et al. (2020)	CS depression with dementia	Older adults	1. ≥ 65 years	1. End-stage renal disease	6239	0	4666 (74.79)	NR
			2. Dementia	2. Liver disease				
			3. Depression CS or greater (ICD-9-CM: 296.2, 296.3, 309.1, 300.4 or 311)					
Chen et al. (2010)	MDD	Adults	1. MDD (ICD-9-CM: 296.20-296.24)	1. Age < 18	4102	0	2679 (65.31)	40 (12)
				2. Bipolar disorder or schizophrenia				
			2. AD second generation	3. AD (previous 6 months)				NR
				4. AD empowerment				
Cohen et al. (2004)	MDE	Adults	1. MDE	1. Substance abuse or dependence (previous 6 months)	65	57	34 (52.31)	41.4 (11.4)
			2. AD.	2. Bipolar disorders or schizophrenia (previous 12 months)				NR
				3. CS unstable medical condition				
Demyttenaere et al. (2001)	MDD	Adults	1. 18–65 years	NR	272	0	196 (72.06)	43 (13)
			2. MDD (DSM-IV-TR)					NR
			3. AD.					
Donohue et al. (2004)	MDD	Adults	1. 18–64 years	1. Bipolar disorder or schizophrenia	36062	0	24342 (67.5)	44 (NR)
			2. AD	2. No AD medical coverage				NR
			3. MDD (DSM-IV)					
Ereshefsky et al. (2010)	Depression	Adults	1. ≥ 18 years	NR	45481	0	NR	NR
			2. SSRIs					
			3. Depression (ICD-9: 296.2, 296.3, 300.4 or 311.x9)					
			4. Without AD (6 months before)					
Gerlach et al. (2017)	CS depression	Older adults	1. ≥ 60 years	1. Bipolar disorder or schizophrenia	452	0	108 (23.98)	NR
			2. CS depression (PHQ-9 > 5)	2. Cognitive impairment				
			3. Start of AD.	3. Suicidal risk				
Gerlach et al. (2019)	CS depression	Older adults	1. ≥ 60 years	1. Bipolar disorder or schizophrenia	278	12	8 (2.88)	65 (6.3)
			2. CS depression (PHQ-9 > 5)	2. Cognitive impairment				NR

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TABLE 2 (*Continued*) Main demographic and baseline clinical characteristics of the participants in the included studies.

Study	Diagnosis of depression	Population subgroup	Inclusion criteria	Exclusion criteria	N	N loss	N women (%)	Mean (SD) range
			3. New AD prescription	3. Suicidal risk				
Goethe et al. (2007)	MDD	Mixed population	1. MDD (DSM-IV: 296.2x or 296.3x)	1. Bipolar disorder or schizophrenia or dementia	445	39	291 (65.39)	41.0 (12.7)
			2. 18–75 years	2. Electroconvulsive therapy				18–75
			3. SSRI.	3. ≥ 1 AD.				
Holma et al. (2010)	MDD	Adults	1. Depressive symptoms (previous 18 months)	NR	542	360	128 (23.62)	41.5 (11.1)
			2. MDD (DSM-IV)					NI
Holvast et al. (2019)	Depression	Older adults	1. ≥ 60 years	NR	1512	0	1052 (69.58)	68* (NR)
			2. Depression (ICPC P03 or P76)					63–75*
Hung et al. (2011)	MDD	Mixed population	1. 18–65 years old	1. Substance dependence or abuse (prior 1 month)	135	0	101 (74.81)	30.2 (NR)
			2. MDD (DSM-IV-TR)	2. Psychotic, catatonic symptoms or psychomotor retardation				18–65
				3. Chronic medical conditions				
Kales et al. (2013)	CS depression	Older adults	1. ≥ 60 years	1. Suicidal ideation, bipolar disorder or schizophrenia or impairment	198	10	102 (51,52)	67.3 (NR)
			2. CS depression (GDS ≥ 5)	2. Not Caucasian or African-American				NR
			3. New AD.	3. Not English				
Kales et al. (2016)	CS depression	Older adults	1. ≥ 60 years	1. Cognitive decline	311	0	8 (2.57)	64.9 (6.3)
			2. Depression (PHQ-9 > 5)					60–86
			3. AD (1 week)					
Keeley et al. (2000)	Depression	Adults	1. Start of AD	1.Organic mental disorders	30	0	23 (76.67)	41.2 (12.9)
				3. Not English				
			2. Depression	3. Suicidal risk				NR
				4. Bipolar disorder				
Keeley et al. (2007)	MDD	Adults	1. TDM (DSM-IV, PHQ-9)	1. Pregnant or nursing	20	0	14 (70)	48.3 (8.6)
			2.AD	2. Bipolar disorder				NR
			3. English	3. Cognitive impairment				
			4. ≥ 18 years					
Kogut et al. (2016)	Depression	Adults	1. New AD	NR	1983	0	1502 (75.74)	NR
			2. Depression					
Lin et al. (1995)	Episode of depression	Mixed population	1. 18–65 years old	NR	164	NR	118 (71.95)	47 (NR)
			2. A new AD prescription					18–75

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TABLE 2 (*Continued*) Main demographic and baseline clinical characteristics of the participants in the included studies.

Study	Diagnosis of depression	Population subgroup	Inclusion criteria	Exclusion criteria	N	N loss	N women (%)	Mean (SD) range
			3. Depression					
Lin et al. (2011)	MDD	Adults	1. MDD (ICD-9 codes: 296.2x or 296.3x)	1. Bipolar disorder	2111615	0	64678 (30,63)	NR
			2. AD.	2. Mood stabilizers and antipsychotics				
				3. Childish				
Liu et al. (2010)	MDD	Adults	1. Start of duloxetine	NR	6132	0	4539 (74.02)	45.6–47.2 (NR)
			2. MDD (ICD-9-CM: 296.2 or 296.3) 1 year before duloxetine					18–64
			3. 18–64 years old					
			4. Insured (≥12 months)					
Liu et al. (2011)	MDD	Adults	1. Start of SNRI or SSRI	1. >1 SNRI or SSRI.	44026	0	31366 (71.24)	NR
			2. MDD (ICD-9-CM: 296.2 or 296.3)					
			3. 18 to 64 years					
McLaughlin et al. (2007)	Depression	Adults	1. ≥ 18 years	1. Prior use of AD (previous 9 months)	3138	0	2219 (70.71)	46.18 (13.94)
			2. Depression (ICD-9-CM: 296.2, 296.3, 300.4 or 311)					NR
Merrick et al. (2012)	Depression	Adults	1. ≥ 18 years	1. Bipolar disorder	383	0	276 (72.06)	NR
			2. Depressive disorders (ICD-9-CM: 296.20-296-.25, 296.30-296.35, 298.0, 300.4 or 309.1, 311)					
			3. New AD prescription					
Milea et al. (2010)	DD	Adults	1. New episode	1. Combined treatment	134287	0	91485 (68.13)	NR
			2. New DD (ICD-9-CM: 296.2, 296.3, 300.4 or 311)					
			3. Monotherapy					
Nam-Ju and yeon-pyo (2020)	Depression	Adults	1. Depression (ICD-10: F32.x, F33.x or F34.1)	1. Bipolar disorder or schizophrenia	142336	NR	91800 (64.50)	NR
			2. ≥ 1 AD.					
Noh et al. (2022)	Depression	Pregnant	1. Women	1. AD not prescribed (30 days prior)	5207	0	5207 (100)	32.3 (4.8)
			2. 15–50 years					
			3. One or more live births					NR
			4. Depression (ICD-10: F32.x, F33.x, F34.1x or F41.2x)					
Olfson et al. (2006)	Depression	Adults	1. ≥ 18 years	NR	390	0	258 (66.15)	NR
			2. Depression (ICD-9-CM: 296.2, 296.3, 300.4 or 311)					

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TABLE 2 (*Continued*) Main demographic and baseline clinical characteristics of the participants in the included studies.

Study	Diagnosis of depression	Population subgroup	Inclusion criteria	Exclusion criteria	N	N loss	N women (%)	Mean (SD) range
Shin et al. (2022)	Depression	Adults	1. ≥ 19 years	1. Previous depression	176745	0	115458 (65.32)	NR
			2. Depression (ICD-10: F32–34 or F43)					
Sirey et al. (2001)	MDD	Adults	1) MDD	1. Cognitive impairment	1242	NR	82 (6.6)	NR
			2) Seeking treatment	2. Alcohol or substance abuse (prior 1 month)				
				3. Another axis I disorder				
Stang et al. (2007)	Depression	Adults	1) 18–64 years	1. Benzodiazepines or AD (previous 6 months)	2991	NR	1898 (63.46)	40.84 (NR)
			2) Depression (ICD-9-CM: 296.2, 296.3, 300.4 or 311)					NR
			3) Bupropion					
ten Doesschate et al. (2009)	MDE	Adults	1. ≥ 2 MDE (last 5 years - DSM-IV)	1. Bipolar disorder or schizophrenia	172	81	NR	NR
			2. Current referral status	2. Organic brain damage, alcohol or substance abuse				
			3. HAM-D < 10	3. Anxiety disorder				
				4. Cognitive electroconvulsive therapy or psychotherapy				
Vlahiotis et al. (2011)	An episode or rMDD	Adults	1. New SSRI or SNRI	NR	16659	0	10885 (65.34)	NR
			2. ≥ 18 years					
			3. Single episode or rMDD.					
Woolley et al. (2010)	MDD	Mixed population	1. 18–75 years	1. Bipolar disorder, schizophrenia or dementia	403	NR	290 (71.96)	41 (NR)
			2. SSRIs	2. Electroconvulsive therapy				NR
			3. MDD (DSM-IV: 296.2x or 296.3x)	3. ≥ 1 AD.				
Wu et al. (2012)	MDD	Adults	1. 18 and 64 years old	1. Bipolar disorder	3083	0	2384 (77.33)	18–64
			2. MDD (ICD-9-CM: 296.2 or 296.3)					
Wu et al. (2013)	DD	Adults	1. DD (ICD-9-CM: 296.2, 296.3 or 300.4)	1. Bipolar disorder, schizophrenia or dementia	25744	NR	16244 (63.1)	43.6 (16.4)
				2. Antipsychotics or mood stabilizers				NR
				3. ≥ 1 types of antidepressants on the index date				
Wu and Davis-Ajami (2014)	Depression	Pregnant	1. Pregnant	1. AD (previous 6 months)	804	0	804 (100)	25.8 (6.2)
			2. ≥ 18 years					
			3. Single or multiparous live births					
			4. Depression (ICD-9-CM: 296.2, 296.3, 300.4 or 311)	2. Bipolar disorder or schizophrenia				NR

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TABLE 2 (*Continued*) Main demographic and baseline clinical characteristics of the participants in the included studies.

Study	Diagnosis of depression	Population subgroup	Inclusion criteria	Exclusion criteria	N	N loss	N women (%)	Mean (SD) range
			5. Use of AD 280 days before calving					
			6. ≥ 2 AD prescriptions during pregnancy					
Yau et al. (2014)	MDD	Adults	1. ≥ 18 years	1. Another axis I disorder	189	0	71 (37.57)	46.1 (14.8)
			2. AD	2. Dementia or mental retardation				20–88
			3. MDD (ICD-10)	3. AD (previous 6 months)				
				4. Follow-up by psychiatry				
				5. History of overdose or suicide				
Yen et al. (2009)	DD	Adults	1. DD (DSM-IV)	1. Mental retardation	164	43	81 (49.39)	42.7 (12.9)
			2. CES-D ≥17	2. Substance use				17–75
				3. Psychotic disorders				

AD: antidepressant; Older adults: adults >60 years; CES-D; depression scale of the center for epidemiological studies; CS: clinically significant; DD: depressive disorder; ICD: international classification of diseases; MDE: major depressive episode; GDS: geriatric depression scale; HAM-D: hamilton scale for depression; SSRIs: Selective Serotonin Reuptake Inhibitors; SNRI: serotonin and norepinephrine reuptake inhibitors; NR: not report; PHQ-9: patient health questionnaire; MDD: major depressive disorder; rMDD: recurrent major depressive disorder.

compliance. Once 1 year of treatment had been completed, the percentage of patients began to decrease to 31%, returning to a similar rate to the initial rates after 1 year (16%).

Regarding the discontinuation phase, 31% of the patients who were prescribed an AD treatment completed their treatment between the first three and 6 months of treatment and this rose to 52% of the patients at 40–52 weeks.

3.3.2 Predictors of the initiation phase of adherence

The results relating to the predictive factors of adherence during the initiation phase (Holvast et al., 2019), are described below.

When considering the different AD treatments together, no predictive factor (physical comorbidities, chronic drug use, age, sex, and socioeconomic status) was associated with non-initiation. However, specifically for the SSRIs, it was observed that not starting pharmacological therapy was associated with a higher socioeconomic level (OR = 1.13; 95% CI: 1.01, 1.27). Regarding other types of ADs (N06AF -monoamine oxidase inhibitors- and N06AX—other ADs), being a woman was associated with the risk of non-initiation (OR = 7.89; 95% CI: 1.50, 41.68), however, the increase in the number of medications for chronic use decreased this risk (OR = 0.65; 95% CI: 0.46–0.90).

3.3.3 Predictors of the implementation phase of adherence

The results obtained relating to the predictive factors of adherence during the implementation phase are described below.

3.3.3.1 Age

Five studies (Akincigil et al., 2007; Chen et al., 2010; Liu et al., 2010; 2011; Wu et al., 2012) provided synthesizable data on the predictor variable age through an MA.

Between the first 12–16 weeks, patients older than 65 years of age (OR = 2.23; 95% CI: 1.61, 3.10; I^2 = 13%; k = 2), patients between the ages of 35–49 ($OR_{35\text{-}49}$ = 1.51; 95% CI: 1.23, 1.85; I^2 = 58%; k = 2) and between 50 and 65 ($OR_{50\text{-}65}$ = 1.85; 95% CI: 1.05, 3.26; I^2 = 93%; k = 2) had better adherence rates when compared to younger ones (18–34 years).

Between 33 and 39 weeks, patients older than 65 years did not present better adherence rates (vs. 18–34 years) (OR = 1.32; 95% CI: 0.88, 1.97; I^2 = 0%; k = 2). However, patients aged 35–49 and 50–65 did maintain better adherence rates than younger patients ($OR_{35\text{-}49}$ = 1.35; 95% CI: 1.11, 1.63; I^2 = 0%; k = 2; $OR_{50\text{-}65}$ = 1.65; 95% CI: 1.31, 2.09; I^2 = 4%; k = 2).

Between 39 and 52 weeks, middle-aged patients (50–65 years of age) when compared to younger ones (18–35 years), continued to present better adherence rates (OR = 2.03; 95% CI: 1.91, 2.15; I^2 = 0%; k = 6). However, this effect disappeared in patients aged between 25 and 50 years (OR = 1.02; 95% CI: 0.69, 1.52; I^2 = 67%; k = 2).

From week 39 to 52, patients between 35 and 49 years, compared to those between 18 and 34, showed a better treatment adherence rate (OR = 1.49; 95% CI: 1.38, 1.62; I^2 = 15%; k = 3).

Additionally, data were available in 17 studies assessing the implementation phase, but could not be synthesized through an MA. Four studies (McLaughlin et al., 2007; Stang et al., 2007; Yen et al., 2009; Yau et al., 2014) that evaluated age (continuous) as a predictor found that the treatment adherence rate was higher among older individuals. Among the studies comparing different age

TABLE 3 Main characteristics of the predictive factors and the measure of adherence.

Study	Predictive factors					Adherence				
	Measure moment (week)	Sociodemographic	Definition	Clinics	Definition	Initiation	Implementation	Discontinuation	Adherence measure	Adherence criteria
Akincigil et al. (2007)	16, 33	Sex		Medical comorbidity	Alcohol/ substances; cancer; migraine; CVD/diabetes	No	Yes	No	MPR	≤ 75%
		Age	18–25; 25–39; 40–49; 50–66; ≥ 65	Psychiatric comorbidity	Anxiety					
Bhattacharjee et al. (2020)	16, 50	Age	65–74; ≥ 75	NA	NA	No	Yes	No	MPR	≤ 80%
		Sex								
		Ethnicity	White vs. others							
Chen et al. (2010)	39	Age	18–34; 35–49; 50–64; ≥ 65	Psychiatric comorbidity	Anxiety	No	Yes	No	MPR	≤ 80%
		Sex		Medical comorbidity	Alcohol/ substances					
Cohen et al. (2004)	14	Age	Years	Severity of depression	MDE status	No	Yes	No	*Medication Event Monitoring System*	Continuous (% days of container opening/ prescription days)
		Sex		Previous episodes	Previous MDE					
Demyttenaere et al. (2001)	24	Age	Years	NA	NA	No	No	Yes	Self-report	Continue with the medication
		Sex								
Donohue et al. (2004)	26	Age	NA	Diagnostic subtype	NI	No	Yes	No	Prescription record	≥ 60 days
Ereshefsky et al. (2010)	26	Age	18–34; 35–49; 50–64	Psychiatric comorbidity	Alcohol/ substances	No	No	Yes	Prescription record	≥ 30 days
Gerlach et al. (2019)	52	Age	60–64; 65–74; 75–90	Psychiatric comorbidity	PTSD; Anxiety; Substances	No	Yes	No	BMQ	≤ 80%
		Sex	Male/female	Medical comorbidity	CCI					
		Ethnicity	White vs. African-American							
		Education								

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TABLE 3 (*Continued*) Main characteristics of the predictive factors and the measure of adherence.

Study	Predictive factors					Adherence				
	Measure moment (week)	Sociodemographic	Definition	Clinics	Definition	Initiation	Implementation	Discontinuation	Adherence measure	Adherence criteria
			Some higher education							
		Civil status	Spouse/partner vs. Single/no partner							
Gerlach et al. (2017)	16	Sex		NA	NA	No	Yes	No	MPR	≤ 80%
		Ethnicity	White vs. African-American	NA	NA					
Goethe et al. (2007)	12	Sex		Psychiatric comorbidity	Anxiety	No	No	Yes	Self-report	Yes/no
		Age	18–75							
		Ethnicity	White/No white							
		Employment situation	Presence (yes/no)	NA	NA					
Holma et al. (2010)	26, 78, 260	Civil status	Living alone (yes/no)	NA	NA	No	Yes	No	Self-report	1. Regularly; 2. Something irregular, no; 3. Very irregularly; 4. Not at all
Holvast et al. (2019)	2, 42, 52	Age	Years	Psychiatric comorbidity	Presence (yes/no)	Yes	Yes	Yes	MPR	≤ 80%
		Sex	NA	Medical comorbidity	Number					
		Income	Socioeconomic level							
Hung et al. (2011)	16	Age	Continuous	Severity of depression	Chronic (yes/no)	No	No	Yes	Self-report	Continue with medication
		Sex		Medical comorbidity	Migraine					
		Education	Years	Psychiatric comorbidity	Anxiety					
		Employment situation	Unemployed or employed							

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TABLE 3 (*Continued*) Main characteristics of the predictive factors and the measure of adherence.

Study	Predictive factors					Adherence				
	Measure moment (week)	Sociodemographic	Definition	Clinics	Definition	Initiation	Implementation	Discontinuation	Adherence measure	Adherence criteria
Kales et al. (2013)	16	Ethnicity	White; African-American	NA	NA	No	Yes	No	BMQ	Skip ≥ 2 daily doses
Kales et al. (2016)	16	Ethnicity	White; African-American	Medical comorbidity	CCI	No	Yes	No	MPR + BMQ	≤ 80%
		Civil status	Partner (yes/no)							
Keeley et al. (2000)	14	Age	Years	Medical comorbidity	Number	No	No	Yes	Self-report	Continue with medication
		Ethnicity	Hispanic (yes/no)							
Keeley et al. (2007)	12	Age	NA	Psychiatric comorbidity	Somatoform disorder	No	Yes	Yes	Self-report + Prescription record	Continuous (% days supplied/total days) × 100
		Sex		Medical comorbidity	NA					
		Ethnicity	NI							
		Employment situation	Presence (yes/no)							
		Education								
Kogut et al. (2016)	12	Age	18–34; ≥ 35	NA	NA	No	Yes	No	MPR	≤70%
		Sex		NA	NA					
Lin et al. (1995)	4, 16	Sex		Severity of depression	Dysthymia	No	Yes	No	Self-report	NI
					Number of episodes					
		Age	Years							
		Education	Years							
Lin et al. (2011)	52	Sex		Psychiatric comorbidity	Psychotic disorders	No	Yes	No	Prescription record	Continuous (% days supplied/365)
					Anxiety					
		Age	28–25; 26–49; 50–64; ≥ 65	NA	NA					
		Ethnicity	Non-Hispanic White; Non-							

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TABLE 3 (*Continued*) Main characteristics of the predictive factors and the measure of adherence.

Study	Predictive factors					Adherence				
	Measure moment (week)	Sociodemographic	Definition	Clinics	Definition	Initiation	Implementation	Discontinuation	Adherence measure	Adherence criteria
			Hispanic Black; Hispanic; Other							
		Income	< $20000; $20000-$40000; $40000-$60000; > $60000							
Liu et al. (2010)	52	Age	18–25; 26–35; 36–45; 46–55; 56–64	Perceived health perceived health	NA	No	Yes	Yes	MPR	≤ 80%
Liu et al. (2011)	52	Age	18–25; 26–35; 36–45; 46–55; 56–64	Medical comorbidity	Headaches and lower back	No	Yes	Yes	MPR	≤ 80%
		Sex		Psychiatric comorbidity	Fibromyalgia, hypersomnia, Alcohol/ Substances					
McLaughlin et al. (2007)	39	Age	Years	NA	NA	No	Yes	No	Prescription record	≤ 70%
		Sex								
Merrick et al. (2012)	16	Age	49–59; 60–74; ≥ 75	Diagnostic subtype	Major depression (yes/no)	No	Yes	No	Prescription record	≤ 70%
		Sex		Medical comorbidity	CCI					
		Raza	White; not white							
Milea et al. (2010)	4, 42	Age	< 18; 18–39; 40–64; ≥ 65	NA	NA	No	No	Yes	Prescription record	≠ days dispensing and prescription
		Sex								
Nam-Ju and yeon-pyo (2020)	12; 26	Income	Class 1–5	NA	NA	No	Yes	No	MPR	≤ 80% (non-adherent)
Noh et al. (2022)	26	Age	Years	Psychiatric comorbidity	Psychotic, anxiety, stress, substance, eating, personality and sleep disorder	No	No	Yes	Prescription record	≥ 45 days

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TABLE 3 (*Continued*) Main characteristics of the predictive factors and the measure of adherence.

Study	Predictive factors					Adherence				
	Measure moment (week)	Sociodemographic	Definition	Clinics	Definition	Initiation	Implementation	Discontinuation	Adherence measure	Adherence criteria
				Medical comorbidity	CVD/diabetes/ epilepsy					
Olfson et al. (2006)	12	Age	18–44; 45–64; ≥ 65	NA	NA	No	No	Yes	Self-report	≥ 30 days
		Sex	NA							
		Ethnicity	White; black; Hispanic; other							
		Civil status	Married; not married; divorced or separated; widower							
		Employment situation	Unemployed (yes/no)							
Shin et al. (2022)	26	Age	19–34; 35–49; 50–64; ≥65	NA	NA	No	Yes	No	1. MPR	1. ≤ 80% (non-adherent)
		Sex							2. Duration	2. ≥ 39 days
Sirey et al. (2001)	12	Age	< 60, ≥ 60	Severity of depression	NI	No	Yes	No	Self-report + Prescription record	Likert scale 6 + concordance with pill count
Stang et al. (2007)	39	Sex		NA	NA	No	Yes	No	Prescription record	≤ 70%
		Age	Years							
ten Doesschate et al. (2009)	104	Sex		Medical comorbidity	Presence (yes/no)	No	Yes	No	MAQ	Score
		Age	Years	Previous episodes	Number					
		Civil status	Lives alone (yes/no)	Severity of depression	HAM-D					
		Employment situation	Presence (yes/no)							
		Education	Superior/other							
Vlahiotis et al. (2011)	26	Sex	NA	Medical comorbidity	CCI	No	No	Yes	Prescription record	Days supplied/days dispensed

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TABLE 3 (*Continued*) Main characteristics of the predictive factors and the measure of adherence.

Study	Predictive factors					Adherence				
	Measure moment (week)	Sociodemographic	Definition	Clinics	Definition	Initiation	Implementation	Discontinuation	Adherence measure	Adherence criteria
		Age	18–25; 26–40; 41–55; 56–64	Psychiatric comorbidity	Anxiety, bipolar disorder and OCD					
Woolley et al. (2010)	NI	Sex		NA	NA	No	No	Yes	Self-report	Continue with medication
		Age	Years							
Wu et al. (2012)	52	Age	18–30; 31–40; 41–50; 51–60; 61–64	Psychiatric comorbidity	Anxiety	No	Yes	No	1. MPR	≤ 80%
		Ethnicity	Caucasian; Afro-American	Medical comorbidity	0, 1, 2, o ≥ 3				2. Duration	≤ 15 days
		Sex								
Wu et al. (2013)	4, 12, 26	Age	18–44, 45–64, ≥ 65	Psychiatric comorbidity	Anxiety, sleep disorder, alcohol/ substances	No	No	Yes	Prescription record	≥ 30 days
		Sex		Medical comorbidity	CCI					
Wu and Davis-Ajami (2014)	26	Age	Years	Medical comorbidity	CCI	No	Yes	No	Prescription record	≤ 80%
		Ethnicity	White; not white							
Yau et al. (2014)	26	Age	Years	NA	NA	No	Yes	No	Prescription record	≤ 80%
		Sex								
Yen et al. (2009)	52	Sex		Diagnostic subtype	Major depression	No	Yes	No	Medication Adherence Behavior Scale	Score
		Age	Years							
		Education	Years							

BMQ: brief medication questionnaire; CCI: charlson comorbidity index; CVD: cardiovascular disease; MAQ: medication adherence questionnaire; MPR: medication possession ratio; NA: not applicable; NR: not report; OCD: obsessive-compulsive disorder; PTSD: post-traumatic stress disorder.

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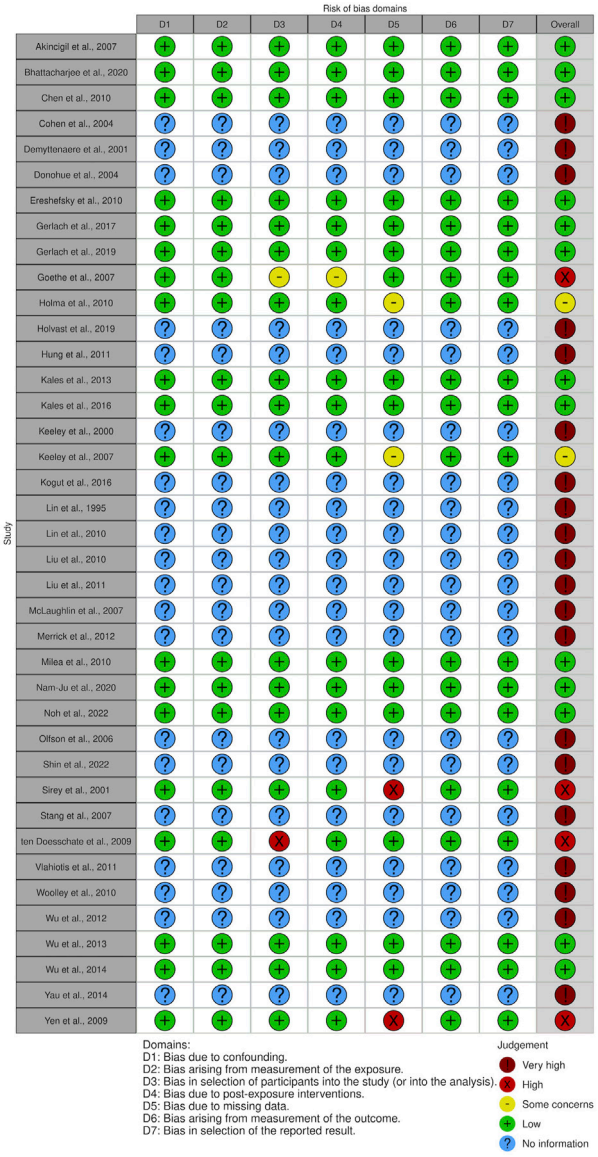

FIGURE 2
Risk of bias assessment of included studies.

groups, one study indicated a higher likelihood of treatment adherence among individuals between the ages of 35–65 compared to younger individuals (Shin et al., 2022). Three other studies also provided similar data, indicating that elderly patients have better adherence rates than patients under 60 years (Sirey et al., 2001), 45 years (Merrick et al., 2012) or 35 years (Kogut et al., 2016) of age. In the remaining nine studies (Lin et al., 1995; Lin et al., 2011; Cohen et al., 2004; Keeley et al., 2007; ten Doesschate et al., 2009; Wu and Davis-Ajami (2014); Gerlach et al., 2017; Holvast et al., 2019; Bhattacharjee et al., 2020), no significant differences of adherence during the implementation phase were found among different age groups.

3.3.3.2 Sex

The MA incorporated the findings from 11 studies (Donohue et al., 2004; Akincigil et al., 2007; Stang et al., 2007; Yen et al., 2009; Chen et al., 2010; Liu et al., 2011; Merrick et al., 2012; Yau et al., 2014; Kogut et al., 2016; Gerlach et al., 2019; Holvast et al., 2019).

Women adhered better to treatment than men between weeks 12 and 16 (OR = 1.10; IC95%: 1.01, 1.20; I^2 = 0%; k = 4), although as the weeks progressed (26–39 and 52 weeks), this effect subsided ($OR_{26\text{-}39}$ = 1.10; 95% CI: 0.98, 1.24; I^2 = 47%; k = 5; OR_{52} = 1.05; 95% CI: 1.00, 1.10; I^2 = 0%; k = 4).

Eleven additional studies could not be included in the MA. One of them (Shin et al., 2022) reported that female individuals presented a better treatment adherence rate than male individuals. The rest of the studies (Lin et al., 1995; Lin et al., 2011; Cohen et al., 2004; Keeley et al., 2007; McLaughlin et al., 2007; ten Doesschate et al., 2009; Wu et al., 2012; Kales et al., 2013; Gerlach et al., 2017; Bhattacharjee et al., 2020) did not find significant differences in adherence rates by sex.

3.3.3.3 Ethnicity

The MA incorporated the findings from five studies (Merrick et al., 2012; Wu et al., 2012; Kales et al., 2013; Kales et al., 2016; Gerlach et al., 2019).

White patients had higher treatment adherence rates than African-Americans at both 16 and 52 weeks (OR_{16} = 2.67; 95% CI: 1.86, 3.83; I^2 = 0%; k = 3; OR_{52} = 1.85; 95% CI:1.25, 2.74; I^2 = 37%; k = 2).

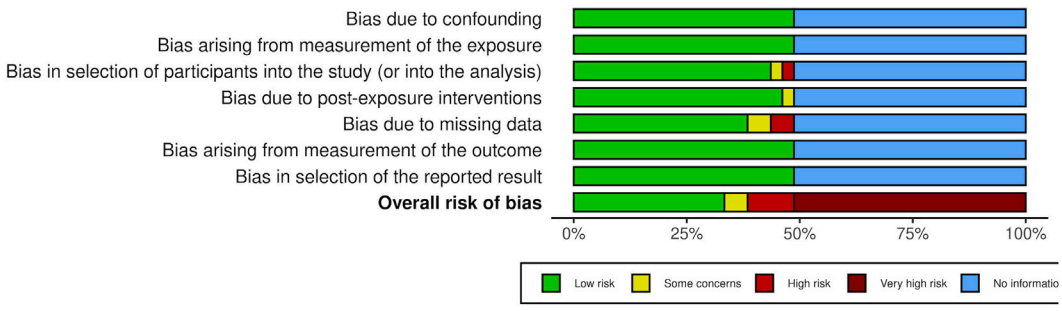

FIGURE 3
Risk of bias assessment across included studies.

TABLE 4 Results of the meta-analyses. Implementation.

EXPOSURE FACTOR/*Variable*	Model	K	OR/HR*	95% CI	I^2 (%)	Test for subgroup differences (%) (*p*-value)
AGE						
Subgroup: 25–50 years by follow-up (*ref.: 18–24 years*)						
Total	Random	2	1.02	(0.69, 1.52)	67	NA
39–52 weeks, Univariate	Random	2	1.02	(0.69, 1.52)	67	NA
Subgroup: 35–49 years by follow-up (*ref.: 18–34 years*)						
Total (*ref.: 18–34 years*)	Random	7	1.47	(1.40, 1.55)	1	0 (0.61)
12–16 weeks, *Univariate*	Random	2	1.51	(1.23, 1.85)	58	NA
33–39 weeks, *Univariate*	Random	2	1.35	(1.11, 1.63)	0	NA
39–52 weeks, *Preferably multivariate*	Random	3	1.49	(1.38, 1.62)	15	NA
Subgroup: 50–65 years by follow-up (*ref.: 18–34 years*)						
Total (*ref.: 18–34 years*)	Random	4	1.73	(1.29, 2.32)	79	0 (0.72)
12–16 weeks, *Univariate*	Random	2	1.85	(1.05, 3.26)	93	NA
33–39 weeks, *Univariate*	Random	2	1.65	(1.31, 2.09)	4	NA
39–52 weeks, *Univariate*	Random	6	2.03	(1.91, 2.15)	0	NA
Subgroup: >65 years by follow-up (*ref.: 18–34 years*)						
Total (*ref.: 18–34 years*)	Random	4	1.80	(1.29, 2.53)	46	75 (0.05)
12–16 weeks, *Univariate*	Random	2	2.23	(1.61, 3.10)	13	NA
33–39 weeks, *Univariate*	Random	2	1.32	(0.88, 1.97)	0	NA
SEX						
Subgroup: sex by follow-up (*ref.: male*)						
Total (*ref.: male*)	Random	13	1.07	(1.03, 1.11)	0	0 (0.52)
12–16 weeks, *Preferably multivariate*	Random	4	1.10	(1.01, 1.20)	0	NA
26–39 weeks, *Univariate*	Random	5	1.10	(0.98, 1.24)	47	NA
52 weeks, *Preferably multivariate*	Random	4	1.05	(1.00, 1.10)	0	NA
ETHNICITY						
Subgroup: ethnicity (African American) by follow-up (*ref.: white*)						
Total	Random	5	2.19	(1.63, 2.94)	42	44.8 (0.18)
16 weeks, *Multivariate*	Random	3	2.67	(1.86, 3.83)	0	NA
52 weeks, *Multivariate*	Random	2	1.85	(1.25, 2.74)	37	NA
PSYCHIATRIC COMORBIDITY						
Subgroup: anxiety by follow-up (*ref.: no*)						
Total	Random	6	1.14	(0.97, 1.34)	64	84 (0.002)
12–16 weeks, *Univariate*	Random	2	1.02	(0.90, 1.15)	0	NA
33–39 weeks, *Univariate*	Random	2	1.04	(0.87, 1.24)	0	NA
52 weeks, *Preferably multivariate*	Random	2	1.50	(1.25, 1.81)	0	NA

Note: HR: hazard ratio; NA: not applicable OR: odds ratio; Random: random effect; ref.: reference.

Additionally, data from five studies (Keeley et al., 2007; Lin et al., 2011; Wu and Davis-Ajami (2014); Gerlach et al., 2017; Bhattacharjee et al., 2020) could not be synthesized through an MA. Only one study (Keeley et al., 2007) did not find differences in adherence rates between Caucasian, African-Americans and Hispanic patients. Among the remaining studies, two of them reported a higher likelihood of treatment adherence in the implementation phase among white/Caucasian individuals compared to African-American or non-white/non-Caucasian patients (Wu et al., 2012; Wu and Davis-Ajami, 2014). In one study (Bhattacharjee et al., 2020), white patients showed better adherence compared to non-white race and Hispanic patients. The remaining study (Lin et al., 2011) provided similar results, finding that Hispanic patients have lower levels of adherence compared to Caucasian or other ethnic patients. However, this study found no differences between Hispanics and African-Americans.

3.3.3.4 Education

Five studies evaluated the impact of education in the implementation phase of adherence (Lin et al., 1995; Keeley et al., 2007; ten Doesschate et al., 2009; Yen et al., 2009; Gerlach et al., 2019).

TABLE 5 Results of the meta-analyses. Discontinuation.

EXPOSURE FACTOR/*Variable*	Model	K	OR/ HR*	95% CI	I^2 (%)	Test for subgroup differences (%) (*p*-value)
AGE						
Continuous						
Total	Random	2	0.98	(0.97, 0.99)	0	NA
12 weeks, *Multivariate*	Random	2	0.98	(0.97, 0.99)	0	NA
Subgroup: 25–40 years by follow-up (*ref.: 18–24 years*)						
Total	Random	2	0.81	(0.72, 0.93)	55	NA
26–52 weeks, *Univariate*	Random	2	0.81	(0.72, 0.93)	55	NA
Subgroup: 56–64 years by follow-up (*ref.: 18–24 years*)						
Total	Random	2	0.55	(0.44, 0.68)	83	NA
26–52 weeks, *Univariate*	Random	2	0.55	(0.44, 0.68)	83	NA
Subgroup: 40–65 years by follow-up (*ref.: 18–39 years*)						
Total	Random	2	0.73	(0.64, 0.82)	73	NA
52 weeks, *Univariate*	Random	2	0.73	(0.64, 0.82)	73	NA
SEX						
Subgroup: sex by follow-up (*ref.: male*)						
Total	Random	2	1.00	(0.98, 1.02)	0	NA
4 weeks, *Multivariate*	Random	2	1.00	(0.98, 1.02)	0	NA
PSYCHIATRIC COMORBIDITY						
Subgroup by psychiatric comorbidity (*26 weeks*) (*ref.: no*)						
Total	Random	3	0.99*	(0.87, 1.11)	93	91.1 (<0.00001)
Alcohol-related disorders, *Multivariate*	Random	2	1.16*	(1.08, 1.23)	0	NA
Sleep disorder, *Univariate*	Random	2	0.85*	(0.76, 0.95)	88	NA
Substance-related disorder, *Preferably univariate*	Random	2	0.98	(0.87, 1.11)	0	NA

Note: HR: hazard ratio; NA: not applicable; OR: odds ratio; Random: random effect; ref.: reference.
*HR.

Two of the studies reported sufficient data on the influence of education on the implementation phase of adherence between week 54 and 104 to be included in an MA (ten Doesschate et al., 2009; Gerlach et al., 2019). However, the analysis showed very high heterogeneity rates (I^2 = 76%), and as such the pooled data are not presented.

All studies (Lin et al., 1995; Keeley et al., 2007; ten Doesschate et al., 2009; Yen et al., 2009; Gerlach et al., 2019) reported a non-significant effect of years of education on the implementation phase of adherence.

3.3.3.5 Civil status

Four studies (ten Doesschate et al., 2009; Holma et al., 2010; Kales et al., 2016; Gerlach et al., 2019) analyzed the effect of civil status on adherence. Three of them (Holma et al., 2010; Kales et al., 2016; Gerlach et al., 2019) found a significant result. Individuals with spouse, partner or not living alone presented higher rates of adherence than individuals without spouse, partner or living alone. Due to disparities in follow-up, the results presented could not be effectively synthesized using MA.

Please refer to Supplementary Table S3 in the Supplementary Material to access the data from individual studies.

3.3.3.6 Income

Four studies (Akincigil et al., 2007; Holvast et al., 2019; Nam-Ju and Yeon-Pyo, 2020) examined the influence of income on adherence during the implementation phase. However, an MA could not be conducted due to the wide variability in categorizing income levels. Despite this limitation, three of them (Akincigil et al., 2007; Holvast et al., 2019; Nam-Ju and Yeon-Pyo, 2020) consistently found that adherence was lower among individuals with lower incomes compared to those with higher incomes. The remaining study (Lin et al., 2011) reported a non-significant result.

3.3.3.7 Medical comorbidities

MA could not be performed. Eight studies explored the impact of medical comorbidities on adherence (Akincigil et al., 2007; Keeley et al., 2007; Liu et al., 2011; Merrick et al., 2012; Wu et al., 2012; Kales et al., 2016; Gerlach et al., 2019; Bhattacharjee et al., 2020).

Three studies (Merrick et al., 2012; Kales et al., 2016; Gerlach et al., 2019) analyzed the impact of medical comorbidities using the Charlson Comorbidity Index (CCI) on adherence. The CCI is a medical tool for assessing both

the number and severity of comorbid diseases, which helps to predict mortality (Charlson et al., 1987). Of the three studies, two (Kales et al., 2016; Gerlach et al., 2019) found that individuals with a CCI score greater than zero had a higher rate of adherence during the implementation phase in contrast to individuals with other CCI scores. However, the remaining study (Merrick et al., 2012) did not find significant differences in adherence between individuals with a CCI score of two and those with a CCI score between 0 and 1. Additionally, one study used the Elixhauser Comorbidity Index (Wu et al., 2012). The said study found higher levels of adherence in patients who scored 2 or more on the Elixhauser Comorbidity Index compared to those who scored lower. However, patients who scored 1 did not differ from those who scored 0.

Two studies analyzed the impact of comorbid chronic pain conditions (such as low back pain, migraines, fibromyalgia, or headaches) on treatment adherence and found significant differences. One study (Liu et al., 2011) indicated that individuals with headaches, low back pain, or fibromyalgia had a lower likelihood of treatment adherence compared to those without these conditions. In the other study (Akincigil et al., 2007), patients with headaches or migraines were less likely to be adherent at 16 weeks, although this difference was not observed at the 33-week follow-up.

One study (Bhattacharjee et al., 2020) reported that people with Parkinson's disease had a slightly higher probability of treatment adherence compared to people without Parkinson's, Additionally, individuals with cardiovascular disease and diabetes showed a lower probability of adherence compared to those without these health conditions at 16 weeks, but this effect was not observed at the 33-week follow-up (Akincigil et al., 2007).

3.3.3.8 Psychiatric comorbidities

The MA incorporated the findings from four studies with regard to anxiety comorbidity. Presenting this type of disorder simultaneously with depression, between weeks 12–16 and 33–39, did not influence the rates of adherence to pharmacological treatment for depression ($OR_{12\text{-}16}$ = 1.02; 95% CI: 0.90, 1.15; I^2 = 0%; k = 2; $OR_{33\text{-}39}$ = 1.04; 95% CI: 0.87, 1.24; I^2 = 0%; k = 2). However, after week 52, suffering from anxiety at the same time as depression increased adherence rates (OR = 1.50; 95% CI: 1.25, 1.81; I^2 = 0%; k = 2).

Additional data related to psychiatric comorbidities from five studies could not be included in the MA. Three studies (Keeley et al., 2007; Lin et al., 2011; Gerlach et al., 2019) revealed that the presence of several psychiatric comorbidities (i.e., anxiety disorder, somatoform complaints, substance use or post-traumatic stress disorders) did not significantly impact the implementation process. Furthermore, one study (Chen et al., 2010) reported that patients with a comorbid substance use disorder had a lower probability of adherence at 12 weeks, but not at 39 weeks of follow-up. The last study (Liu et al., 2011) found results consistent with the ones mentioned earlier. The finding was that patients with alcohol related-disorders and the use or abuse of substances had worse adherence rates compared to those who do not suffer from them. Conversely, patients with hypersomnia had a higher likelihood of continuing to adhere to treatment. On the contrary, patients with anxiety or comorbid fibromyalgia had worse implementation rates.

3.3.3.9 Diagnostic subtype previous episodes and severity

Threes studies (Cohen et al., 2004; Donohue et al., 2004; Yen et al., 2009) investigated the impact of diagnostic subtype on treatment adherence and did not observe any significant differences.

A single study (Cohen et al., 2004) investigated the impact of previous episodes on adherence and did not observe any significant differences.

MA could not be performed. Four studies (Lin et al., 1995; Sirey et al., 2001; Cohen et al., 2004; Merrick et al., 2012) investigated the impact of severity on treatment implementation and did not observe any significant differences.

3.3.4 Predictors of the discontinuation phase of adherence

The results obtained relating to the predictors of adherence during the discontinuation phase (non-persistence) are described below.

3.3.4.1 Age

The MA incorporated the findings from six studies (Goethe et al., 2007; Liu et al., 2010; 2011; Milea et al., 2010; Woolley et al., 2010; Vlahiotis et al., 2011).

The increase in age generated a slight decrease in discontinuation rates at 12 weeks (OR = 0.98; 95% CI: 0.97, 0.99; I^2 = 0%; k = 2).

Between weeks 26–52, patients aged 25–40 (OR = 0.81; 95% CI: 0.72, 0.93; I^2 = 55%; k = 2) and 56–64 (OR = 0.55; 95% CI: 0.44, 0.68; I^2 = 83%; k = 2) presented lower rates of discontinuation of AD treatment compared to those aged 18–24.

At week 52, only patients aged 40–64 (vs. 18–39) maintained lower discontinuation rates (OR = 0.73; 95% CI: 0.64, 0.82; I^2 = 73%; k = 2) compared to those aged 18–39.

Data from another eight studies could not be synthesized using MA. In five studies, no significant differences were found among different age groups (Keeley et al., 2000; 2007; Demyttenaere et al., 2001; Olfson et al., 2006; Noh et al., 2020). However, two studies (Ereshefsky et al., 2010; Wu et al., 2013) reported that there was a lower likelihood of treatment discontinuation among individuals older than 35 and 45 years compared to younger individuals. A similar result was found in another study that evaluated age as a continuous variable (Hung et al., 2011), where a greater age independently predicted a lower risk of early discontinuation. In contrast, one study (Hung et al., 2011) found the opposite effect, where older people were at a higher risk of discontinuation.

Please refer to Supplementary Table S5 in the Supplementary Material to access the data from individual studies.

3.3.4.2 Sex

The MA investigating the influence of sex on adherence during the discontinuation phase included findings from two studies (Olfson et al., 2006; Milea et al., 2010). Sex did not affect the discontinuation rates at 4 weeks (OR = 1.00; 95% CI: 0.98, 1.02; I^2 = 0%; k = 2).

Another seven studies (Demyttenaere et al., 2001; Goethe et al., 2007; Keeley et al., 2007; Hung et al., 2011; Vlahiotis et al., 2011; Wu et al., 2013; Holvast et al., 2019) were not included in the MA. Among them, two studies (Goethe et al., 2007; Vlahiotis et al., 2011) consistently reported that men had a significantly higher risk of discontinuation than women. Milea et al. (2010) reported a similar result, although this was observed as only a trend. In contrast, one study (Wu et al., 2013) reported that men presented a significantly lower risk than women. The remaining studies found no significant impact of gender on discontinuation.

3.3.4.3 Ethnicity

MA could not be performed. Three studies examined the impact of ethnicity on discontinuation (Keeley et al., 2000; Keeley et al., 2007; Olfson et al., 2006). Two of them did not observe any significant differences (Keeley et al., 2000;Keeley et al., 2007), while another study found that Hispanic patients had a higher rate of treatment discontinuation than non-Hispanic patients (Olfson et al., 2006).

3.3.4.4 Education

Two of the three studies (Olfson et al., 2006; Woolley et al., 2010) provided sufficient data regarding the impact of educational level on discontinuation within 12 weeks to conduct an MA. However, the analysis revealed a high level of heterogeneity ($I^2 = 83$), and as such pooled data are not presented.

One study reported a higher rate of treatment discontinuation among patients with less than 12 years of formal education. However, the remaining two studies (Keeley et al., 2007; Woolley et al., 2010) did not observe significant differences.

3.3.4.5 Civil status

MA could not be performed. The civil status of the patients did not influence the discontinuation rates at 4 weeks (Olfson et al., 2006).

3.3.4.6 Income

MA could not be performed. Two studies (Olfson et al., 2006; Holvast et al., 2019) investigated the impact of income level on discontinuation. Only Olfson et al. (2006) observed that individuals with a low income had a significantly higher rate of treatment discontinuation compared to those with a high income.

3.3.4.7 Medical comorbidities

MA could not be performed. Six studies (Keeley et al., 2000; Keeley et al., 2007; ten Doesschate et al., 2009; Vlahiotis et al., 2011; Wu et al., 2013; Wu and Davis-Ajami (2014)) explored the impact of medical comorbidities on discontinuation and did not observe significant differences.

Three studies suggested that the presence of various medical comorbidities could actually lead to a decreased risk of discontinuation of AD treatment. For instance, one study (Noh et al., 2022) reported that a reduced likelihood of AD discontinuation was found in women with a higher obstetric comorbidity index or the presence of cardiovascular disease. Similarly, another investigation highlighted the impact of somatic comorbidities, including hypertension, lipid metabolic disorder, and diabetes, which were associated with a lower occurrence of treatment discontinuation (Milea et al., 2010). Furthermore, in one study (Hung et al., 2011), patients with migraines were less inclined to discontinue treatment when compared to those without migraine conditions.

3.3.4.8 Psychiatric comorbidities

The MA included data from three studies (Ereshefsky et al., 2010; Wu et al., 2013; Noh et al., 2022) concerning psychiatric comorbidities. Overall, the presence of a psychiatric comorbidity did not significantly affect adherence rates (HR = 0.99; 95% CI 0.87, 1.13; $I^2 = 93\%$; k = 3).

However, when examining specific comorbidities, it was found that patients with alcohol-related disorders presented worse adherence rates to AD treatment at 26 weeks (HR = 1.16; 95% CI: 1.08, 1.23; $I^2 = 0\%$; k = 2) (Ereshefsky et al., 2010; Wu et al., 2013). Conversely, the presence of sleep disorders did not influence adherence rates at 26 weeks (HR = 0.85; 95% CI: 0.76, 0.95; $I^2 = 88\%$; k = 2) (Wu et al., 2013; Noh et al., 2022), nor did substance abuse-related disorders (HR = 0.98; 95% CI: 0.87, 1.11; $I^2 = 0\%$; k = 2) (Wu et al., 2013; Noh et al., 2022).

Additional data relating to psychiatric comorbidities from nine studies could not be synthesized using MA. One study (Liu et al., 2011) reported similar findings to the previous ones, suggesting that patients with alcohol related-disorders and the use or abuse of substances had worse adherence rates compared to those without these conditions at 52 weeks. However, patients with hypersomnia were more likely to continue complying with treatment. Another study (Holvast et al., 2019) found that the presence of psychological comorbidity was not associated with discontinuation. However, sensitivity analysis for different types of ADs revealed an association between the psychological comorbidity and discontinuation of SSRIs.

Concerning anxiety comorbidity, there is some variation in the findings. In one study (Wu et al., 2013), patients with anxiety comorbidity were less likely to discontinue AD treatment at 26 weeks. Conversely, another study (Vlahiotis et al., 2011) suggested that anxiety disorders often led to increased discontinuation. However, two other studies (Goethe et al., 2007; Wu et al., 2012) did not find this association at 12 and 52 weeks.

Different studies reported that comorbidities such as panic/agoraphobia or post-traumatic stress disorder (Hung et al., 2011), or sleep disorder and anxiety/stress related disorder (Noh et al., 2022), were associated with reduced treatment discontinuation rates. However, the presence of a psychosomatic comorbidity was associated with an increased discontinuation rate (Milea et al., 2010).

Finally, two studies (Keeley et al., 2007; Noh et al., 2020) found that the presence of somatoform complaints, mood disorders, eating disorders or personality disorders did not significantly affect the AD discontinuation process.

3.3.4.9 Previous episodes and severity

Two studies (ten Doesschate et al., 2009; Wu and Davis-Ajami, 2014) investigated the impact of previous episodes on discontinuation and did not observe any significant differences.

MA could not be performed. Two studies (ten Doesschate et al., 2009; Hung et al., 2011) explored the relation between depression severity and discontinuation. A single study (Hung et al., 2011) found that patients with chronic depression were less likely to discontinue treatment. Conversely, another study (ten Doesschate et al., 2009) did not identify any significant differences.

Finally, with the data reported in the included studies, it was not possible to synthesize the relationship between cognitive impairment, and perceived health or health-related quality of life with adherence (for more information on the results obtained in the included studies see Supplementary Table S6).

4 Discussion

The main objective of this SR was to evaluate the possible sociodemographic and clinical predictive factors that influence adherence to AD treatment in adult patients diagnosed with a depressive disorder.

The data obtained in this SR show worrying rates of adherence to pharmacological treatment in the three phases, initiation, implementation and discontinuation (Vrijens et al., 2012). Specifically, non-adherence rates in the first months of therapy exceed 80%, which places this problem in a more unfavorable scenario than those reported in previous studies, which reported values close to 50% (Sansone and Sansone, 2012). These high rates of non-adherence may be influenced by factors such as the side effects of medication, especially given that this occurs in the early weeks of AD treatment. This underscores the need for a professional approach concerning the experience of the disease and the treatment (feelings, ideas, function and expectations) to adequately manage the condition and improve therapeutic adherence. This is particularly important in scenarios where pharmacological therapy is the only viable option for the patient (Samalin et al., 2018; González de León et al., 2022).

In relation to the predictive factors, advanced age, was found to be a predictor of good adherence in both the implementation phase and in the discontinuation phase, which is consistent with the literature (Rivero-Santana et al., 2013; Holbrook et al., 2021). However, in the present SR, this effect was maintained over time in middle-aged people (35–65 years), while it was less evident in older people (>65 years). In the latter population group, the use of patient reminders or alerts could play an important role in reducing involuntary lack of adherence (Hamine et al., 2015; González de León et al., 2021). Additionally, it is important to consider the role of patient's beliefs and preferences about medication at the start of treatment, as well as patient preferences about treatment, as they may be correlated with therapeutic efficacy and adherence, especially in younger patients (Horne et al., 2013; Kong et al., 2021).

In the present SR, it was observed that being female was associated with better adherence rates during the first weeks of treatment, but correlated with the risk of SSRIs non-initiation. However, as treatment time progresses, this association became less conclusive. Previous studies similarly reported a better adherence rate between female patients nevertheless, this finding could not be consistently confirmed due to many studies not yielding statistically significant results (Rivero-Santana et al., 2013).

On the other hand, white patients showed better levels of adherence compared to Afro-American or Hispanic patients, consistent with some previous literature (Rivero-Santana et al., 2013) that mainly pointed to the age and ethnicity of the patients as the most consistent factors influencing non-compliance with treatment. This finding contrasts with the results of the SR of Holbrook et al. (2021), where they did not consider ethnicity as a predictive factor. This controversial relationship may be mediated by confounders such as economic resources, educational level or healthcare access, as in other outcomes in depression (Finegan et al., 2018). Therefore, future studies designed to corroborate these results are needed.

Although having a low educational level has often been considered a potential risk factor for poor adherence, as people with less education may have more difficulty understanding treatment regimens, medical recommendations, or the nature of their disease; the educational level of the patients did not influence treatment adherence rates. This finding is consistent with previous studies (Burra et al., 2007; Rivero-Santana et al., 2013; Roca et al., 2013).

Another possible association, in line with previous research on chronic conditions, was found between marital or cohabitation status and medication adherence. Studies conducted on other chronic diseases have found a relationship between marital status and adherence, with a greater adherence in those people who were in a relationship (Trivedi et al., 2008; Wu et al., 2012).

Marital or cohabitation status may also be associated with medication adherence. Research on various chronic conditions has suggested that individuals in relationships tend to present better adherence (Trivedi et al., 2008; Wu et al., 2012).

Previous studies suggest that socioeconomically disadvantaged individuals, characterized by factors such as low income, unemployment, financial struggles, lack of homeownership, or limited formal education, have poorer prognoses regardless of the type of treatment they receive and the severity of depression (Buckman et al., 2022). In the present SR, low income appears to have a negative impact on both the initiation of SSRI treatment and adherence levels to AD therapy, and possibly on discontinuation rates, which could be influencing the poor progression of the disease.

Regarding psychiatric comorbidities, the findings in the present SR showed varied results. During the first weeks, the presence of anxiety disorders did not seem to influence adherence. However, over time, the absence of anxiety disorders was associated with better adherence rates. Consistent with previous research on chronic conditions (Grodensky et al., 2012), it appears that patients with comorbid depression and alcohol abuse disorder may present reduced adherence to treatment. Nevertheless, no significant results were found for sleep disorders and substance abuse-related disorders. These results highlight a potentially important gap in the evidence about the effect of psychiatric comorbidities on medication adherence.

On the other hand, patients with a higher medical comorbidity index score showed better adherence during the implementation phase. However, contrary to expectations, studies examining the role of comorbid chronic pain found lower adherence rates among patients with these conditions (Akincigil et al., 2007; Liu et al., 2011). Both of these studies reported a similar difference in the adherence ratio between patients with or without chronic pain of around 4%, although this was relatively small, it is significant. Non-adherence to prescribed analgesic medication in chronic pain is quite common, influenced by factors such as polymedication and concerns about pain medication, which are commonly associated with non-adherence in this condition (Timmerman et al., 2019). These aspects might also affect adherence to antidepressants. This finding emphasizes the need for further studies to draw more robust conclusions. Furthermore, it is necessary to understand how these findings translate into real clinical practice situations.

For individuals dealing with comorbid conditions, simplifying the medication regimen may prove beneficial. As seen in prior literature (Rivero-Santana et al., 2013), medical comorbidities have been shown to have significant associations with both positive and negative adherence outcomes in the studies examined here. Patients coping with multiple health conditions may develop a more profound understanding of medication management. However, when combined with other factors like limited education, or incomplete or unclear physician instructions, this can lead to a complex treatment regimen that complicates adherence. It is also important to address patients' myths and beliefs with scientific information and explanations (Marasine and Sanki, 2021). This combined approach could help improve adherence in patients with comorbidities and contribute to better treatment outcomes.

The evidence in the present SR suggests that the severity of depression by itself does not significantly predict adherence, which is consistent with previous SR (Rivero-Santana et al., 2013). However, older patients experiencing severe and persistent depressive symptoms are more inclined to tend to perceive medication as a necessary treatment for their condition. Conversely, in younger patients with severe initial depression, the dropout rate from pharmacotherapy tends to be higher (Aikens et al., 2008). Data from databases usually lack essential information, such as disease severity and prior episode history, which is required to understand the disease. The loss of information derived from incomplete coding during the diagnosis process and its subsequent updating complicates the analysis of possible relationships between these factors and treatment adherence (Donohue et al., 2004). Hence, additional scientific evidence is needed to shed light on what is happening with the more purely clinical characteristics of these patients.

The findings here suggest that depression severity alone might not significantly predict adherence, which is consistent with previous systematic reviews (Rivero-Santana et al., 2013). Nevertheless, older individuals experiencing severe and persistent depressive symptoms are more inclined to view medication as a necessary treatment for their condition. Conversely, in younger individuals with severe initial depression, the dropout rate from pharmacotherapy tends to be higher (Aikens et al., 2008).

The study of all the potential predictive factors influencing the decision-making about starting (or not), maintaining (or not), and discontinuing (or not) the treatment is necessary to enhance the existing theoretical models and develop more precise and adjusted interventions for different subgroups of the population. The identification of these predictors of adherence holds significant value for primary care and mental health professionals in their everyday clinical practice. It enables them to identify patients who may be at a higher risk of non-adherence, allowing for the implementation of targeted interventions for these individuals. By doing so, it becomes possible to enhance clinical outcomes in the recovery process and optimize the utilization of public health resources efficiently. This proactive approach can ultimately lead to better patient outcomes and a more effective allocation of healthcare resources.

4.1 Strengths and limitations

This SR has a series of strengths, namely, 1) it is the most extensive work to date in relation to the number of participants, which in addition to incorporating MA, 2) used a transparent and rigorous methodology according to the SR and MA standards, and 3) each of the steps is explained in detail, as well as providing all the necessary data to be able to replicate this SR.

With regard to the weaknesses of this study, the following should be mentioned: 1) despite conducting an exhaustive bibliographic search in the main databases of indexed journals, there may be studies not included in these databases that have therefore been left out of this SR, 2) only studies published in English and/or Spanish were taken into account, 3) a large number of the studies presented a high overall risk of bias, which limits the certainty of the evidence, 4) there was heterogeneity between the selected studies, especially in how and when adherence is assessed, and in the definition and categorization of the predictors, which, in some cases, has meant that it has not been possible to obtain an estimate of the effect of some of the predictive factors and, 5) despite ongoing consensus efforts, the considerable variability in defining adherence and its phases has posed a challenge to comparing studies.

Other limitations, mainly concern the low number of studies per predictor factor, are 6) the absence of a meta-regression analysis, 7) the lack of sensitivity analysis and the adherence measurement method in included studies. Adherence is a multifactorial phenomenon, and as such, it should ideally be evaluated from various perspectives. Relying solely on a single measurement method, whether objective or subjective, through the use of validated scales, might prove insufficient. In the future, studies should incorporate the gold standard—electronic monitoring—(Hess et al., 2006) and, when the reference standard is not used, two evaluation methods should be applied: one using objective measures and the other subjective measures of adherence (Sajatovic et al., 2010).

Finally, despite the efforts, the profile obtained, due to its restriction to unmodified predictors of adherence, is limited in its usefulness in clinical practice for effectively identifying a well-defined non-adherence patient profile.

4.2 Conclusion

According to the results obtained here, middle-aged, elderly and Caucasian participants have higher rates of adherence, although time determines whether these rates are maintained in older patients. Despite finding data that support age and ethnicity as predictors of pharmacological adherence, further studies of a higher methodological quality that can obtain more data, but, above all, that explore other possible factors that may influence adherence are recommended.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

TP-S: Conceptualization, Methodology, Writing–original draft, Writing–review and editing, Funding acquisition, Project administration. DI-V: Conceptualization, Methodology, Writing–original draft, Writing–review and editing. DH-G:

Methodology, Writing–original draft, Writing–review and editing. YG-H: Methodology, Writing–original draft, Writing–review and editing. BG: Methodology, Writing–original draft, Writing–review and editing. AR-S: Conceptualization, Supervision, Writing–review and editing. IH–N: Conceptualization, Supervision, Writing–review and editing. FA: Conceptualization, Supervision, Writing–review and editing, Funding acquisition.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work has been carried out within the framework of a project financed by the Canary Islands Health Research Institute Foundation (FIISC) in the Call for Research, Development and Innovation Projects aimed at satisfying the health needs of the population of the Canary Islands and improving the sustainability and solvency of the Canary Health Service (SCS) (PIFIISC20_05).

Acknowledgments

The authors would like to thank Leticia Rodríguez for her guidance in developing the search strategy and Wenceslao Peñate for his revision of the final manuscript. We are also grateful to Patrick Dennis for English language editing support with the final manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1327155/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 24 January 2024
DOI 10.3389/fphar.2024.1294436

OPEN ACCESS

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RECEIVED 14 September 2023
ACCEPTED 04 January 2024
PUBLISHED 24 January 2024

CITATION
Bandiera C, Dotta-Celio J, Locatelli I, Nobre D, Wuerzner G, Pruijm M, Lamine F, Burnier M, Zanchi A and Schneider MP (2024), The differential impact of a 6-*versus* 12-month pharmacist-led interprofessional medication adherence program on medication adherence in patients with diabetic kidney disease: the randomized PANDIA-IRIS study.
Front. Pharmacol. 15:1294436.
doi: 10.3389/fphar.2024.1294436

The differential impact of a 6-*versus* 12-month pharmacist-led interprofessional medication adherence program on medication adherence in patients with diabetic kidney disease: the randomized PANDIA-IRIS study

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Background: For every 100 patients with diabetes, 40 will develop diabetic kidney disease (DKD) over time. This diabetes complication may be partly due to poor adherence to their prescribed medications. In this study, we aimed to evaluate the differential impact of a 6- *versus* 12-month pharmacist-led interprofessional medication adherence program (IMAP) on the components of adherence (i.e., implementation and discontinuation) in patients with DKD, during and after the intervention.

Methods: All included patients benefited from the IMAP, which consists in face-to-face regular motivational interviews between the patient and the pharmacist based on the adherence feedback from electronic monitors (EMs), in which the prescribed treatments were delivered. Adherence reports were available to prescribers during the intervention period. Patients were randomized 1:1 into two parallel arms: a 12-month IMAP intervention in group A *versus* a 6-month

Abbreviations: BMI, body mass index; CHUV, Centre hospitalier universitaire vaudois; CI, confidence interval; CONSORT, Consolidated Standards of Reporting Trials; COVID, coronavirus disease; CRF, case report form; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; EMs, electronic monitors; EMERGE, ESPACOMP Medication Adherence Reporting Guidelines; GEE, generalized estimating equation; HbA1c, glycated hemoglobin; IMAP, interprofessional medication adherence program; IQR, interquartile range; LADA, latent autoimmune diabetes in adults; LCD, liquid-crystal display; LDL, low-density lipoprotein; PANDIA-IRIS, Patients diabétiques et insuffisants rénaux: un programme interdisciplinaire de soutien à l'adhésion thérapeutique; PART-PANDIA, participation to the PANDIA-IRIS study; SD, standard deviation.

intervention in group B. Adherence was monitored continuously for 24 months post-inclusion during the consecutive intervention and follow-up phases. In the follow-up phase post-intervention, EM data were blinded. Blood pressure was measured by the pharmacist at each visit. The repeated measures of daily patient medication intake outcomes (1/0) to antidiabetics, antihypertensive drugs, and statins were modeled longitudinally using the generalized estimated equation in both groups and in both the intervention and the follow-up phases.

Results: EM data of 72 patients were analyzed (34 in group A and 38 in group B). Patient implementation to antidiabetics and antihypertensive drugs increased during the IMAP intervention phase and decreased progressively during the follow-up period. At 12 months, implementation to antidiabetics was statistically higher in group A *versus* group B (93.8% *versus* 86.8%; Δ 7.0%, 95% CI: 5.7%; 8.3%); implementation to antihypertensive drugs was also higher in group A *versus* B (97.9% *versus* 92.1%; Δ 5.8%, 95% CI: 4.8%; 6.7%). At 24 months, implementation to antidiabetics and antihypertensive drugs remained higher in group A *versus* B (for antidiabetics: 88.6% *versus* 85.6%; Δ 3.0%, 95% CI: 1.7%; 4.4% and for antihypertensive drugs: 94.4% *versus* 85.9%; Δ 8.5%, 95% CI: 6.6%; 10.7%). No difference in pharmacy-based blood pressure was observed between groups. Implementation to statins was comparable at each time point between groups. Three patients discontinued at least one treatment; they were all in group B. In total, 46% (16/35) of patients in the 12-month intervention *versus* 37% (14/38) of patients in the 6-month intervention left the study during the intervention phase, mainly due to personal reasons.

Conclusion: The IMAP improves adherence to chronic medications in patients with DKD. The longer the patients benefit from the intervention, the more the implementation increases over time, and the more the effect lasts after the end of the intervention. These data suggest that a 12-month rather than a 6-month program should be provided as a standard of care to support medication adherence in this population. The impact on clinical outcomes needs to be demonstrated.

Clinical Trial Registration: Clinicaltrials.gov, identifier NCT04190251_PANDIA IRIS.

KEYWORDS

medication adherence, electronic adherence monitoring, adherence interventions, diabetes complication, diabetic kidney disease, nephropathy, interprofessionality, digital technology

1 Introduction

1.1 Background

The pandemic of diabetic disease keeps growing worldwide. It is estimated that in 2021, 537 million adults were living with diabetes and 6.7 million died from this disease. It is expected that 783 million patients will be diagnosed with diabetes by 2045 (International-Diabetes-Federation, 2021). The global health economic burden of adult patients with diabetes keeps rising, reaching USD 966 billion worldwide in 2021 (International-Diabetes-Federation, 2021). Thus, diabetes is an urgent public health concern and an important economic burden for the healthcare systems. Several types of diabetes exist, all characterized by hyperglycemia. Uncontrolled hyperglycemia severely degrades tissues and organs, leading to microvascular (i.e., retinopathy, kidney disease, and neuropathy) and macrovascular complications (i.e., atherosclerosis) (Fowler, 2008). Among these complications, diabetic kidney disease (DKD) is characterized by a chronically reduced estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 (in 70% of patients) (Sheen and Sheu, 2014) and/or the presence of increased albuminuria (Gheith et al., 2016). DKD is the leading cause of end-stage kidney disease (Stewart et al., 2004; Johansen et al., 2022) defined as an eGFR of less than 15 mL/min/1.72 m^2 (MFMER, 2023). It is estimated that 40% of patients with diabetes will develop DKD over time (Gross et al., 2005; Gheith et al., 2016).

The goals of pharmacological treatments for diabetes focus on delaying the progression of the renal impairment and preventing cardio-renal events and complications by intensively controlling blood pressure, lipids, and glycemic blood levels and providing cardio-protection with evidence-based therapies. As a consequence, patients with DKD are polypharmacy patients, which may contribute to treatment nonadherence.

Medication adherence is described by three interrelated and quantifiable phases, following ideally a shared decision-making process regarding prescribing: initiation (i.e., first dose taken), implementation (i.e., the extent to which the patient takes the treatment as prescribed), and discontinuation (i.e., the patient stops taking the treatment earlier than planned by the prescriber) (Vrijens et al., 2012). Treatment persistence is the time between initiation and discontinuation (Vrijens et al., 2012). Literature reports that 40% of patients with DKD are not adherent to their medications (Williams et al., 2012; Kefale et al., 2018;

Balasubramaniam et al., 2019), while medication nonadherence leads to poor clinical outcomes and increases mortality (Chang et al., 2015; Shani et al., 2017; Paranjpe et al., 2022). Medication adherence must become a priority for interprofessional healthcare teams. However, studies evaluating interventions aiming to improve adherence in patients with DKD are scarce, and their impact on adherence and clinical outcomes remains limited (Williams et al., 2012; Helou et al., 2016; Zimbudzi et al., 2018). As a consequence, the type and duration of interventions to improve adherence are largely unknown in this patient population.

The PANDIA-IRIS (*Patients diabétiques et insuffisants rénaux: un programme interdisciplinaire de soutien à l'adhésion thérapeutique*) study was developed at the community pharmacy of the Center for Primary Care and Public Health *Unisanté* to support medication adherence in patients with DKD. The intervention consists in a pharmacist-led interprofessional medication adherence program (IMAP), implemented since 1995 at the community pharmacy of *Unisanté*, aiming to support medication adherence in chronically ill patients (Lelubre et al., 2015).

1.2 Objectives

The main objective of the PANDIA-IRIS study was to evaluate the differential impact of a 6-month *versus* 12-month pharmacist-led IMAP on implementation and persistence to antihypertensive drugs, antidiabetics, statins, and aspirin in patients with DKD at different time points, i.e., at 6, 12, 18, and 24 months post-inclusion. The secondary objective was to evaluate the impact of the intervention on the United Kingdom Prospective Diabetes Study (UKPDS) and the Action in Diabetes and Vascular disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) clinical scores.

1.3 Outcomes

The medication intake is a binary variable (1 = correct intake; 0 = incorrect intake) measured using an electronic monitor (EM) in a patient at each day of the monitoring period. To be considered optimal, the medication intake has to be correct (=1) for every EM used. On each day, medication implementation is the proportion of patients with a correct medication intake among patients still under observation on that day. Persistence to treatment is characterized by the time between study initiation and treatment discontinuation (= 1) for each patient. The secondary outcomes were the ADVANCE and UKDPS clinical scores, systolic and diastolic blood pressures measured at each visit at the pharmacy, and the number of patients with an electronic medication implementation of less than 30% for at least one medication throughout two successive pharmacy visits during the post-intervention phase.

1.4 Hypothesis and research questions

We hypothesized that patients in both groups would benefit from the IMAP, yet the impact of the intervention on medication adherence, i.e., implementation and persistence, would be higher and would last longer post-intervention in participants included in the IMAP for 12 months (group A) compared to patients who benefited from the IMAP during 6 months (group B). We hypothesized that during the follow-up period post-intervention, patients included in group A would maintain a higher implementation compared to patients included in group B.

2 Methods

2.1 Ethical considerations and guidelines

The PANDIA-IRIS study was approved by the local Ethics Committee "*Commission cantonale d'éthique de la recherche sur l'être humain*" (Vaud, Switzerland, ID 2016-01674). All patients signed an informed consent form to participate in this study. The study was conducted in accordance with the Declaration of Helsinki. Both the ESPACOMP Medication Adherence Reporting Guidelines (EMERGE) (De Geest et al., 2018) and Consolidated Standards of Reporting Trials (CONSORT) guidelines (Schulz et al., 2010) were used to report findings.

2.2 Design of the PANDIA-IRIS medication adherence study

The protocol of the PANDIA-IRIS study has been published elsewhere (Bandiera et al., 2021). The PANDIA-IRIS study was monocentric, open, and randomized. Patients were recruited from April 2016 to October 2020 from the Service of Nephrology and Hypertension, the Service of Endocrinology, Diabetes and Metabolism of the Lausanne University Hospital (*Centre hospitalier universitaire vaudois*, CHUV), and at the policlinic of the Center for Primary Care and Public Health *Unisanté*, located in the same hospital complex. The first patient was included in April 2016, and the data collection ended on the last visit of the last patient in December 2022.

Eligible patients were adults with a diagnosis of diabetes—either type 2, type 1, latent autoimmune diabetes in adults (LADA) or glucocorticoid-induced—with chronic kidney disease (an eGFR of less than 60 mL/min/1.73 m^2). In October 2019, an amendment was accepted by the local Ethics Committee to expand recruitment from adults diagnosed with type 2 diabetes only to adults with the four types of diabetes listed above in order to increase recruitment.

Patients were excluded if they did not self-manage their treatments (i.e., home care services and nursing homes) or had cognitive disorders. Patients who were pregnant or had an active cancer were also excluded. The calculation of the sample size was detailed in the published protocol (Bandiera et al., 2021) and showed that 72 patients (36 patients in each group) should be included. Enrolled patients were randomized 1:1 at inclusion into two parallel arms, each lasting 24 months. Participants in the first arm received the intervention for 12 months (group A) *versus* 6 months (group B) in the second arm (Figure 1 adapted from Bandiera et al. (Bandiera et al., 2021)). To stratify randomization according to the risk of nonadherence due to the adverse effects of statins or the complexity of drug regimen, four randomization groups were created (i.e., patients monitored with at least a statin, patients monitored with at least one medication with multi-dose regimen, patients with both of the former conditions, and patients with none of the former conditions) (Bandiera et al., 2021).

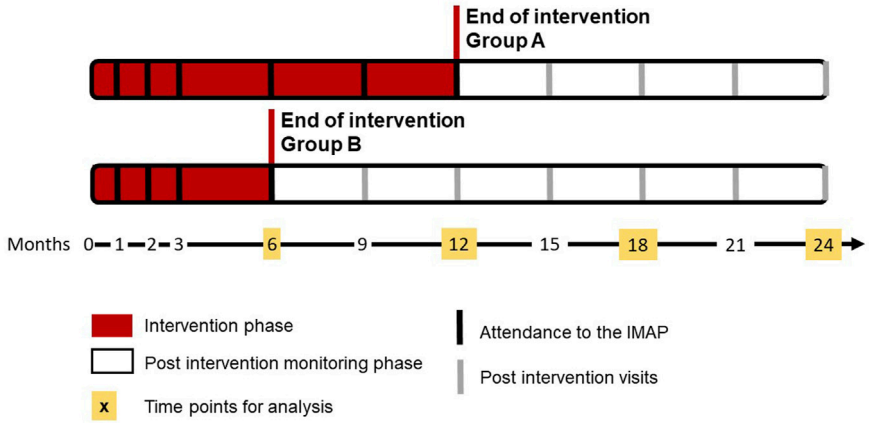

FIGURE 1
Design of the PANDIA-IRIS study, adapted from Bandiera et al., 2021. IMAP, interprofessional medication adherence program.

2.2.1 Intervention phase: *the* interprofessional medication adherence program (IMAP)

As part of the IMAP (Lelubre et al., 2015), all included patients used at least one electronic monitor (EM, Medication Event Monitoring System, MEMS, and MEMS AS, AARDEX Group, Sion, Switzerland), an interactive digital technology, to monitor their medication adherence. Each EM contained one oral prescribed chronic treatment. Monitoring priority was determined for each consecutive patient as follows: 1) antidiabetics, 2) antihypertensive drugs, diuretics, beta- and alpha-blockers, and calcium antagonists, 3) statins, and 4) aspirin. Before randomization, while investigators offered patients to monitor all eligible medications in EM, patients' preferences on the number of EM to be used were taken into consideration so as not to burden their medication management habits. On the top of the EM cap, a liquid-crystal display (LCD) screen indicated the number of EM opening(s) during 24 h from 3:00 am to 2:59 am the day after. The EM registers the date and time of each EM opening, which is considered a proxy for the timing of drug intake. By reading EM data, the medAmigo™ software (AARDEX Group, Sion, Switzerland) establishes a chronology graph of medication intake during the current inter-visit intervention period. At each pharmacy visit, the pharmacist investigated EM deviation use by asking the patient to report i) non-monitored periods during which the medication was taken without opening the EM (i.e., during hospitalizations and holidays); ii) the use of pocket-doses (i.e., when the patient took a tablet outside of the EM to swallow it more than 24 h later) and curiosity checks (i.e., when the patient opened the EM without taking the dose); and iii) the usual time between EM openings and the medication intake. In addition, pharmacy technicians calculated an aggregated value of days covered by the pill count for conciliation with EM data. Any significant discrepancy was immediately investigated during the interview by the pharmacist.

The intervention consisted in face-to-face 15–20-min motivational interviews between the patient and the pharmacist based on the electronic adherence feedback presented in the form of a chronology plot. The intervention was built upon the Fisher et al. (2006) socio-cognitive theoretical framework "information–motivation–behavior". Pharmacists and patients investigated together the patient's habits and skills in self-managing medication and side effects. The pharmacist explored the patient's own beliefs, preferences, and motivation to take the treatment and delivered information according to the patient's needs. If necessary, goals for improving medication adherence were set collaboratively by the patient with the pharmacist, according to patient engagement, from one interview to the next interview. After the end of the interview, the pharmacist sent a report summarizing the content of the intervention to the healthcare team (i.e., endocrinologist, nephrologist, general practitioner, diabetes specialist nurses, psychologists, and dieticians).

2.2.2 Post-intervention (follow-up) monitoring phase

After the end of the intervention phase, medication adherence was continuously monitored by EM until the end of the study (i.e., 24-month post-inclusion). During the post-intervention phase, the patient did not receive any intervention. EM data were blinded to the patient, the pharmacy team, the medical team, and the researchers. At each follow-up pharmacy visit, the pharmacist evaluated EM use deviations through the same set of questions as during the intervention phase and reported the answers in a case report form (CRF). In addition, pharmacy technicians counted pills left in the EM without calculating any adherence rate.

At each pharmacy visit during both the intervention and the follow-up phases, pharmacists measured prospectively patients' systolic and diastolic blood pressures and heart rate, using a systematic methodology and a standardized device (e.g., measuring seated blood pressure on the same arm at each visit, after a 5-min rest period, measured three times, and then calculating a mean). They measured and reported patients' abdominal circumference every 6 months. At 18 to 21 months post-inclusion in both groups, in patients still participating in the study, a blood sample allowed collecting laboratory values at this time point. In order to prevent patients from coming to the pharmacy during the lockdown enforced by the coronavirus disease (COVID)-19 pandemic (from March to June 2020), the medications were sent by mail so that patients could fill their EMs at home (Bourdin et al., 2022). The motivational interviews were delivered by phone,

yet without EM feedback (Bourdin et al., 2022) for patients in the intervention phase. In order to guarantee homogeneity of the interventions between patients, the intervention phase was extended for 3 months after the lockdown in all patients (n = 15), who were in the intervention phase.

2.3 Database construction

2.3.1 Collection of patients' clinical and sociodemographic data

Patients' demographic data (age, gender, marital status, ethnicity, and education level) and clinical data at inclusion (type of diabetes, time since diabetes diagnosis, body mass index (BMI), abdominal circumference, diagnosis of retinopathy, presence of atrial fibrillation, systolic and diastolic blood pressures and heart rate, eGFR decline per year, current or past diagnosis of depression or anxiety, smoking status, number of chronic treatments prescribed, and patient use of adherence support tools) were collected in patients' electronic medical and administrative records.

The historical eGFR decline per year was calculated from patients' blood creatinine concentrations available from 2000 to 2021, upon a previously described methodology (Bandiera et al., 2022a; Trucello et al., 2023).

The following clinical variables were collected for each patient as the mean of the values measured in the 12 months prior to study inclusion: glycated hemoglobin (HbA1c), eGFR, creatinine blood concentration, and low-density lipoprotein (LDL)-cholesterol. Missing data were clearly depicted. All data were collected on the secure web platform REDCap™ version 6.13.3 (Vanderbilt University) (Harris et al., 2009).

2.3.2 EM adherence database

Patients' EM raw data were cleaned and enriched using the CleanADHdata.R script (available on https://github.com/jpasquier/CleanADHdata), developed by our research team. The script truncates the EM database from the first to the last date of each EM use. The periods during which the EM was not used but the medication was taken (e.g., during holidays or hospitalizations) were set as non-monitored periods, and implementation was not calculated during these non-monitored periods. The number of pocket-doses reported by the patients was reconciled with pill count (i.e., the difference between the number of pills delivered and returned between two consecutive pharmacy visits) (Rotzinger et al., 2016). Covariables were inserted in each EM (e.g., the international nonproprietary name of the molecule monitored and its dose strength) and for each patient (e.g., randomization group, phase of the study, gender, and age).

2.4 Statistical analysis

2.4.1 Descriptive analysis

Continuous sociodemographic and clinical variables were described by medians and interquartile ranges (IQRs) and qualitative data by proportions of patients in each group.

2.4.2 Implementation and discontinuation

For each electronic monitor (EM) used by the patient, the medication intake is considered correct (= 1) a given day if the number of observed EM opening(s) is at least equal to the number of expected EM opening(s) based on the regimen provided in the prescription sheet and is considered incorrect otherwise (= 0). For every patient at each day of the monitoring period, an overall optimal medication intake (= 1) is defined by the product of each EM medication intake outcome: the medication intake needs to be correct (= 1) for all EM monitored in each drug class (i.e., antidiabetics, antihypertensive drugs, and statins) to consider a global correct medication intake for that day. Empirical medication implementation is then expressed as the proportion of patients with a global correct medication intake (proportion of outcomes = 1) at each day of the monitoring period among patients still participating in the study at that day.

From study inclusion to the end of the intervention (6 *versus* 12 months) and in the follow-up phase until 24 months post-inclusion, longitudinal implementation was described using the generalized estimating equation (GEE) model on the daily medication intake 0/1. Implementation was then estimated using the model for two representative patients: one who benefited from the intervention during 12 months (a patient from group A) *versus* one who benefited from the intervention during 6 months (a patient from group B). Implementation was estimated in three different GEE models, showing implementation to antidiabetics, antihypertensive drugs, and statins, respectively. The probability of treatment implementation was estimated for each drug class at 6, 12, 18, and 24 months for both representative patients A and B. The difference in implementation between both representative A and B patients (Δ) was presented with the 95% confidence interval (95% CI).

A discontinuation was defined when patients stopped taking at least one of their treatments earlier than planned by the prescriber, due to side effects or for any other patients' unilateral and personal reasons. Other reasons for premature treatment stop (i.e., clinical reasons other than side effects) or study interruption without treatment discontinuation were considered censoring times. We represented graphically the moments of discontinuation in each model.

2.4.3 Systolic and diastolic blood pressures

In patients treated with antihypertensive drugs, we analyzed systolic and diastolic blood pressures using linear mixed-effects models with polynomials of time.

The statistical analysis was performed using the statistical software R (R-development-core-team, 2005).

3 Results

3.1 Included patients

The PANDIA-IRIS study was offered to 275 patients, 73 of which accepted to participate. The main reasons for non-participation were investigated as part of the "participation to the PANDIA-IRIS" study, the results of which have been published elsewhere (Bandiera et al., 2022a). The sociodemographic and clinical variables of the 73 included patients at baseline (group A n = 35 and group B n = 38) are presented in Table 1. Most of the patients were male, Caucasian, diagnosed with type 2 diabetes, and

TABLE 1 Baseline demographic and clinical characteristics of patients included in the PANDIA-IRIS study.

	Group A (n = 35)	Group B (n = 38)
	12-month intervention	6-month intervention
Demographic data		
Age (years), median (IQR)	66.3 (58.9; 70.9)	62.0 (56.0; 69.2)
Female gender, n patients (%)	4 (11.4)	8 (21.1)
Marital civil status[a], n patients (%)	16 (45.7)	16 (42.1)
Caucasian, n patients (%)	29 (82.9)	33 (86.8)
Education level, n patients (%)	Without training after mandatory school, 11 (31.4)	Without training after mandatory school, 6 (15.8)
	Professional training, 17 (48.6)	Professional training, 21 (55.3)
	General training, 3 (8.6)	General training, 1 (2.6)
	Higher education, 2 (5.7)	Higher education, 4 (10.5)
	Universities, 2 (5.7)	Universities, 6 (15.8)
Clinical data		
Type 2 diabetes[b], n patients (%)	34 (97.1)	34 (89.5)
Time since diabetes diagnosis (years), median (IQR)	9.6 (4.7; 16.3)	9.1 (4.3; 18.8)
	Missing data n = 1	
BMI, median (IQR)	31.3 (27.6; 33.1)	31.9 (28.1; 34.7)
	Missing data n = 3	Missing data n = 3
Abdominal circumference (cm), median (IQR)	115 (105–122)	113 (100–119)
Diagnosis of retinopathy, n patients (%)	8 (22.9)	17 (44.7)
Presence of atrial fibrillation, n patients (%)	2 (5.7)	5 (13.2)
Systolic blood pressure (mmHg), median (IQR)	135 (125; 152)	133 (121; 143)
Diastolic blood pressure (mmHg), median (IQR)	71 (62; 80)	77 (69; 84)
Heart rate, median (IQR)	72 (62; 79)	78 (65; 86)
HbA1c (%), median (IQR)	7.6 (6.8; 8.2)	7.2 (6.8; 8.2)
	Missing data n = 4	Missing data n = 9
eGFR (mL/min/1.73 m^2), median (IQR)	40 (34.2; 42.5)	43 (37.5; 52.6)
	Missing data n = 19	Missing data n = 18
eGFR decline per year (mL/min/1.73 m^2/year), median (IQR)	−2.4 (−4.42; −0.29)	−2.4 (−4.27; −0.84)
Creatinine blood concentration (μmol/L), median (IQR)	128 (88.0; 154.5)	120 (97.5; 147.1)
LDL-cholesterol (mmol/L), median (IQR)	2.2 (1.85; 2.65)	2.2 (1.50; 2.60)
	Missing data n = 7	Missing data n = 9
Current or past diagnosis of depression or anxiety, n patients (%)	11 (31.4)	6 (15.8)
Current smokers, n patients (%)	11 (31.4)	14 (36.8)
Number of prescribed chronic medications, median (IQR)	9 (7–12)	9 (7–12)
Previous use of adherence tools, n patients (%)	21 (60.0)	19 (50.0)
Adherence personal tools used among those who had used an adherence tool, n patients (%)	Electronic pillbox, 6(28.6)	Electronic pillbox, 5 (26.3)
	Weekly pillbox, 19 (90.5)	Weekly pillbox, 14 (73.7)

(Continued on following page)

TABLE 1 (*Continued*) Baseline demographic and clinical characteristics of patients included in the PANDIA-IRIS study.

	Group A (n = 35)	Group B (n = 38)
	12-month intervention	6-month intervention
	Personal items, 2 (9.5)	Personal items, 3 (15.8)
	No adherence tools used, n = 14	No adherence tools used, n = 19
Stratification list, n patients (%)	Statins, n = 10	Statins, n = 11
	Multi-dose regimen, n = 8	Multi-dose regimen, n = 10
	Statins and multi-dose regimen, n = 12	Statins and multi-dose regimen, n = 12
	No statin nor multi-dose regimen, n = 5	No statin nor multi-dose regimen, n = 5
Number of EMs dispensed, n patients (%)	1 EM, n = 5 (14.3)	1 EM, n = 4 (10.5)
	2 EMs, n = 9 (25.7)	2 EMs, n = 15 (39.5)
	3 EMs, n = 11 (31.4)	3 EMs, n = 5 (13.2.)
	4 EMs, n = 8 (22.9)	4 EMs, n = 10 (26.3)
	5 EMs, n = 1 (2.9)	5 EMs, n = 3 (7.9)
	6 EMs, n = 1 (2.9)	6 EMs, n = 1 (2.6)
Number of EMs used per patient, median (IQR)	3 (2–4)	2.5 (2–4)

NB: EM, electronic monitor; IQR, interquartile range; BMI, body mass index; LDL, low-density lipoprotein; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate.
[a]The other patients are in partnership, separated, divorced, widow, or single.
[b]The other patients have diabetes type 1, latent autoimmune diabetes in adults, post-transplantation, or glucocorticoid-induced diabetes. From October 2019, the eligibility criteria were expanded to include types of diabetes other than type 2, which explains the low proportion of patients in these categories.

had a basic- to intermediate-level schooling. Patients were polypharmacy, and most of them already used a weekly pillbox to manage a median of 9 chronic prescribed treatments. More than one-third of patients in each group were current smokers at study inclusion.

For patients still in the study at 18–21 months, from whom a blood sample was collected, the median glycated hemoglobin (HbA1c) was 7.6% (IQR 7.1; 7.9) in group A (n = 15 patients) and 7.8% (6.6; 8.4) in group B (n = 12 patients). The median albumin–creatinine ratio (ACR) was 15.6 mg/mmol (IQR: 4.7; 38.7) in group A (n = 14 patients) and 5.8 mg/mmol (IQR: 2.8; 38.0) in group B (n = 6 patients). The median LDL-cholesterol level was 1.6 mmol/L (IQR: 1.5; 2.4) in group A (10 patients) and 1.8 mmol/L (IQR: 1.3; 2.4) in group B (n = 7 patients).

At study inclusion, the eGFR decline (−2.4 mL/min/1.73 m^2/year in both groups) was faster in patients included in our study compared to patients with type 2 diabetes in the Swiss ambulatory care (−1.2 mL/min/1.73 m^2/year (standard deviation (SD) 0.05) in men and −1.0 mL/min/1.73 m^2/year (SD 0.06) in women (Lamine et al., 2016)).

Figure 2 shows patient enrollment and follow-up in the study. In groups A and B, respectively, 20 and 26 patients dropped out, mainly due to logistical reasons or because the study was perceived as an additional burden in their care. Of note, patients' satisfaction about the intervention was reported elsewhere (Bandiera et al., 2022a). Patients in groups A and B spent, respectively, a median time of 539 days (IQR 124; 747) and 366 days (IQR 145; 740) in the study. The EM data of one patient included in group A were not analyzed as the patient used a weekly pillbox instead of the EM. After completion of the study at 24 months, 4 *versus* 3 patients in groups A and B, respectively, decided to continue attending the routine IMAP. There was no patient with an electronic medication implementation of less than 30% for at least one medication throughout two successive pharmacy visits during the post-intervention phase.

3.2 Medication implementation by drug classes

3.2.1 Implementation to antidiabetics and antihypertensive drugs

Empirical implementation to antidiabetics and antihypertensive drugs in patients who were prescribed antidiabetics (n = 57, 28 patients in group A and 29 patients in group B) and antihypertensive drugs (n = 57, 25 patients in group A and 32 patients in group B) is presented in Figures 3 and 4, respectively. Not enough patients were treated by aspirin (n = 6, 2 patients in group A and 4 patients in group B) to allow a reliable analysis of implementation to aspirin. The equations of the GEE models are presented in Supplementary Material S1.

The GEE models represent implementation for a representative patient participating in the intervention during 12 months (red line) or 6 months (blue line). Patient implementation to antidiabetics and antihypertensive drugs increases steadily during the intervention period. At the end of the intervention (at 6- and 12-month post-inclusion), the model shows that implementation drops and then gradually decreases

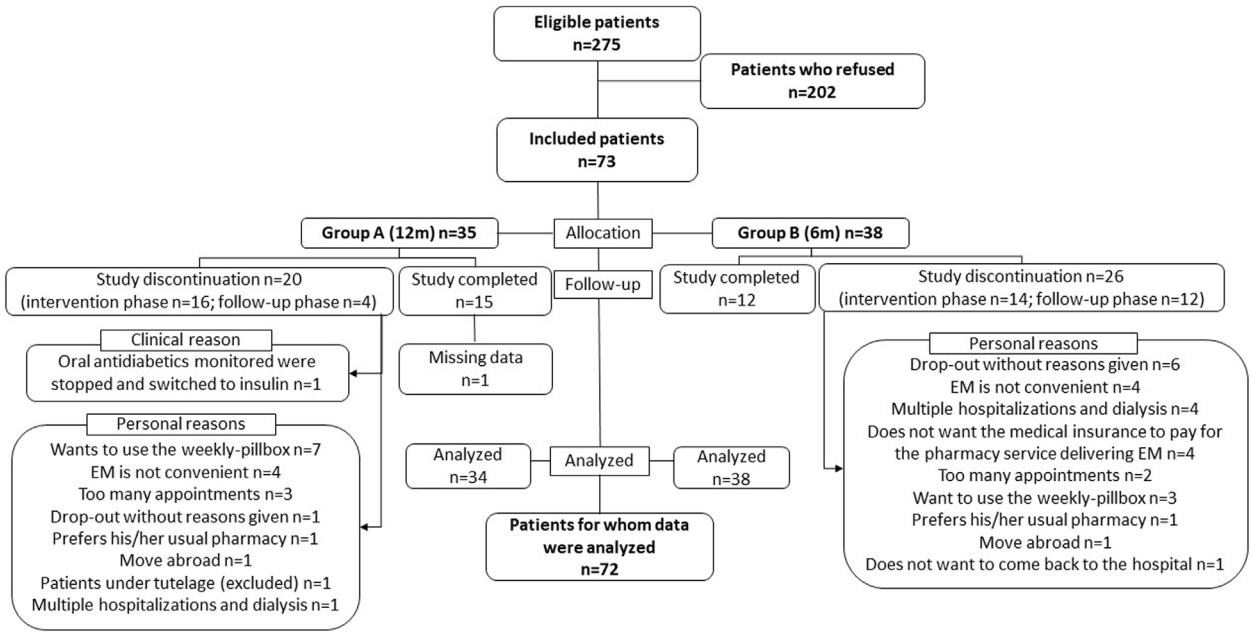

FIGURE 2
Flow of patients from enrollment to data analysis in the PANDIA-IRIS study. EM, electronic monitor.

over time during the follow-up phase. In this follow-up phase, patients who benefited from the intervention during 12 months maintained a higher implementation than patients who received the intervention during 6 months. At 6, 12, 18, and 24 months, implementation to antidiabetics and antihypertensive drugs in patients who benefited from the intervention for 12 months was continuously higher than that in patients who received the intervention for 6 months.

At 12 months, implementation to antidiabetics in a patient completing the 12-month intervention (patient A) was statistically higher than that in a patient who completed the 6-month intervention 6 months earlier (patient B) (93.8% *versus* 86.8%; Δ 7.0%, 95% CI: 5.7%; 8.3%) (Table 2). At 12 months, implementation to antihypertensive drugs in patient A was also higher *versus* patient B (97.9% *versus* 92.1%; Δ 5.8%, 95% CI: 4.8%; 6.7%).

At 24 months, implementation to antidiabetics in patient A was statistically higher compared to that in patient B (88.6% *versus* 85.6%; Δ 3.0%, 95% CI: 1.7%; 4.4%), and implementation to antihypertensive drugs was also higher in patient A than B (94.4% *versus* 85.9%; Δ 8.5%, 95% CI: 6.6%; 10.7%) (Table 2).

No patient of group A *versus* three patients of group B discontinued at least one of their monitored treatments. The moments of treatment discontinuation are shown in Figures 3 and 4 by the blue dots on the green curve showing the number of participants over time.

3.2.2 Implementation to statins

Empirical implementation in patients who were prescribed statins (n = 44, 20 patients in group A and 24 patients in group B) and implementation to statins modeled by GEE are presented in Figure 5. Implementation remained stable during the intervention until 12 months. At the end of the intervention at 6 and 12 months post-inclusion, implementation increases slightly and then decreases steadily in the follow-up phase. At 12 months, implementation to statins in a representative patient of group A *versus* B was, respectively, 95.0% and 95.4% (Δ −0.4%, 95% CI: −1.7%; 0.7%). At 24 months, implementation to statins was comparable between both representative patients: implementation was 93.7% in patient A and 92.6% in patient B (Δ 1.1%, 95% CI: 0.1%; 2.4%).

3.3 Office systolic and diastolic blood pressure

During the coronavirus disease (COVID)-19 pandemic lockdown in 2020, we had to stop collecting blood samples from patients for research purposes. Therefore, numerous laboratory data were missing at different time points (e.g., HbA1c, eGFR, LDL-cholesterol, and ACR), which prevented us from analyzing the impact of medication adherence on clinical outcomes and from calculating the UKPDS and the ADVANCE clinical scores.

The estimated tendency of individual systolic and diastolic blood pressures for the 57 patients treated with antihypertensive drugs (25 patients in group A and 32 patients in group B) is presented in Figure 6, along with confidence and prediction intervals and all individual blood pressure trajectories. A slight downward trend was observed for systolic and diastolic blood pressures. At inclusion, systolic blood pressure was estimated at 135.1 mmHg (95% CI: 130.7; 139.6), while the estimation was 136.3 mmHg (95% CI: 131.6; 140.8) at 6 months, 134.5 mmHg (95% CI: 129.8; 139.3) at 12 months, 132.8 mmHg (95% CI: 127.9; 137.7) at 18 months, and 133.9 mmHg (95% CI: 125.5; 142.3) at 24 months. At inclusion, diastolic blood pressure was estimated at 75.3 mmHg (95% CI: 72.3; 78.2), while the estimation was 74.4 mmHg (95% CI: 71.6; 77.3) at 6 months, 73.4 mmHg (95% CI: 71.6; 77.3) at

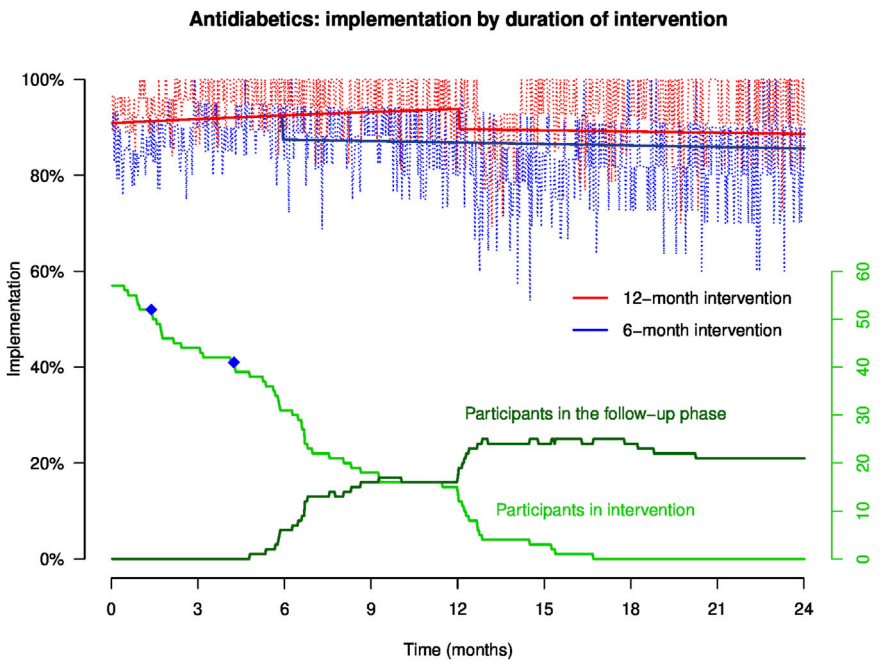

FIGURE 3
Implementation to antidiabetics in representative patients of groups **(A, B)** throughout the study. NB: the light red and blue curves show empirical implementation, and the thick red and blue lines represent implementation to antidiabetics modeled by GEE. The green curves represent the number of participants over time in the intervention and the follow-up phases, and the blue dots on the green curve show the moment when patients discontinued at least one of their antidiabetics.

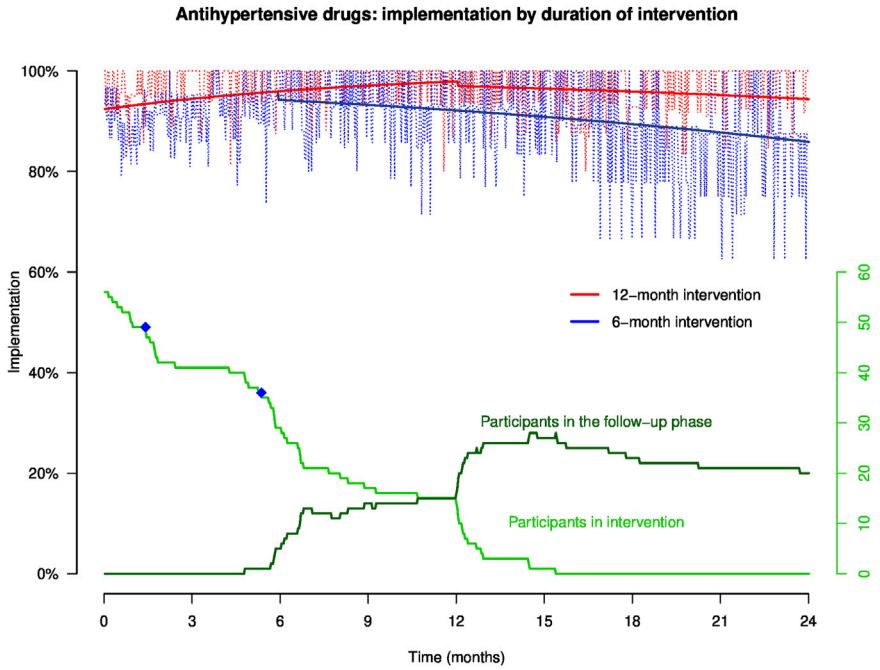

FIGURE 4
Implementation to antihypertensive drugs in representative patients of groups **(A, B)** throughout the study. NB: the light red and blue curves show empirical implementation, and the thick red and blue lines represent implementation to antihypertensive drugs modeled by GEE. The green curves represent the number of participants over time in the intervention and the follow-up phases, and the blue dots on the green curve show the moment when patients discontinued at least one of their antihypertensive drugs.

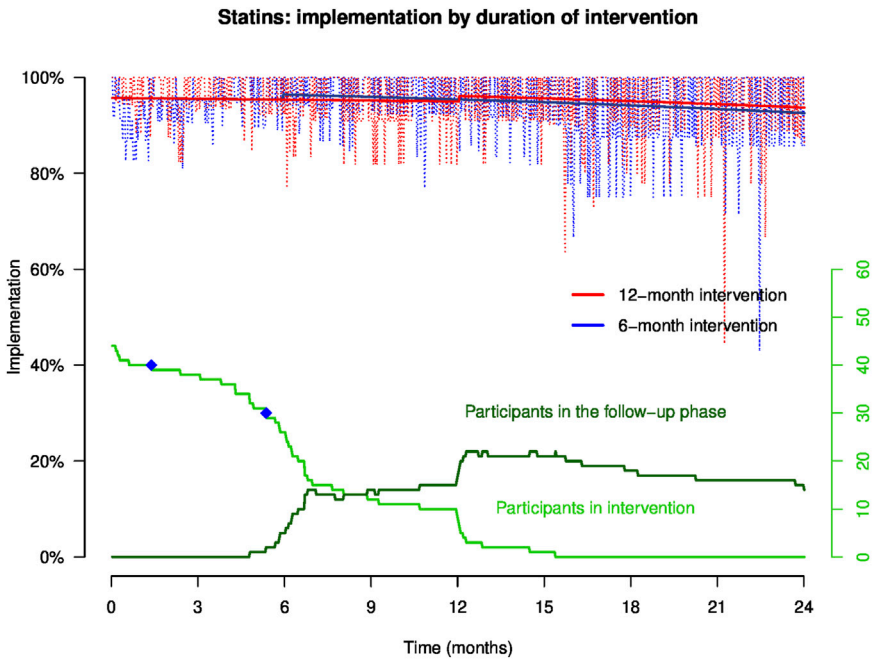

FIGURE 5
Implementation to statins in representative patients of groups **(A, B)** throughout the study. NB: the light red and blue curves show empirical implementation, and the thick red and blue lines represent implementation to statins modeled by GEE. The green curves represent the number of participants over time in the intervention and the follow-up phases, and the blue dots on the green curve show the moment when a patient discontinued the statin.

12 months, 71.8 mmHg (95% CI: 68.7; 75.0) at 18 months, and 69.0 mmHg (95% CI: 64.5; 74.0) at 24 months. No differences were observed between groups (data not shown).

4 Discussion

4.1 Main results

The pharmacist-led interprofessional medication adherence program improved implementation to antidiabetics and antihypertensive drugs but not to statins in patients with DKD, and the effect persisted 24 months after inclusion. Therefore, the duration of the intervention is important to ensure a lasting effect on the maintenance of medication implementation: the longer the patients benefit from the intervention, the more the implementation increases over time, and the more the effect lasts after the end of the intervention. Office blood pressure decreased slightly over time, but no difference was observed between groups.

4.2 Effect of the IMAP on implementation

The effect of the IMAP on implementation to antihypertensives and antidiabetics was significant, whereas no change was observed in the implementation to statins. This can be explained by several hypotheses. First, antidiabetics and antihypertensive drugs are often prescribed with a regimen more complex than that of statins (i.e., multiple drug intakes per day), whereas statins are mostly prescribed with a once-daily regimen. In addition, drug, dose, and regimen changes occurred more often with antidiabetics and antihypertensive drugs than with statins. These factors may contribute to the difficulty for patients to adhere optimally to antidiabetics and antihypertensive drugs compared to statins, and the room for improvement in treatment implementation may be larger in these drug classes than with statins. Patients were used to taking their statins for several years, and there was no major complaint on usual statin side effects. Second, as the implementation to statins was already high (>95%) at study start in both groups, pharmacists focused the discussion more on antidiabetics and antihypertensive drugs during the motivational interviews than on statins (based on qualitative study monitoring data).

4.3 Definition of treatment implementation

Our definition of treatment implementation states that patients need to implement optimally all their medications monitored on day x in order to have an overall optimal medication implementation at day x. This definition has been commonly used in previous research studies (Schneider et al., 2019; Bandiera et al., 2022b; Pasquier et al., 2022). However, patients with DKD are polypharmacy, and patients included in the PANDIA-IRIS study often used more than one EM. Each additional EM used reduced the probability to have a daily optimal overall implementation. For instance, in a patient who used five EMs and optimally implemented four of these, the overall

TABLE 2 Implementation to antidiabetics, antihypertensive drugs, and statins at 6, 12, 18, and 24 months post-inclusion.

	Time since inclusion, months (m)	Number of patients	Implementation in group A (intervention lasted 12 months) (%)	Implementation in group B (intervention lasted 6 months) (%)	Difference (Δ) (%)	95% CI (%)	
Antidiabetics	6	37	92.5	87.4	5.1	3.7	6.5%
	12	31	93.8	86.8	7.0	5.7	8.3%
	18	24	89.1	86.2	2.9	1.7	4.1%
	24	21	88.6	85.6	3.0	1.7	4.4%
Antihypertensive drugs	6	34	95.9	94.2	1.7	0.7	2.8%
	12	30	97.9	92.1	5.8	4.8	6.7%
	18	23	95.9	89.5	6.5	5.4	7.6%
	24	20	94.4	85.9	8.5	6.6	10.7%
Statins	6	31	95.4	96.4	−1.1	−1.8	−0.2%
	12	25	95.0	95.4	−0.4	−1.7	0.7%
	18	18	95.1	94.2	0.9	0.1	1.8%
	24	14	93.7	92.6	1.1	0.1	2.4%

NB: CI, confidence interval.

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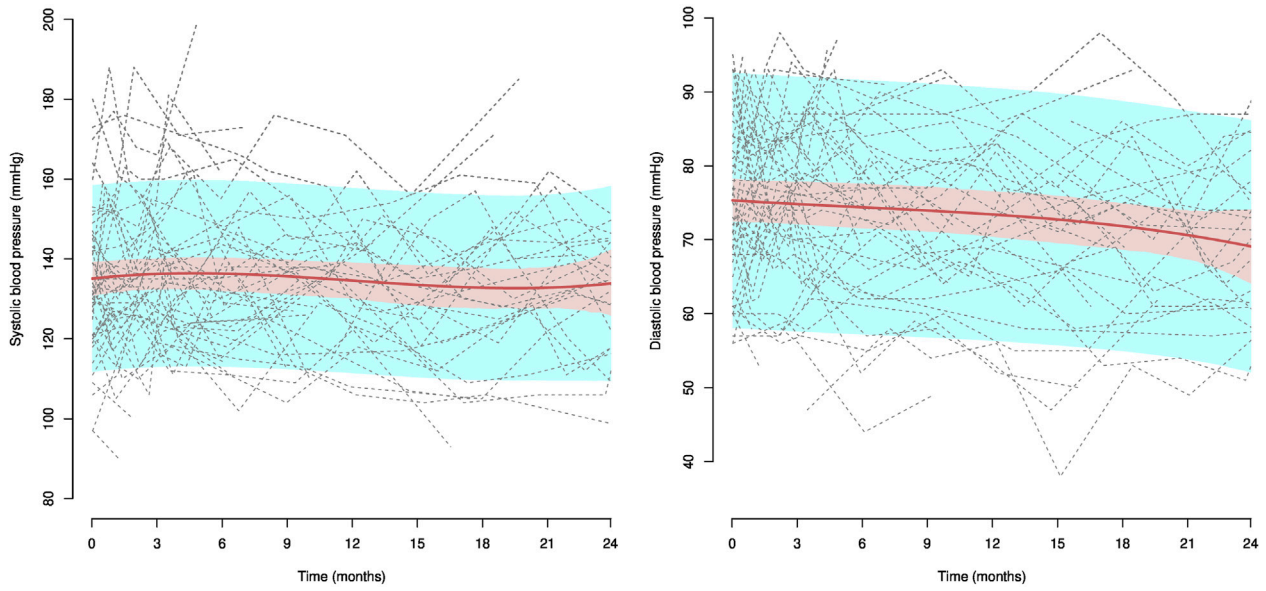

FIGURE 6
Systolic and diastolic blood pressure in patients treated with antihypertensive drugs. NB: dotted lines represent individual trajectories, and confidence intervals around the predicted mean are presented in pink and the prediction intervals in blue.

implementation would depend on the implementation of the fifth treatment, leading to an underestimation of the actual treatment implementation. As the number of EMs used per patient is distributed evenly in our sample, probably reinforced by the stratification of the randomization, our analysis is valid. Additionally, we analyzed medication implementation by drug classes to limit the risk. Nevertheless, the definition of treatment implementation monitored through EM with the binary variable 1/0 needs to be further adapted for polypharmacy patients. The probability of an optimal implementation could be determined by the ratio of treatments taken optimally to the total number of monitored treatments (i.e., on day x, if patients have an optimal implementation to 4/5 of their medications, the probability of an optimal implementation at day x would be 80%). Our research raises the point that the operational definitions of implementation should be evaluated further in polypharmacy patients, as well as the statistical methodology (Pasquier et al., 2022).

4.4 Effect of the study on clinical practice

Patients were overall satisfied about the IMAP (Bandiera et al., 2022a). A substantial number of patients left the study during the intervention phase, mainly owing to personal reasons (cf. Figure 2, i.e., 46% (16/35) of patients in the 12-month intervention *versus* 37% (14/38) of patients in the 6-month intervention). This important number of dropouts shows the difficulty in conducting behavioral interventions in routine practice. To improve retention in the intervention while limiting the inclusion bias, interventions such as the IMAP should be considered an integrated component of the standard of care for polypharmacy patients. Including all consecutive chronically ill patients to the IMAP would allow a prospective evaluation of the effect of the IMAP on clinical outcomes. For example, early in their therapeutic itinerary, polypharmacy patients would be invited to experience the IMAP for 12 months to co-construct their medication adherence with healthcare providers, tailored to their individual needs, before deciding whether they would benefit from continuing the intervention or repeating it later based on defined clinical outcomes, personal experiences, and indicators (Bandiera et al., 2022a). The interprofessional collaborations between patients, pharmacists, physicians, nurses, and other healthcare providers should be strengthened in order to synergistically promote the IMAP to patients and to better define the roles and responsibilities of each healthcare provider in supporting medication adherence (Bandiera et al., 2022c).

A trend toward a decrease in blood pressure was observed, which may be related to improved adherence to treatment. However, differences in blood pressure between groups were not significant. The sample size was probably too small to draw any firm conclusion on the effect of a difference of 3%–5% in implementation to antihypertensive drugs on blood pressure. Accurate modeling of blood pressure as a function of adherence levels is needed as a decision aid for patients and healthcare professionals to better characterize the expected clinical benefit in relation to patient's adherence effort (Polychronopoulou et al., 2021).

4.5 Limitations and strengths of the study

The strengths of the PANDIA-IRIS study are described as follows: first, the IMAP is a proven, theory-based, semi-structured intervention program implemented in routine practice. As part of the intervention, pharmacists i) explore patients' capability to acquire knowledge and skills to strengthen their self-efficacy, ii) explore and participate in the development of patients' motivation to take the

treatment, and iii) explore opportunities in the patients' environment that encourage behavioral changes to improve or maintain medication adherence. These three components affect patient health behaviors and are the main components of the Behavior Change Wheel model designed by Michie et al. (2011) to lead effective interventions.

Second, the design of the PANDIA-IRIS study is innovative as it provides an analysis of the duration of an intervention, which is insufficiently studied in the literature, by comparing between 6- and 12-month interventions. To the best of our knowledge, this is also the first time that medication adherence was monitored during an extended period of time of more than a year (24 months), including the post-intervention period in order to understand the durability of the intervention. Our results suggest that medication adherence interventions should be delivered over long periods of time based on patients' needs by adapting the level of the intervention to short-, middle-, and long-term objectives. Our experience with the IMAP in routine care shows that some chronic patients stay in the program for years, whereas others leave it after a semester and sometimes return afterward.

Third, we reported findings through a robust methodology. We used electronic monitoring for 24 months, which is considered the most robust methodology to objectively and longitudinally measure medication implementation over time providing an adherence history. The statistical analysis procedures used on repeated adherence electronic monitoring measures were previously developed and validated (Schneider et al., 2019; Pasquier et al., 2022), and the analysis of the implementation to the different drug classes allowed determining the differential effect of the IMAP on implementation to antidiabetics, antihypertensive drugs, and statins.

Some limitations are to be acknowledged. First, even if the target sample size was reached, a significant number of patients either refused inclusion or dropped out during the study. Refusal to enroll has been addressed previously (Bandiera et al., 2022a). Our high level of patient adherence since inclusion may indicate a possible selection bias. This bias is difficult to address in clinical practice, unless a medication adherence program is embedded in usual clinical practice because "the very people with the worst adherence may be the least likely to accept inclusion in a non-routine medication adherence program" to paraphrase the famous quote by Tourangeau and Smith (1996): "The very persons with the most sensitive information to report may be the least likely to report it" (Tourangeau and Smith, 1996).

Regarding dropouts, we cannot exclude that patients who refused to participate or who left the study had a different medication adherence than those who completed the study. This needs further exploration.

Second, patients used the EM during the follow-up period, which could have been a supportive tool in their medication management. The LCD screen on the top of the EM cap indicated the number of daily EM opening(s), which can help prevent forgetfulness. Furthermore, patients had to refill their EMs at the pharmacy every 3 months, and they were recalled by phone calls if they missed the appointment, which is not the standard of care. Pharmacists had to check EM use deviation at each follow-up visit for methodological reasons, which may have raised patient awareness on medication adherence during the follow-up period. In addition, the repeated blood pressure and the abdominal circumference measured by pharmacists during the follow-up phase may have influenced patient medication adherence. Thus, medication adherence measured during the follow-up period might have been higher than that in the standard of care.

Third, owing to the low prevalence of treatment discontinuations, we did not analyze medication persistence. We would need a larger database with a larger sample size to carefully evaluate the effect of the IMAP on medication persistence in patients with DKD after the intervention. Finally, the number of blood pressure measurements collected was limited to the number of pharmacy visits. The individual variability in blood pressure over time was high; the ambulatory blood pressure measurements would have provided a more accurate evaluation of blood pressure control over 24 h than the office blood pressure. Future studies should increase the number of data collected and organize a retrospective collection of blood pressure measurements during the 12 months before the intervention to better describe blood pressure trajectories.

5 Conclusion

The interprofessional medication adherence program (IMAP) supports adherence in terms of implementation to antidiabetics and antihypertensive drugs in patients with diabetic kidney disease. The longer the patients benefit from the intervention, the more the implementation increases over time, and the more the effect lasts after the end of the intervention. The IMAP should be recommended for at least 12 months, or longer, with the intensity adjusted depending on the needs of the patients, to have a positive and sustained effect on treatment implementation in patients with diabetic kidney disease. The effect on clinical outcomes needs to be further investigated in the long term.

Data availability statement

The datasets for this article are not publicly available due to concerns regarding participant/patient anonymity. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

This study involving humans were approved by "Commission cantonale d'éthique de la recherche sur l'être humain" (Vaud, Switzerland, ID 2016-01674). This study was were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CB: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, writing–original draft, and writing–review and editing. JD-C:

conceptualization, investigation, methodology, project administration, resources, and writing–review and editing. IL: conceptualization, data curation, formal analysis, methodology, resources, validation, visualization, and writing–review and editing. DN: conceptualization, investigation, resources, and writing–review and editing. GW: conceptualization, investigation, resources, and writing–review and editing. MP: conceptualization, investigation, resources, and writing–review and editing. FL: conceptualization, investigation, resources, and writing–review and editing. MB: conceptualization, investigation, resources, and writing–review and editing. AZ: conceptualization, investigation, project administration, resources, supervision, and writing–review and editing, methodology, validation. MS: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, writing–original draft, and writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, and/or publication of this article. The PANDIA-IRIS study was funded by the LOA IV fund, managed by curafutura, pharmaSuisse, and santésuisse (Switzerland).

Acknowledgments

The authors sincerely thank all patients who participated in the PANDIA-IRIS study, the collaborators of the community pharmacy of *Unisanté* for the implementation of the study within the IMAP, the interprofessional teams at the Service of Endocrinology, Diabetes and Metabolism, the Service of Nephrology and Hypertension, and at the medical policlinic of *Unisanté*, and Dr Akram Farhat for their support in patient recruitment. The authors thank Dr Pierre Chodanowksi (Data Sciences Research, CHUV) for demographic and clinical data extraction.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1294436/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 23 February 2024
DOI 10.3389/fphar.2024.1345482

OPEN ACCESS

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RECEIVED 27 November 2023
ACCEPTED 12 February 2024
PUBLISHED 23 February 2024

CITATION
Turcu-Stiolica A, Udristoiu I, Subtirelu M-S, Gheorman V, Aldea M, Dumitrescu EA, Volovat SR, Median DM and Lungulescu CV (2024), Digging in real-word electronic database for assessing CDK 4/6 inhibitors adherence in breast cancer patients from Romania.
Front. Pharmacol. 15:1345482.
doi: 10.3389/fphar.2024.1345482

Digging in real-word electronic database for assessing CDK 4/6 inhibitors adherence in breast cancer patients from Romania

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Introduction: It is imperative for patients to respect the prescribed treatments to achieve the anticipated clinical outcomes, including the outpatients receiving oral anti-cancer drugs such as selective cyclin-dependent kinase 4/6 inhibitors (CDK 4/6i). With the introduction of three CDK 4/6i drugs in the Romanian pharmaceutical market in 2018, our study aimed to evaluate medication adherence and the influencing factors among patients undergoing treatment with palbociclib, ribociclib, or abemaciclib for advanced or metastatic breast cancer.

Methods: Medication adherence was assessed using the Proportion of Days Covered (PDC) method, and Spearman correlation analysis was conducted to explore the relationships between adherence, age, gender, and follow-up duration.

Results: The study enrolled 330 breast cancer patients, with an average follow-up period of 14.6 ± 12.5 months for palbociclib, 10.6 ± 7.1 months for ribociclib, and 8.6 ± 6.4 months for abemaciclib-treated patients. A small proportion of patients demonstrated non-adherence: 12.8% for palbociclib, 14.6% for ribociclib, and 14.7% for abemaciclib. Among patients receiving palbociclib, there was no significant correlation between adherence, age (rho = 0.07, p = 0.35), or gender (rho = −0.144, p = 0.054). However, a significant correlation was found with the duration of follow-up (rho = −0.304, $p < 0.0001$). Similar results were observed for patients receiving ribociclib or abemaciclib. Most patients received combination therapy with letrozole (46%) and exemestane (13%) for palbociclib, letrozole (48%) and fulvestrant (19%) for ribociclib, and fulvestrant (39%) and letrozole (27%) for abemaciclib,

Discussion: High adherence rates were observed among patients treated with CDK 4/6i drugs, with no significant differences noted among the three drugs in this class. However, the collected patient data was limited, lacking information on adverse reactions that could potentially lead to treatment discontinuation, as

determined by the oncologist's decision not to prescribe. Consequently, a comprehensive understanding of all factors contributing to the low adherence levels is hindered.

KEYWORDS

palbociclib, abemaciclib, ribociclib, CDK 4/6 inhibitors, breast cancer, adherence, proportion of days covered (PDC)

Introduction

Breast cancer is the second most common cancer in women after skin cancer with a percentage of 15.2% from all new cancer cases and 7.1% from all cancer deaths in 2023 (National Cancer Institute, 2023. https://www.cancer.gov/types/breast). The identification of cyclin-dependent kinases (CDK) and their regulatory mechanisms in cell cycle processes marked a pivotal advancement in cancer therapy. Among these, cyclin-dependent kinase 4 and 6 (CDK4/6) are enzymes crucially involved in cell cycle regulation. They exert significant control over the transition from the G1 (gap 1) phase to the S (synthesis) phase, where DNA replication occurs (Suryadinata et al., 2010). Maintaining a delicate equilibrium between CDK4/6 activation by cyclin D and their inhibition by cyclin-dependent kinase inhibitors (CDKi) is essential for the orderly progression of the cell cycle. Any disruption in this balance can result in uncontrolled cell division, contributing to various diseases, notably cancer (Barnum et al., 2014). In the realm of cancer treatment, CDK 4/6 inhibitors (CDK 4/6i) are employed to target overactive CDK4/6-cyclin D complexes. This is particularly pertinent in cancers like breast cancer, where this pathway often plays a central role in unregulated cell proliferation (Mariotto et al., 2017).

Palbociclib, ribociclib, and abemaciclib stand as prominent examples of CDK 4/6i widely employed in the treatment of specific forms of advanced/metastatic breast cancer (A/mBC) (Roskoski et al., 2019). Although these inhibitors demonstrate efficacy in impeding cancer cell proliferation, they are not devoid of adverse reactions and side effects (Jin et al., 2019). Previous research has indicated that abemaciclib is associated with a lower preference weight in comparison to other CDK4/6i due to adverse events, including diarrhea, abdominal pain, grade 3/4 neutropenia, tromboembolitic disease (Maculaitis et al., 2020), or acute liver injury (Beachler et al., 2021). Additionally, findings from a singular study (Cejuela et al., 2023) underscored diarrhea as a significant adverse reaction experienced by all patients, highlighting its clinical importance (Arbuckle et al., 2000). A meta-analysis regarding the risk of other side effects, such as stomatitis, demonstrated that especially palbociclib, among all CDK4/6i, could increase this risk impacting on patient adherence to the treatment (Long et al., 2021).

The global market for CDK 4/6i drugs is segmented across various categories, including drug types such as palbociclib (@Ibrance), ribociclib (@Kisqali), and abemaciclib (@Verzenio) (Finn et al., 2015). The first CDK4/6 inhibitor drug approved by the FDA was palbociclib in February 2015 (Dhillon et al., 2015; Fin et al., 2016). Subsequent approvals were granted for its utilization in combination with other hormonal therapies, rendering it a pivotal treatment option for specific breast cancer patients. Ribociclib received FDA approval in March 2017 (Hortobagyi et al., 2016). Similar to palbociclib, it was sanctioned for the treatment of hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2-negative) advanced or metastatic breast cancer in conjunction with an aromatase inhibitor. Its scope has been broadened since then, with additional approvals for diverse hormonal therapies (Salmon et al., 2020). Abemaciclib obtained FDA approval in September 2017. It was endorsed as a standalone agent for HR+, HER2-negative advanced or metastatic breast cancer in patients who had previously undergone endocrine therapy (Dickler et al., 2017). According to the submission of its dossier to EMA, abemaciclib was approved in combination with an aromatase inhibitor (AI, as letrozole, anastrozole, or examestan) as initial endocrine-based therapy or in combination with fulvestrant as initial endocrine-based therapy or following endocrine therapy.

These CDK4/6i have substantially enhanced treatment options for patients with HR+ breast cancer by targeting the cell cycle regulation process, which plays a pivotal role in cancer growth (Wells 2020). Typically, they are utilized in combination with endocrine therapies, significantly prolonging progression-free survival (PFS) and overall survival (OS) for numerous patients (Cristofanilli et al., 2016; Finn et al., 2016; Sledge et al., 2017; Slamon et al., 2018). CDK 4/6i are also utilized together with endocrine therapy for male patients diagnosed with HR+/HER2- metastatic breast cancer (Kraus et al., 2022). It is crucial to note that approval dates and availability can vary by country, and new applications and indications for these drugs may have emerged (Bandiera et al., 2023).

In Romania, approximately 12,000 new cases of breast cancer are diagnosed annually, rendering it the second leading cause of cancer-related deaths, following lung cancer (Furtunescu et al., 2021). According to research on the effects of COVID-19 pandemic in Romania on the breast cancer patients, even if the number of patients remained the same, the cancer treatment costs have risen exponentially from 2018 to 2021 (Turcu-Stiolica et al., 2022). Following Health Technology Assessment (HTA), the National Agency for Medicines and Medical Devices (NAMMD) in Romania unconditionally approved the inclusion of palbociclib in the Positive Drug List in November 2017 (Ministry of Health of Romania, 2017). Ribociclib was unconditionally included in the Positive Drug List in August 2022 (Inclusion of ribociclib in Romania, 2022), while abemaciclib was included in April 2022 (Inclusion of abemaciclib in Romania, 2022). All three medications were recommended for the treatment of women with locally advanced or metastatic breast cancer (a/mBC), who are HR+/HER2-, in combination with an AI or fulvestrant, as initial hormonal therapy, or in women who have received prior hormonal therapy. In premenopausal or perimenopausal women, hormonal therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.

Medication adherence is a hey enabler of best health outcomes and some medication adherence supporting activities were reported in order to guide research and practice on enhancing medication adherence (Kardas et al., 2023). Treatment nonadherence is associated with disease progression and mortality among patients with breast cancer (Chirgwin et al., 2016). The existing research on adherence to CDK4/6i anticancer agents is limited. Consequently, the primary aim of our research was to assess the adherence levels of CDK 4/6i and to explore potential correlations with variables such as age, gender, and the duration of patient follow-up. In addition to this primary objective, our study also sought to investigate potential disparities in medication adherence among the three distinct CDK 4/6i currently available within the pharmaceutical market in Romania. Through this research, we aimed to contribute valuable insights into the patterns of medication adherence and its associations with demographic factors, thereby enhancing our understanding of the real-world usage of these CDK 4/6i in clinical practice from Romania.

Methods

In the context of our study conducted in Romania, electronic information pertaining to reimbursed medications is exclusively accessible through the database maintained by the Romanian Health Insurance House. Ethical approval for our research endeavor, granted under Ethics Council approval number 175/29.10.2021, allowed us access to anonymized patient data sourced from community pharmacies in Dolj County, Romania, which were reported to the Health Insurance House of Dolj. The study focused on data spanning the past 5 years, from 2018 to 2022, corresponding to the period during which the first CDK 4/6 inhibitor, palbociclib, was approved for entry into the Romanian pharmaceutical market.

Specifically, our study inquired about patient records identified by the ICD-10 code C50, denoting breast cancer, with a subsequent focus on individuals receiving treatment with palbociclib, ribociclib, and abemaciclib. The data obtained for analysis encompassed essential demographic information, namely, age and gender, as well as details concerning prescription refills, including the quantity of medicines dispensed and the dates of prescription release from community pharmacies. Notably, our access to information was limited to these parameters, and we did not have access to additional patient-specific data such as comorbidities or other health covariates. This approach was undertaken within the confines of ethical guidelines and regulations, ensuring the confidentiality and privacy of patient information while enabling us to analyze patterns of CDK 4/6i usage in the studied population. The utilization of this restricted dataset was essential for our investigation into medication adherence and its potential correlations with demographic factors within the Romanian context.

Study population

All patients with breast cancer (code of disease = 124) who raised their reimbursed prescriptions from a community pharmacy from Dolj County, Romania, in the period 1 January 2018 -31 December 2022. The first patient received the first palbociclib prescription from the community pharmacy in July 2018, and she was a female of 75 years old, whereas for abemaciclib, the first patient was a female of 73 years old, in February 2021. We included all patients who had at least two fills of CDK 4/6i because it is required to compute medication adherence.

CDK 4/6i cycle dates were determined based on the electronic records from the Dolj Health Insurance House for the reimbursed prescriptions written by the oncologist.

Outcomes

The duration of follow-up was defined as the time in months from the first prescription issuing by the pharmacist in the community pharmacy to the last prescription reimbursed by the Dolj Health Insurance House according to the analyzed period (1 January 2018-31 December 2022). We considered it as the time elapsed from the medication's starting date to the last treatment's discontinuation date, which could be death or treatment modification.

There is no universally standardized method for measuring medication adherence. An ISPOR Report authored by Pednekar et al. highlighted the most frequently employed techniques found in the literature, which include self-reported questionnaires, proportion of days covered (PDC), and medication possession ratio (MPR). The PDC is the leading method used to calculate medication adherence using prescription refill data from electronic records at the population level. PDC was defined as the number of days that drugs were available to the patient over a time interval, but it has many formulas (Pednekar et al., 2019). We calculated the adherence using the formula as the report between Σ cycles/months of supply for medication and Σ months between last month of prescription and the first month of prescription. By definition, PDC ranges from 0 to 1. We used the conventional cutoff point of 0.8 to classify the patients into adherent ($0.8 \leq PDC \leq 1$) and non-adherent ($0 \leq PDC < 0.8$) patients (Dima et al., 2017).

Statistical analysis

We conducted descriptive analysis of continuous variables (age, adherence) using means±standard deviations (SD), median and interquartile range (IQR) and range (minimum-maximum) and of categorical variables (gender, categories of age) using frequencies and percentages. Additionally, to demonstrate the potential correlation between medication adherence and age, gender of patients, we calculated the Spearman's coefficients and visually presented with heatmaps. To evaluate the differences between the characteristics and medication adherence of patients with different treatment, we used Kruskal–Wallis H test for continuous variables and Chi-square test for categorical variables. We visually presented the differences of medication adherence among patients with different treatments using violin graphs. We conducted statistical analysis using GraphPad Prism 10.1 (GraphPad Software Boston, USA), with the statistical significance level set at p less than 0.05, two-tailed.

TABLE 1 Characteristics of the patients treated with CDK 4/6 inhibitors.

Characteristics	Palbociclibum (n = 180)	Ribociclibum (n = 82)	Abemaciclibum (n = 68)	*p*-value
Age, years mean ± SD	64.88 ± 11.72	68.46 ± 12.37	66.22 ± 11.38	0.068[a]
median (IQR)	66 (57–74)	70.5 (60.75–77)	66 (58.25–73.75)	
range	30–90	36–92	43–93	
Age, frequencies (%)	4 (2.2%)	2 (2.4%)	0	0.621[b]
30–39	16 (8.9%)	6 (7.3%)	6 (8.8%)	
40–49	34 (18.9%)	9 (11.0%)	12 (17.6%)	
50–59	60 (33.3%)	23 (28.0%)	23 (33.8%)	
60–69	47 (26.1%)	27 (32.9%)	18 (26.5%)	
70–79	19 (10.6%)	15 (18.3%)	9 (13.2%)	
80–93				
Gender, female, n (%)	174 (96.7%)	81 (98.8%)	67 (98.5%)	0.498[b]
Adherence mean ± SD	0.925 ± 0.137	0.92 ± 0.15	0.93 ± 0.14	0.368[a]
median (IQR)	1 (0.89–1)	1 (0.88–1)	1 (0.94–1)	
range	0.11–1.00	0.15–1.00	0.43–1.00	
Follow-up, months mean ± SD	14.6 ± 12.5	10.6 ± 7.1	8.6 ± 6.4	0.004**[a]
median (IQR)	10 (5–21.3)	9 (5.25–16.75)	7 (3–13.25)	
range	1–52	1–26	1–21	

[a]Kruskal–Wallis H test; b, Chi-square test. **, *p*-value <0.01.

Results

During the study period from 1 January 2018, to 31 December 2022, a total of 330 patients were prescribed CDK 4/6i. Among these, 180 patients (55%) were administered palbociclib, 82 (25%) received ribociclib, and 68 (20%) were prescribed abemaciclib.

Table 1 summarizes descriptive statistics of patient characteristics, and adherence, for each group of patients, as well as the *p*-value after performing the comparison between them. The median (range) age was 66 (30–90) years for the palbociclib group, 71 (36–92) years for the ribociclib group, and 66 (43–93) years for the abemaciclib group of patients. Most of the patients were more than 60 years old: 70% in palbociclib patients, 79.3% in ribociclib patients and 73.5% in abemaciclib patients. Most of the patients were female, but more male patients were treated with palbociclib (3.3%) than with ribociclib (1.2%) or abemaciclib (1.5%). The follow-up varies significantly between the three groups of patients (*p*-value = 0.004), with higher follow-up for patients treated with palbociclib, because it was earlier introduced on the Romanian pharmaceutical market.

The eligible patients were included in our study with an average follow-up period of 14.6 ± 12.5 months for the patients treated with palbociclib, 10.6 ± 7.1 months for the patients treated with ribociclib, and 8.6 ± 6.4 months for the patients treated with abemaciclib, respectively. CDK 4/6i were generally combined with either letrozole, fulvestrant, exemestane, anastrozole, goserelin or tamoxifen as in Figure 1. No ribociclibum or abemaciclib were combined with tamoxifen in our database. Most of the patients had treatment in combination with letrozole (45.9%) and exemestan (13.4%), in case of palbociclib, letrozole (45.9%) and fulvestrant (19%), in case of ribociclib, and fulvestrant (39.1%) and letrozole (27.4%), in case of abemaciclib, as shown in Table 2. Gosereline was more combined with ribociclibum (5.4%).

The proportion of non-adherent patients taking CDK 4/6i with PDC <0.8 was 13.6%, splitting into 12.8% for palbociclib, 14.6% for ribociclib, 14.7% for abemaciclib, respectively. For a cut-off equal to 0.85, the proportion of non-adherent patients taking CDK 4/6i was 16.1%, splitting into 16% for palbociclib, 17% for ribociclib, and 16.2% for abemaciclib. For a cut-off equal to 0.90, the proportion of non-adherent patients taking CDK 4/6i was 24.8%, splitting into 25% for palbociclib, 27% for ribociclib, and 22.1% for abemaciclib. No significant difference was obtained for adherence levels among patients treated with the three CDK 4/6i, as shown in Figure 2. We observed the peaks in the CDK 4/6i and the most patients had 100% adherence for all three groups of patients. Better adherence, but not significantly higher, was observed among patients treated with abemaciclib (mean ± SD, 0.93 ± 0.14) than among patients treated with palbociclib (mean ± SD, 0.92 ± 0.14) or ribociclib (mean ± SD, 0.92 ± 0.15). The smallest adherence was observed for a patient treated with palbociclib (0.11), while the smallest adherence observed for a patient treated with ribociclib was 0.15 and the smallest adherence observed for a patient treated with abemaciclib was 0.43.

As in Figure 3A, in patients treated with palbociclib, there was no significant correlation between the level of adherence, age (rho = 0.07, $p = 0.35$) or gender (rho = −0.144, $p = 0.054$), but a significant correlation was observed with the duration of follow-up

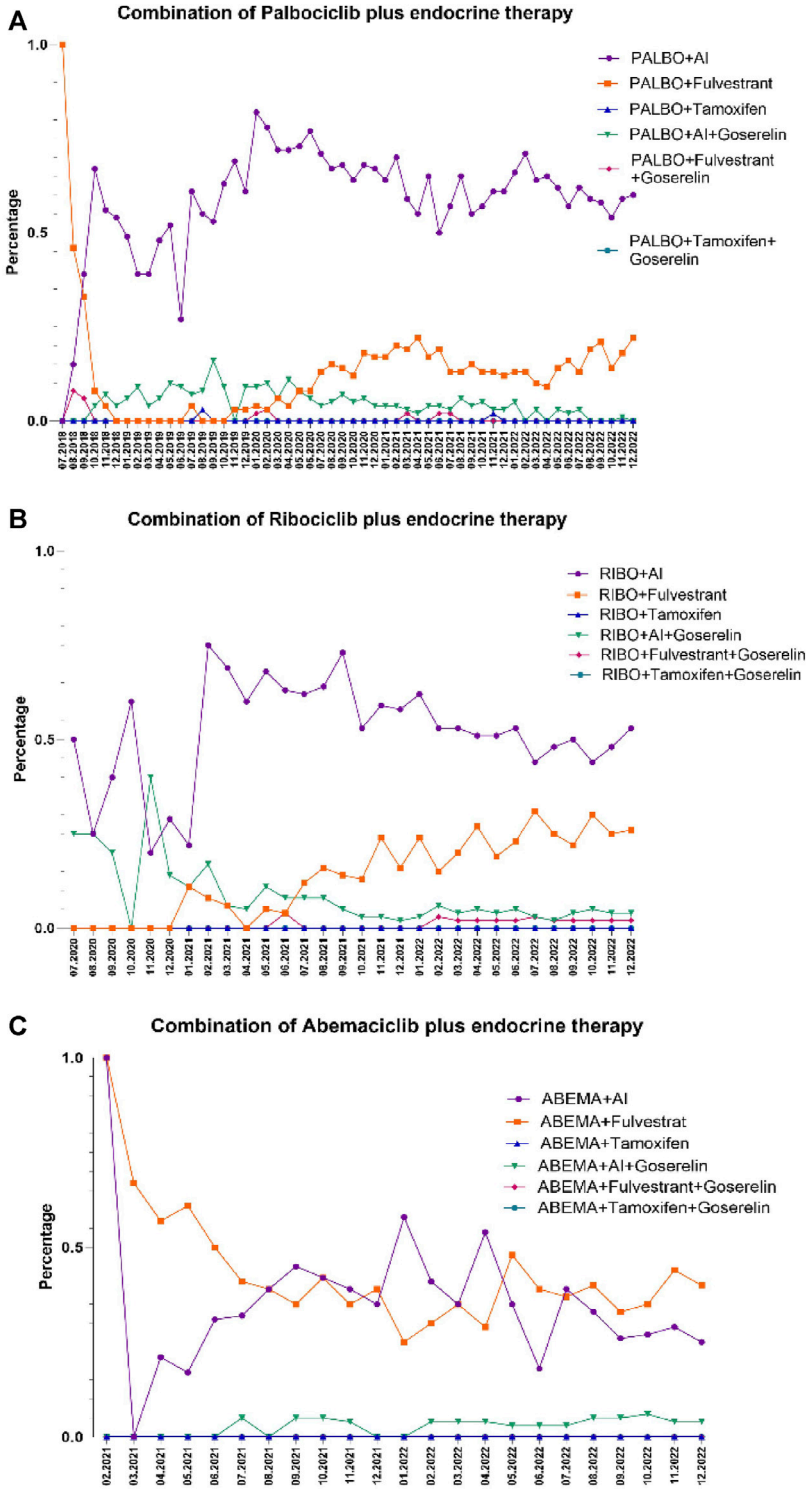

FIGURE 1
Combination of CDK 4/6i with endocrine therapy by month over the study period. **(A)**. Combination of palbociclib (PALBO) with endocrine therapy. **(B)**. Combination of ribociclib (RIBO) with endocrine therapy. **(C)**. Combination of abemaciclib (ABEMA) with endocrine therapy. AI (aromatase inhibitor). The percentages were computed based on the total number of patients undergoing treatment with both CDK 4/6i and endocrine therapy.

(rho = −0.304, $p < 0.0001$). Similarly, in patients receiving ribociclib, no significant correlation was found between adherence levels and age (rho = −0.097, $p = 0.388$) or gender (rho = −0.082, $p = 0.466$), but a significant correlation was identified with the follow-up duration (rho = −0.394, $p < 0.0001$), as is shown in Figure 3B. The same results were obtained for patients treated with abemaciclib, where no significant correlation was found between adherence levels and age (rho = 0.007, $p = 0.955$) or gender (rho = −0.072, $p = 0.559$), but a significant correlation was observed with the duration of follow-up (rho = −0.25, $p = 0.04$), as is shown in Figure 3C.

TABLE 2 Combinations of the CDK 4/6 inhibitors with aromatase inhibitors or/and luteinizing hormone-releasing hormone agonists.

Combination of CDK 4/6i	Palbociclibum (n = 180)	Ribociclibum (n = 82)	Abemaciclibum (n = 68)
Aromatase inhibitors	61.1%	53.7%	33.3%
Letrozole	45.9%	48.4%	27.4%
Anastrozole	1.8%	-	0.7%
Exemestane	13.4%	5.3%	5.38%
Luteinizing hormone-releasing hormone agonist	12.2%	19%	39.1%
Fulvestrant	12.1%	19%	39.1%
Tamoxifen	0.1%	-	-
Aromatase inhibitors + Gosereline	4.4%	5.4%	3.5%
Fulvestrant + Gosereline	0.3%	1.5%	-
Tamoxifen + Gosereline	-	-	-

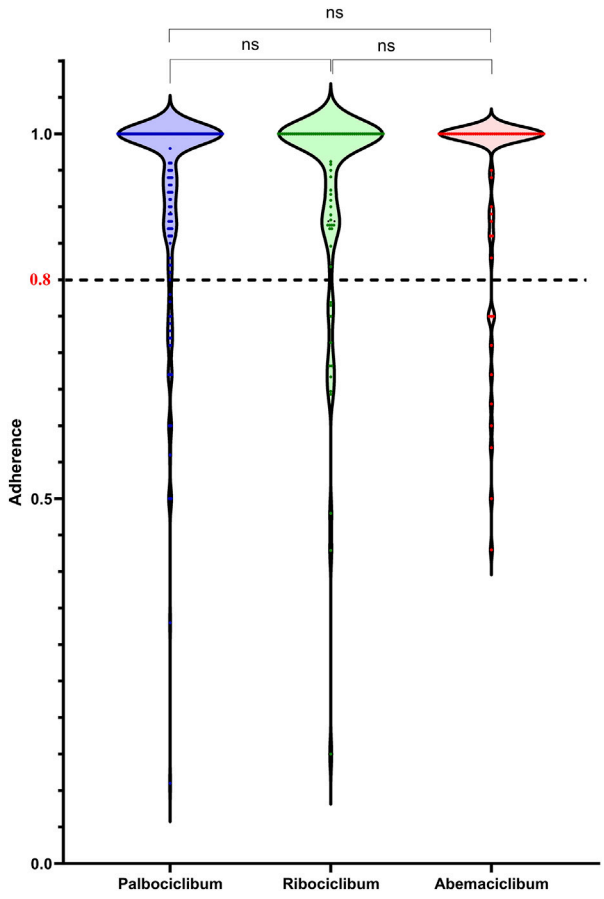

FIGURE 2
Adherence as proportion of days covered (PDC) in patients treated with either CDK 4/6i, palbociclib, ribociclib, and abemaciclib.

Discussion

Maintaining adherence to CDK 4/6i is a mandatory step towards reaching treatment goals for patients with HR+/HER2-a/mBC. We found a proportion of 14% of non-adherent patients taking CDK 4/6i for an 80% adherence cut-off, 16% using an 85% adherence cut-off and 25% using a 90% cut-off, without significant differences between non-adherence for palbociclib, ribociclib and abemaciclib. We obtained an average PDC values of 92.6%, which is comparable with the PDC values of 89.6% obtained by another retrospective study from Canada that included patients receiving either palbociclib or abemaciclib (Marineau et al., 2023). Marineau et al. similar values for mean PDC for palbociclib (90%) and abemaciclib (88.1%), in the same way we obtained for abemaciclib (93%) and palbociclib (92%). Using another method to measure palbociclib adherence, medication possession ratio (MPR), the same results were obtained in a real-world assessment of palbociclib adherence in USA, 88% (Engel-Nitz et al., 2023).

The ribociclib adherence was found to be 92%, similar to the adherence rates measured using patient self-reported questionnaires (87.9%, 91.6%, and 91.6% for EORTC QLQ-C30, QLQ-BR23, and HADS-D, respectively) in RIBANNA trial (Fasching et al., 2022). An ongoing clinical trial LEADER monitored ribociclib adherence by review of patients' diaries and pill count, without still reported the results (https://clinicaltrials.gov/study/NCT03285412).

Lasala et al. reviewed the studies assessing the association between adherence to oral therapies in cancer patients and clinical outcome and found studies that used different adherence cut-offs that could be associated with different clinical outcomes (Lasala, 2021). None of these studies evaluated CDK 4/6i adherence, but we could compare with studies which included patients with breast cancer under endocrine treatment (tamoxifen, anastrozole, letrozole and exemestane) (Ma et al., 2008; Partridge et al., 2010; Xu et al., 2012; Weaver et al., 2013; Seneviratne et al., 2014; Rodrigues Guedes et al., 2017; Le Saux et al., 2018; Font et al., 2019). Twenty-five percent of non-adherence breast cancer patients were observed in a study that recorded capecitabine adherence by microelectronic monitoring system (MEMS) with a cut-off of 0.80 (Partridge et al., 2010).

The routine of frequent medication intake was proved to be one of the important barriers of adherence to oral anticancer medications among patients with breast cancer (Onwusah et al., 2023). It is important to emphasize that, despite the distinct administration schedules of CDK 4/6 inhibitors (ribociclib and palbociclib are administered once daily for 21 consecutive days followed by 7 days without treatment, while abemaciclib is administered continuously), medication adherence did not differ among the three patient groups.

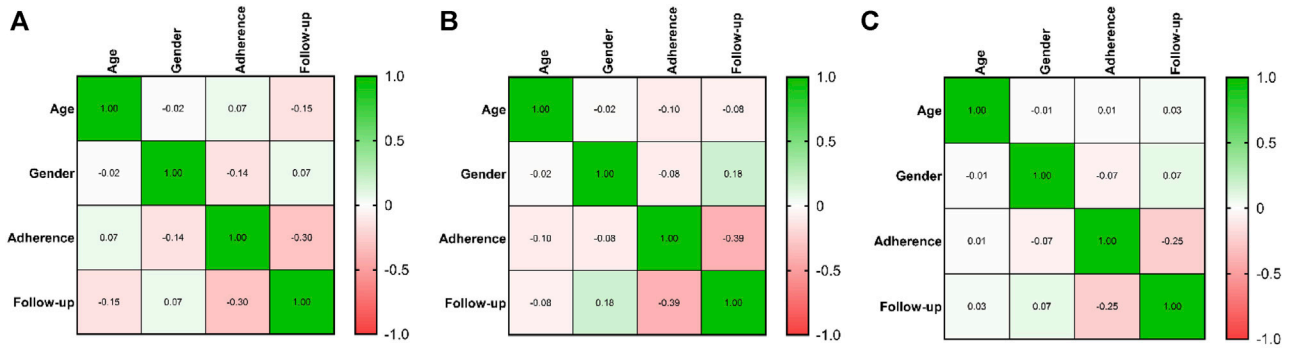

FIGURE 3
Correlation between adherence of CDK 4/6i treatment, age, gender and follow-up of treatment. The colors from heatmaps correspond to the Spearman coefficient from negative values (light orange color) to positive values (green color). **(A)**. Heatmap of correlations in the case of palbociclib therapy. **(B)**. Heatmap of correlations in the case of ribociclib therapy. **(C)**. Heatmap of correlations in the case of abemaciclib therapy.

Seneviratne and Xu showed a statistically significant correlation between medication adherence and OS in breast cancer patients (Xu et al., 2012; Seneviratne et al., 2015). Rodrigues Guedes did not find any correlation (Rodrigues Guedes et al., 2017). Waever et al. did not found significant correlation between adherence and cancer recurrence (Waever et al., 2013). No significant correlation was found between adherence and response according to RECIST (response evaluation criteria in solid tumours) (Le Saux et al., 2018) or relapse-free survival and toxicity (Partridge et al., 2010). Dezentjee et al. demonstrated that tamoxifen adherence was significantly associated with breast cancer event-free time (EFT) for both 80% and 90% adherence cut-offs (Dezentjee et al., 2010).

Few studies were published regarding CDK 4/6i non-adherence negatively effects. Regarding palbociclib adherence, it was measured its impact on pharmacokinetic and pharmacodynamic profiles and proved that catching up on a missed dose at the end of the cycle increases the risk of severe neutropenia in the next cycle (Bandiera et al., 2023).

In our study, we found no significant association between gender and adherence to CDK4/6i, a finding that contrasts with some research indicating gender-specific differences in medication adherence, especially in the context of experiencing adverse effects. For example, a significant difference has been noted in the occurrence of side effects in tamoxifen treatments (Xu et al., 2012). This distinction is important to take into account because the likelihood of side effects is a major factor affecting patients' compliance with their prescription regimens.

The lack of a gender-based difference in adherence to CDK4/6i in our study is particularly intriguing when juxtaposed with these observations. It prompts further inquiry into the distinctive characteristics of CDK4/6i and their reception and tolerance by different genders and it is important to consider the variety of treatments used for male breast cancer patients.

A study published in Breast in 2022 (Yıldırım et al., 2022) highlights that most male patients were treated with CDK4/6i in combination with fulvestrant or AI rather than tamoxifen. This diverges from the general perception and findings in some interviews (Chalasani, 2023), which suggest that tamoxifen is a more commonly used treatment in male breast cancer patients. This discrepancy in treatment choices is noteworthy because it suggests variability in the clinical management of male breast cancer and potentially different side effect profiles and adherence challenges associated with each treatment.

In our study, among the patients who received palbociclib, 61% patients received a combination with AI and 12.2% a combination with LHRH, in almost the same proportions a US real-world study obtained, 76.1%, palbociclib + AI, and 23.9%, palbociclib + fulvestrant (Engel-Nitz et al., 2022). A study assessing the treatment satisfaction in women receiving palbociclib combination for a/mBC in six countries (USA, Canada, Germany, Netherlands, Argentina, and Denmark) included more patients taking palbociclib plus fulvestrant combination (58.6%), but with a smaller median age than our study–41 years old (Darden et al., 2018). In our study, among the patients who received ribociclib, 53.7% patients received ribociclib + AI and 19% patients received ribociclib + LHRH. Regarding the patients who received abemaciclib, more patients were treated in combination with LHRH (39%) than with AI (33%).

The choice of treatment - whether tamoxifen, fulvestrant, AI + GNRH inhibitors, or CDK4/6i - can have significant implications for adherence. Each medication comes with its own set of potential side effects and impacts on quality of life, which can influence a patient's willingness and ability to remain adherent. The fact that different treatments are being chosen for male patients in various studies and clinical settings underlines the need for a deeper understanding of how treatment decisions are made and how these decisions affect adherence. This understanding is crucial in developing strategies to improve adherence, especially considering the unique challenges male breast cancer patients may face.

The finding in our study that adherence to CDK4/6i was not significantly associated with age, with most older women showing adherence, is a notable observation in the context of breast cancer treatment.

This outcome aligns interestingly with other publications as the adherence of older women to CDK4/6i in our study is encouraging, especially considering the potential survival benefits highlighted by Petrelli et al. The high adherence rate among older women in our study may reflect the effectiveness of these medications on quality of life, their tolerability, or possibly a good understanding and acceptance of treatment regimens among older patients. This observation is important as it suggests that age alone may not be a significant barrier to adherence in the context of CDK4/6i therapy, emphasizing the need for

personalized treatment approaches that account for individual patient profiles rather than solely age-based strategies.

Adherence to CDK 4/6i was significantly associated with the follow-up. This aligns with the findings from other studies (Eliassen et al., 2023) which highlights that adherence and persistence to endocrine treatment are critical for improving event-free and overall survival in non-metastatic breast cancer patients. Therefore, it is plausible that the patients in our study who demonstrated better adherence over extended treatment periods might have experienced improved health outcomes, including longer survival. This potential link between sustained adherence and survival emphasizes the importance of strategies to enhance and maintain adherence in breast cancer treatment. Moreover, on the other side, with extended treatment, patients may begin to see the benefits or stabilization of their condition, reinforcing their trust in the effectiveness of the therapy and motivating them to adhere to the regimen.

Based on these results, different interventions could be developed to enhance CDK4/6i adherence. A mobile health intervention was tested integrating a connected electronic adherence monitoring smartbox and automated texting alerts, resulting a palbociclib adherence of 95.8% ± 7.6% (Sadigh et al., 2023). Baseline, before the intervention, the reported barriers were inconvenience to get prescription filled, forgetfulness, cost, and side effects. Our results regarding the adherence to palbociclib were 92.5% ± 13.7%, but without any interventions and costs could not be among the barriers because the drugs are free, with no out-of-pockets costs. The Romanian National Oncology Program covers these medicines for people diagnosed with cancer, being fully reimbursed by the National Health Insurance House in Romania.

Inherent limitations of real-world analyses using data collected during providing reimbursed drugs include the lack of important information (the stage of the disease), incomplete capture of comorbid conditions, and variations in follow-up/short duration of follow-up.

PDC, as a proxy measure of medication adherence based only on community pharmacy claims data, fails to capture the legitimate reasons for not taking CDK 4/6i drugs and does not measure the patient's actual medication-taking behavior as self-reported like questionnaires do. Limitations of this study include the unknown reasons for prescribing treatment transient interruptions or cycle start deferrals. Toxicity or adverse effects could be the main reasons. Some adherence barriers were observed in assessing palbociclib adherence: inconvenience to get prescription filled, forgetfulness, cost, and side effects (Sadigh et al., 2023). Despite these limitations from the information extracted from our data sources, our results are the beginning of future research in measuring CDK 4/6i adherence.

Another limitation of our study is associated with the small sample size, as the investigation was conducted exclusively within one of Romania's counties. Romania lacks patient registries and easily accessible databases. The count of patients in Dolj utilizing CDK4/6i, as reported by the Romanian National Health Insurance House, remained relatively consistent throughout the analyzed years: 8.12% in 2018, 4.72% in 2019, 4.02% in 2020, 4.82% in 2021, and 4.85% in 2022 (calculated as a percentage of the total number of patients using CDK4/6i in Romania). A meta-analysis performing an adjusted indirect comparison among the three CDK 4/6i efficacy and toxicity revealed they are equally effective in either first- or second-line therapy for estrogen receptor-positive advanced breast cancer (Petrelli et al., 2019). Choice of treatment depends on several factors, including patients' adherence, comorbidities, and disease burden. Despite the limitations of our study, the results do not demonstrate a clear superiority of one of the three CDK 4/6i adherence, further studies are needed to understand the adherence influencing factors and the correlations of clinical outcomes with CDK 4/6i adherence (Huang et al., 2016; Murphy et al., 2012; Rugo et al., 2021).

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the University of Medicine and Pharmacy of Craiova, Romania. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

AT-S: Conceptualization, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Validation, Writing–original draft. IU: Investigation, Methodology, Writing–review and editing, Conceptualization. M-SS: Investigation, Data curation, Writing–original draft. VG: Funding acquisition, Investigation, Validation, Writing–review and editing. MA: Validation, Writing–review and editing, Funding acquisition, Investigation. ED: Validation, Writing–review and editing. SV: Validation, Writing–review and editing. DM: Validation, Writing–review and editing. CL: Conceptualization, Investigation, Project administration, Resources, Supervision, Validation, Visualization, Writing–review and editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. The Article Processing Charges were funded by the University of Medicine and Pharmacy of Craiova, Romania.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 13 March 2024
DOI 10.3389/fphar.2024.1340255

OPEN ACCESS

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RECEIVED 17 November 2023
ACCEPTED 23 February 2024
PUBLISHED 13 March 2024

CITATION
Lizano-Barrantes C, Garin O, Mayoral K, Dima AL, Pont A, Caballero-Rabasco MA, Praena-Crespo M, Valdesoiro-Navarrete L, Guerra MT, Bercedo-Sanz A and Ferrer M (2024), Impact of treatment adherence and inhalation technique on asthma outcomes of pediatric patients: a longitudinal study. *Front. Pharmacol.* 15:1340255. doi: 10.3389/fphar.2024.1340255

Impact of treatment adherence and inhalation technique on asthma outcomes of pediatric patients: a longitudinal study

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Introduction: We aimed to evaluate the longitudinal relationships, both at between- and within-person levels, that adherence to inhaled corticosteroid-based maintenance treatment and inhalation technique present with symptom control, exacerbations, and health-related quality of life (HRQoL) in children and adolescents with asthma.

Methods: Participants (6–14 years old) from the ARCA (Asthma Research in Children and Adolescents) cohort—a prospective, multicenter, observational study (NCT04480242)—were followed for a period from 6 months to 5 years via computer-assisted telephone interviews and a smartphone application. The Medication Intake Survey–Asthma (MIS-A) was administered to assess the implementation stage of adherence, and the Inhalation Technique Questionnaire (InTeQ) was used to assess the five key steps when using an inhaler. Symptom control was measured with the Asthma Control Questionnaire (ACQ), and HRQL was measured with the EQ-5D and the Patient-Reported Outcomes Measurement Information System–Pediatric Asthma Impact Scale (PROMIS-PAIS). Multilevel longitudinal mixed models were constructed separately with symptom control, exacerbation occurrence, EQ-5D, and PROMIS-PAIS as the dependent variables.

Abbreviations: ICS, inhaled corticosteroids; ICS plus LABA, inhaled corticosteroids plus long-acting beta-agonist; ICC, intra-class correlation coefficient; VPC, variance partition coefficient; AIC, Akaike information criterion; BIC, Bayesian information criterion.

Results: Of the 360 participants enrolled, 303 (1,203 interviews) were included in the symptom control and exacerbation analyses, 265 (732) in the EQ-5D, and 215 (617) in the PROMIS-PAIS. Around 60% of participants were male subjects, and most of them underwent maintenance treatment with inhaled corticosteroids plus long-acting β-agonists in a fixed dose (73.3%). Within-person variability was 83.6% for asthma control, 98.6% for exacerbations, 36.4% for EQ-5D, and 49.1% for PROMIS-PAIS. At the within-person level, patients with higher adherence had better symptom control (p = 0.002) and HRQoL over time (p = 0.016). Patients with a better inhalation technique reported worse HRQoL simultaneously (p = 0.012), but they showed better HRQoL in future assessments (p = 0.012). The frequency of reliever use was associated with symptom control (p < 0.001), exacerbation occurrence (p < 0.001), and HRQoL (p = 0.042); and boys were more likely to present better symptom control and HRQoL than girls.

Conclusion: Our results confirm longitudinal associations at the within-person level of the two indicators of quality use of inhalers: for adherence to maintenance treatment with symptom control and HRQoL, and for the inhalation technique with HRQoL. Although treatment adherence was shown to be excellent, a third of the participants reported a suboptimal inhalation technique, highlighting the need for actions for improving asthma management of the pediatric population.

KEYWORDS

adherence, inhalation technique, pediatric asthma, health-related quality of life, asthma outcomes, asthma symptom control, asthma exacerbations

1 Introduction

Asthma is the most common non-communicable disease in school-aged children (Bercedo Sanz et al., 2022; The Global Asthma Report, 2022) and a major public health problem worldwide (Asher et al., 2021; Bercedo Sanz et al., 2022; Song et al., 2022). In 2019, an estimated 12,900 deaths occurred and 5.1 million disability-adjusted life years were lost due to childhood asthma (Zhang and Zheng, 2022). According to the latest global report, only 44.1% of children and 55.4% of adolescents with asthma achieved a well-controlled disease stage (García-Marcos et al., 2023).

Childhood asthma is a heterogeneous and fluctuating disease, with symptoms that vary in time and intensity (Global Initiative for Asthma; von Mutius and Smits, 2020). Therefore, management is mainly based on a continuous personalized cycle of assessment of asthma control (symptom control and risk factors for future exacerbations), any comorbidities that could contribute to symptom burden and poor health-related quality of life (HRQoL), and treatment (Global Initiative for Asthma, 2023). Intake of daily inhaled corticosteroids (ICS) is the currently recommended pharmacologic maintenance therapy in individuals of all ages (Montuschi and Barnes, 2011; National Heart Lung and Blood Institute (NHLBI), 2020; Global Initiative for Asthma, 2023). Research has shown that adherence to ICS and inhalation technique are dynamic and complex (Vrijens et al., 2016; Azzi et al., 2017; Almomani et al., 2021), with studies indicating generally low adherence to maintenance medication (20%–70%) (Herndon et al., 2012; Boutopoulou et al., 2018) and suboptimal inhalation technique (8%–22%) (Gillette et al., 2016) in children and/or adolescents.

Most evidence from systematic reviews suggests that whether it is children (Everhart and Fiese, 2009; Engelkes et al., 2015; Silva et al., 2015; Kocks et al., 2018; Usmani et al., 2018), adolescents (Engelkes et al., 2015; Silva et al., 2015; Kocks et al., 2018; Usmani et al., 2018; Vazquez-Ortiz et al., 2020; Roche et al., 2022), or adults (Bårnes and Ulrik, 2015; Engelkes et al., 2015; Kocks et al., 2018; Usmani et al., 2018; Vazquez-Ortiz et al., 2020; Roche et al., 2022), higher levels of adherence (Bårnes and Ulrik, 2015; Engelkes et al., 2015; Vazquez-Ortiz et al., 2020) and better inhalation technique (Kocks et al., 2018; Usmani et al., 2018; Roche et al., 2022), analyzed separately, are associated with better outcomes (symptom control, exacerbations, and/or HRQoL), although an inverse or null association has also been found (Bårnes and Ulrik, 2015; Engelkes et al., 2015; Kocks et al., 2018; Usmani et al., 2018; Vazquez-Ortiz et al., 2020; Roche et al., 2022). Furthermore, impaired HRQoL has also been linked with asthma-associated factors, such as severity (Everhart and Fiese, 2009), disease control, and exacerbations (Silva et al., 2015; Vazquez-Ortiz et al., 2020) in children, adolescents, and young adults.

These systematic reviews (Bårnes and Ulrik, 2015; Engelkes et al., 2015; Silva et al., 2015; Kocks et al., 2018; Usmani et al., 2018; Vazquez-Ortiz et al., 2020; Roche et al., 2022) show that more than 160 studies have been conducted involving patients with asthma that evaluated the relationships between adherence, inhalation technique, asthma control, asthma exacerbation, and/or HRQoL. However, only 22 of these studies included longitudinal analyses, with nine focusing exclusively on children and/or adolescents (Bukstein et al., 2007; Camargo et al., 2007; Delea et al., 2008; Hagmolen of ten Have et al., 2008; Lasmar et al., 2009; Elkout et al., 2012; Herndon et al., 2012; Krishnan et al., 2012; Tiggelman et al., 2015) and 13 encompassing adults as well (Osman et al., 1999; Balkrishnan and Christensen, 2000; McMahon et al., 2000; Stern et al., 2006; Santos et al., 2008; McNally et al., 2009; Smith et al., 2009; Mattke et al., 2010; Rohan et al., 2010; Sundell et al., 2011; Williams et al., 2011; Hyland et al., 2012; Yildiz et al., 2014). Notably, none of them considered the temporal stages of

adherence (initiation, implementation, and discontinuation) described in 2012 (Vrijens et al., 2012). Although the systematic reviews were published between 2015 and 2022, none of the studies including longitudinal analyses, were conducted after 2013. Therefore, they probably do not reflect the Food and Drug Administration (FDA) requirement changes, contraindicating the use of long-acting beta-agonists (LABAs) without concurrent ICS (Chowdhury and Dal Pan, 2010).

The Global Asthma Initiative Guideline (GINA) (Global Initiative for Asthma, 2023) has continued to incorporate changes due to the collection of new evidence related to the efficacy and safety of ICS, LABA, and short-acting beta-agonists (SABAs). More recent longitudinal studies (Azzi et al., 2017; Johnson et al., 2017; Souverein et al., 2017; Papi et al., 2018; Dima et al., 2019; Vervloet et al., 2020; Vervloet et al., 2022; Hale et al., 2023; Sousa-Pinto et al., 2023) have presented further evidence of the long-term role of ICS adherence in asthma. However, none were conducted specifically on a pediatric population, only one included HRQoL (Hale et al., 2023), few specified the adherence stage considered (Souverein et al., 2017; Dima et al., 2019; Vervloet et al., 2020; Vervloet et al., 2022), and only one included medication adherence alongside the inhalation technique (Hale et al., 2023). These last two concepts are closely related, with the poor inhalation technique even being considered an unintentional form of adherence (van Boven et al., 2015), but they are usually identified as independent concepts (Monteiro et al., 2022). Two of the aforementioned systematic reviews (Engelkes et al., 2015; Kocks et al., 2018) have highlighted the scarcity of studies evaluating the impact of adherence and inhalation technique, assessed together, on asthma outcomes, despite the association that has been observed between them (Giraud et al., 2011; Maricoto et al., 2020).

A deeper insight into how adherence and inhaler technique evolve over time and affect the clinical outcomes and HRQoL in children could foster a 'quality use of medications' strategy (Braido et al., 2016), aligning with the current guidelines. Therefore, we aimed to evaluate the longitudinal relationships, both at between- and within-person levels, that adherence to ICS (alone or in combination with LABA) and inhalation technique present with symptom control, exacerbations, and HRQoL in children and adolescents with asthma.

2 Materials and methods

2.1 Study design and participants

Asthma Research in Children and Adolescents (ARCA) is a longitudinal, prospective, multicenter, observational study (NCT04480242) designed to provide evidence about the evolution of young patients with persistent asthma through regular follow-ups.

Patients were consecutively recruited from five outpatient pediatric pulmonology hospital units and nine primary care pediatric centers in Spain from January 2018 to March 2023 and were thus followed for a period from 6 months to 5 years. The inclusion criteria were as follows: aged 6–14, with a clinical diagnosis of asthma (history of characteristic symptoms and objective signs of variable airflow limitation) (Global Initiative for Asthma, 2017), undergoing treatment with ICS (alone or combined with LABA) for more than 6 months in the previous year, no concomitant respiratory diseases, and with access to a smartphone (their own or their parents'). Written informed consent was requested from the parents or legally authorized representatives of all participants, and additionally, oral consent was obtained from the children.

The participants were followed *via* the ARCA smartphone application (Mayoral et al., 2021) monthly and *via* computer-assisted telephone interviews (CATIs) performed by trained interviewers at enrollment, every 6 months (regular CATIs), and after each exacerbation (post-exacerbation CATIs). The ARCA application is available in three age versions: proxy response for children aged 6–7 years and self-response for participants aged 8–11 and ≥12 years. Through the application, participants reported any new exacerbations and completed the HRQoL instruments. Two versions of the CATIs were administered, one for parents or guardians of children under 8 years old (proxy response) and one for participants aged 8 and older (self-response). CATIs collected information on asthma symptom control, exacerbations, asthma treatments (maintenance and reliever), adherence to maintenance medication, inhalation technique, reliever use, and exacerbation occurrence for the period immediately before the interview. Demographic and clinical information was collected from medical records at enrollment.

For this analysis, we selected participants who had valid registries of at least two CATIs during a period with an ICS-based treatment prescribed for regular use (maintenance).

The ESPACOMP Medication Adherence Reporting Guideline (EMERGE) was followed (Adams N. P. et al., 2005).

2.2 Study variables

Medication information was collected at every CATI, including the active drug component, dose, type of inhaler device (pressurized metered-dose inhaler—pMDI and dry-powder inhaler—DPI) for the maintenance treatment, and the frequency of reliever medication use. Maintenance treatment was grouped into two categories: ICS in a fixed-dose combination with LABA (ICS plus LABA) and single ICS inhaler. Both categories were classified following the GINA preferred track steps, according to the ICS dose (low/medium/high) (Global Initiative for Asthma, 2023). The frequency of reliever medication use was measured with the following question: *How often have you usually taken your "reliever medication" (brand name) in the past 4 weeks: every day, almost every day, once or twice every week, or less than once a week?* This variable was grouped into the following: almost never (participants with no SABA prescribed and those reporting *used less than once a week*) and usually (participants reporting the first three response options).

Medication adherence was measured with the Medication Intake Survey–Asthma (MIS-A) (Dima et al., 2017), a validated instrument for telephone interviews, which assesses the implementation stage of adherence separately for each maintenance inhaler based on the self-reported prescription start date, daily dosage recommendations, and questions on maintenance use over increasing periods. Percentages of used *versus* prescribed medication are calculated first for each question and, subsequently, as composite scores. We used 1-month composite scores based on inhalations used the day before (Q1),

days on which no inhalations were taken in the past 7 days (Q2), days on which all prescribed inhalations were used in the past 7 days (Q3), and days on which all prescribed inhalations were used in the past 28 days (Q4). MIS-A was administered at enrollment and at every 6 months in the regular CATIs and in the post-exacerbation CATIs. When patients used more than one inhaler containing ICS, we computed scores for each inhaler and averaged across them. MIS-A has been validated (Dima et al., 2017) using self-response in adult patients and teenagers and a proxy version for the caregivers of children in English and French. The MIS-A was linguistically adapted into Spanish for the pediatric population within the ARCA study, according to the recommended methodology (double direct translation, translation synthesis, back-translation, and cognitive debriefing) (Wild et al., 2005).

The inhalation technique was measured with the Inhaler Technique Questionnaire (InTeQ) (Lizano-Barrantes et al., 2022; Lizano-Barrantes et al., 2023a), an instrument that assesses the frequency of performing five key steps when using the inhaler in the previous 6 months with a five-level Likert scale (from "always" to "never"). The InTeQ was administered in the CATIs at enrollment and yearly. A global score was calculated as a sum of the InTeQ items answered "always," among the four, which demonstrated unidimensionality in children and adolescents (Lizano-Barrantes et al., 2023a), and was categorized into the following: 4–3 (good inhaler technique), 2 (fair), and 1–0 (poor). The InTeQ has been validated for telephone interviews (Lizano-Barrantes et al., 2023a) using self-response in children aged 8 and older and proxy response for parents or guardians of children under 8 years old. As the InTeQ was only administered yearly, the missing values were replaced by data from the previous interview.

Symptom control was measured with the asthma control questionnaire (ACQ)– symptoms only (Juniper et al., 2005a), which was administered in the regular and post-exacerbation CATIs. It assesses the presence and intensity of night-time waking, symptoms on waking, activity limitation, shortness of breath, and wheezing during the previous week on a 7-level Likert scale from 0 (no impairment) to 6 (maximum impairment). The overall score, calculated as the mean item responses, ranges from 0 to 6. Cut-off points of 1.5 and 0.75 were established to define not well- and well-controlled asthma, respectively (Juniper et al., 2006). The ACQ has been validated (Juniper et al., 2005b) using self-administration in adolescents and interviewer administration in children.

Asthma exacerbations were identified in the regular CATIs administered every 6 months or by reporting them through the application, which prompted an alert to the research team that was followed by a post-exacerbation CATI to confirm its occurrence. In both cases, exacerbations were defined through three questions that were constructed applying the definitions by the American Thoracic Society and the European Respiratory Society (Reddel et al., 2009): *Did you visit or phone your family doctor or outpatient emergency department because your asthma got worse? Did you call an ambulance or go to the hospital because of your asthma? Did you take steroid tablets or syrup (such as prednisolone or Deltacortril) for at least 2 days because of your asthma?* If the participant answers "yes" to at least one of the three questions, an asthma exacerbation is confirmed.

Health-related quality of life (HRQoL) was measured using two complementary instruments, the EuroQol generic questionnaire (EQ-5D) (Ravens-Sieberer et al., 2010; Wille et al., 2010; Gusi et al., 2014) and the disease-specific questionnaire Patient-Reported Outcomes Measurement Information System–Pediatric Asthma Impact Scale (PROMIS-PAIS) (Yeatts et al., 2010), which were administered through the ARCA application. The EQ-5D was administered at enrollment and every 6 months. It consists of five dimensions, namely, "mobility," "looking after myself," "doing usual activities," "having pain/discomfort," and "feeling worried/sad/unhappy, with a time frame of "today." According to the age, we used the EQ-5D-Y-3L proxy-version (6–7 years), the self-administered EQ-5D-Y-3L (8–11 years), and the self-administered EQ-5D-5L (≥12 years). A single preference-based utility index was calculated ranging from 1 (the best health state) to negative values (health states valued by society as worse than death), where 0 is equal to death. Preference value sets applied to generate this utility index were those obtained from Spanish adults for the EQ-5D-5L (Ramos-Goñi et al., 2018) and those obtained from Spanish adults thinking as a hypothetical 10-year-old child for the EQ-5D-Y (Ramos-Goñi et al., 2020; Ramos-Goñi et al., 2024). The short form 8a version of the PROMIS-PAIS (v2.0) was administered at 4 months from enrollment and at every 6 months thereafter. Its items ask about the past 7 days in a 5-level Likert response scale (1–5) with the following options: never, almost never, sometimes, often, and almost always. It is available for self-response for ages 8–17 and for proxy response for children starting at age 5. The total raw score is calculated by adding the values of the response to each question, ranging from 8 to 40 (a lower score indicates better HRQoL) (A brief guide to the PROMIS, 2023).

2.3 Analytical strategy

To specifically examine the impact of the implementation stage of adherence to an ICS-based maintenance treatment (i.e., the degree to which patients follow their prescribed doses during treatment), we censored from the dataset reports under certain conditions: no prescribed daily ICS at all, ICS prescribed on an as-needed basis, or prescribed other asthma maintenance treatment (such as tiotropium). Descriptive analyses were performed of patients' follow-up, reports, patient characteristics, treatment, and outcomes by calculating the percentages or means and standard deviations. Differences between the patients included and not included in the analysis of each outcome (asthma symptom control, exacerbation, EQ-5D, and PROMIS-PAIS) were assessed with a chi-squared or *t*-test, according to the type of variable.

Continuous time-varying predictors (adherence and the inhalation technique) were decomposed into three variables to distinguish the between-person effects and the simultaneous and sequential within-person effects. Average adherence was calculated as the mean score for each patient across all reports (one score per patient) and used for examining whether differences in adherence between patients predict the outcomes. Current fluctuation was computed as the difference between a patient's average adherence and their score in a given report (multiple scores per patient) to examine whether changes in adherence within patients are

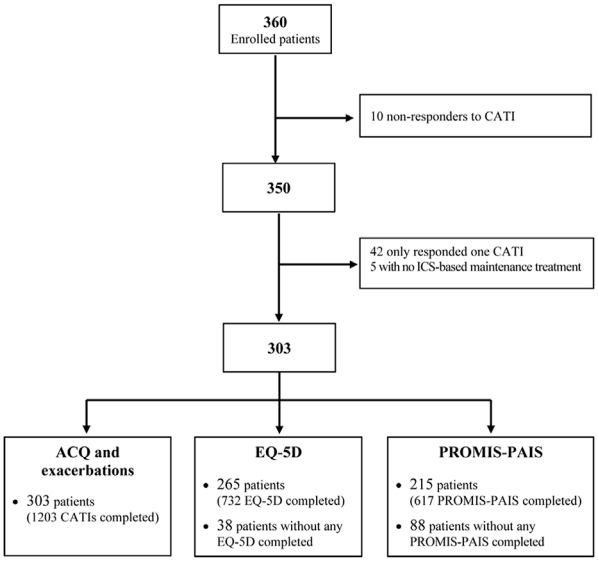

FIGURE 1
Flowchart of the selection of patients meeting the analysis criteria. CATI: computer-assisted telephone interview; ICS: inhaled corticosteroids; ACQ: Asthma Control Questionnaire; PROMIS-PAIS: Patient-Reported Outcomes Measurement Information System–Pediatric Asthma Impact Scale.

associated with concomitant changes in the outcome (i.e., measured in the same report). Prior fluctuation was computed as a lagged variable, i.e., the difference between a patient's average and the score in their previous report, usually 6 months earlier (multiple scores per patient), to examine whether changes in adherence predict the outcomes measured in the subsequent report.

To assess longitudinal relationships of adherence to ICS-based maintenance treatment and the inhalation technique with outcomes, we followed established procedures for hierarchical longitudinal modeling (Singer and Willett, 2003). Four multilevel longitudinal mixed models were constructed separately for asthma symptom control, exacerbation occurrence, EQ-5D, and PROMIS-PAIS (as dependent variables). In all cases, models were constructed to assess the role of the two time-varying variables, adherence and inhalation technique (which are the main explanatory variables), including them together with the type of ICS-based maintenance treatment and sociodemographic variables that can be potential confounders (model A); then, other factors that are part of the implicit standard for asthma management were added (Dima et al., 2016; Global Initiative for Asthma, 2023), namely, the use of a reliever, asthma symptom control, and the occurrence of exacerbations, except in models where they were the dependent variables (model B). Time was modeled as years since the first interview per patient (random and fixed), and interactions between the independent variables and time were tested. In addition to the *p*-values of each coefficient or odds ratio (OR) provided by the models, ANOVA was applied to test the significance corresponding to each independent variable. Sensitivity analyses were performed with 1-week adherence scores.

R (version 4.2.2) and RStudio (2022.07.2 Build 576) were used to construct all the models, except for the exacerbation occurrence, which was constructed with SAS 9.4.

3 Results

Out of the 360 participants enrolled from January 2018 to March 2023 (Figure 1), we excluded the following from the analysis: 10 who did not respond to any CATI, 42 with only one valid CATI, and 5 without ICS-based maintenance treatment. Then, 303 valid participants (who responded to a total of 1,203 CATIs) were included in the analysis of asthma symptom control and exacerbation, 265 participants (with 732 questionnaires completed) in the EQ-5D analysis, and 215 (with 617 questionnaires completed) in the analysis of PROMIS-PAIS. Globally, patients provided 2–9 reports (Q2 (median) = 4, Q1-Q3 = 2–5), with a mean (SD) follow-up of 692 (419) days (range 116–1,759 days) in the analyses of symptom control and exacerbation occurrence. For the EQ-5D and PROMIS-PAIS analyses, reports per patient ranged from 1 to 8, with medians of 2 (Q1–Q3 = 2–4) and 3 (Q1–Q3 = 2–4), respectively.

Figure 2A shows the number of patients who started follow-up in each year and were valid for analysis. For example, of the patients followed since 2018 in the ARCA cohort, 43 were included in the analysis of symptom control and exacerbation occurrence (white bar), 34 in the EQ-5D one (light gray bar), and 28 in the PROMIS-PAIS (dark gray bar) analysis. Enrollment for the study peaked in 2019 and then faced challenges in 2020 due to the SARS-CoV-2 pandemic, but it was sustained through effective mitigation efforts. The mean number of reports completed per patient is shown in Figure 2B. For instance, the 43 patients who started follow-up in 2018 provided a mean of 5.7 reports, while the 66 patients who started follow-up in 2022 provided 2.3 reports on average. These differences in the number of valid reports per participant are due to the duration of the follow-up, according to the year of enrollment, which was 1,318 vs. 299 days of median (Q2) for patients followed since 2018 and 2022, respectively, in the analyses of symptom control and exacerbation occurrence.

The characteristics of the participants are presented in Table 1. The majority were male subjects (60.7%), reported using relievers less than once a week (55.4%), undergoing maintenance treatment with ICS combined with LABA in a fixed dose (73.3%), administered by pMDI (74.6%), and similarly distributed among steps 2–3 (33.0%), step 4 (37.4%), and step 5 (29.5%) of the GINA preferred track, according to the dose of ICS. The mean 1-month adherence score was 87.8%; 45.2% of participants reported a good inhalation technique, and 64.2% had well-controlled symptoms. Experiencing exacerbations were reported by 37.8% of the participants. The HRQoL score measured with the EQ-5D was 0.93 (1, best health state to negative values, worse than death), and when measured with the PROMIS-PAIS, it was 13.0 (8, best health state to 40, worst).

Table 2 shows the results for the longitudinal associations that maintenance treatment adherence and the inhalation technique present with asthma symptom control (left column) and exacerbations (right column). The proportion of between-person variation was 16.4% for asthma control and 1.4% for exacerbations. Model A with asthma symptom control shows that, at the within-person level, patients reporting higher adherence to maintenance medication also reported better control in the next interview (prior fluctuation; $p = 0.002$). On the contrary, both models A and B show that girls ($p = 0.006$ and $p = 0.012$) were more likely to report worse

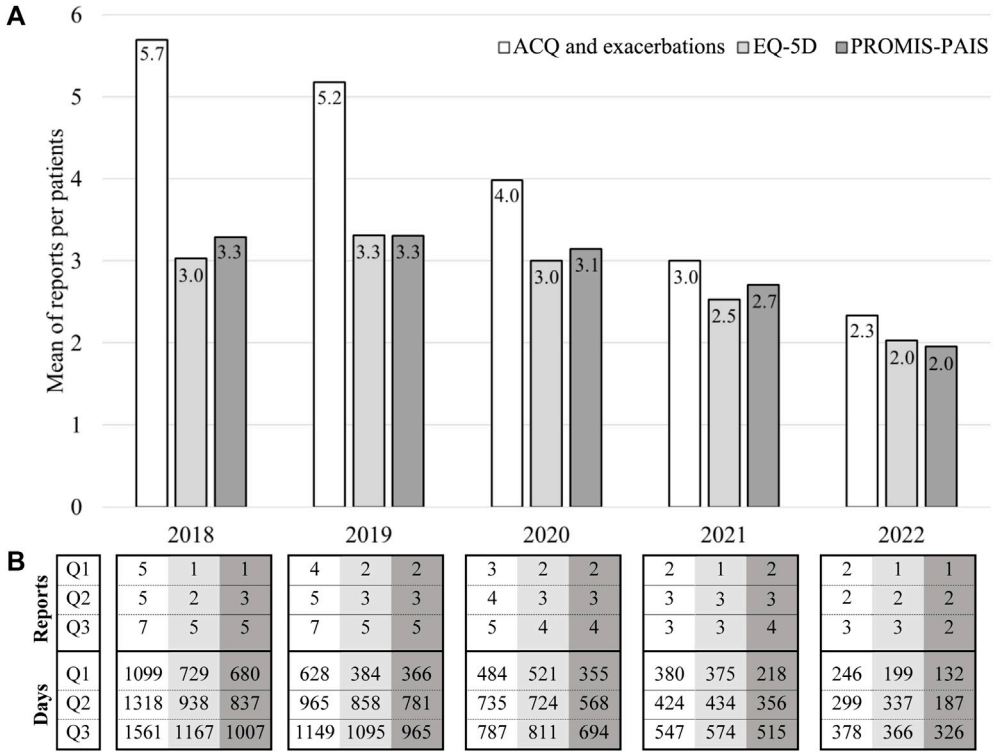

FIGURE 2
Description of patients, reports, and days analyzed by the year of follow-up initiation. ((**A**)-bar chart) Number of patients by the year of follow-up initiation. ((**B**)-table) Number of reports and days analyzed per patient by the year of follow-up initiation. n: number of patients; %: percentage of patients included in the EQ-5D and PROMIS-PAIS analyses relative to those included in the ACQ and exacerbation analyses; Q1: percentile 25; Q2: percentile 50 or median; Q3: percentile 75.

control of asthma symptoms. Furthermore, model B shows that patients who reported using reliever medication ≥1–2 times per week ($p < 0.001$) and having an exacerbation ($p < 0.001$) were also more likely to present uncontrolled asthma symptoms. Age, the inhalation technique, and the type of maintenance treatment (ICS alone or in combination with LABA) did not present any statistically significant association with asthma symptom control.

Exacerbations models A and B show less risk of occurrence in children aged 8 years or older ($p \leq 0.001$ in both models) and participants reporting better asthma symptom control ($p = 0.023$ and $p = 0.008$). Conversely, the risk of exacerbation occurrence is higher in participants reporting using reliever medication ≥1–2 times per week ($p < 0.001$). Neither average adherence and the inhalation technique nor their prior or simultaneous fluctuations were associated with exacerbation occurrence.

The proportion of between-person variation was 63.6% and 50.9% for HRQoL (Table 3), EQ-5D, and PROMIS-PAIS, respectively. The EQ-5D models reveal that when participants reported a better inhalation technique, they reported worse HRQoL simultaneously (current fluctuation; $p = 0.012$ and $p = 0.012$), but they also reported better HRQoL in the next interview (prior fluctuation; $p = 0.005$ and $p = 0.012$). Furthermore, worse HRQoL was more likely in girls ($p = 0.037$ and $p = 0.036$). Age, adherence, type of treatment, the use of reliever medication, and the occurrence of exacerbations were not statistically significantly associated with EQ-5D.

In PROMIS-PAIS models, the interaction between time and adherence reveals an increase in HRQoL over time, correlating with higher levels of patient-reported adherence in subsequent interviews (prior fluctuation; $p = 0.016$). Furthermore, better asthma symptom control was also associated with better HRQoL ($p = 0.004$). Conversely, worse HRQoL was more likely for adolescents compared to children under 12 years of age ($p = 0.043$ and $p = 0.014$), girls ($p = 0.002$ and $p = 0.002$), and the use of reliever medication ≥1–2 times a week ($p = 0.042$). The type of maintenance treatment regimen, the inhalation technique, and exacerbation did not present a statistically significant association with PROMIS-PAIS.

Sensitivity analysis with 1-week adherence scores showed similar results (Supplementary Material).

4 Discussion

This study provides evidence regarding the longitudinal relationships that maintenance treatment adherence and the inhaler technique present with asthma symptom control, exacerbations occurrence, and HRQoL in pediatric asthma patients. We gathered comprehensive patient-reported data using a combination of the ARCA application and CATIs. We found that better asthma symptom control over time (future assessments) was more likely in patients with higher adherence to treatment, while boys and those participants who reported almost never using

TABLE 1 Demographic and clinical characteristics of the participants.

		All (n = 350)	ACQ and exacerbations (n = 303)	EQ-5D (n = 265)	PROMIS-PAIS (n = 215)
Sex, n (%)	Male	216 (61.7%)	184 (60.7%)	160 (60.4%)	130 (60.5%)
	Female	134 (38.3%)	119 (39.3%)	105 (39.6%)	85 (39.5%)
	p-value		0.334	0.364	0.544
Age, n (%)	6–7 years	86 (24.6%)	73 (24.1%)	65 (24.5%)	52 (24.2%)
	8–11 years	166 (47.4%)	147 (48.5%)	131 (49.4%)	110 (51.2%)
	≥12 years	98 (28.0%)	83 (27.4%)	69 (26.0%)	53 (24.7%)
	p-value		0.586	0.297	0.142
Maintenance treatment, n (%)	ICS	101 (28.9%)	81 (26.7%)	72 (27.2%)	56 (26.0%)
	ICS plus LABA	241 (68.9%)	222 (73.3%)	193 (72.8%)	159 (74.0%)
	Other treatment	7 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	No treatment	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	p-value		<0.001	<0.001	0.001
Type of inhaler device, n (%)	pMDI	253 (74.0%)	226 (74.6%)	207 (78.1%)	170 (79.1%)
	DPI	67 (19.6%)	59 (19.5%)	53 (20.0%)	40 (18.6%)
	Unknown	22 (6.4%)	18 (5.9%)	5 (1.9%)	5 (2.3%)
	p-value		0.562	<0.001	<0.001
GINA step, n (%)	Step 2–3 (low-dose ICS)	93 (33.0%)	82 (32.7%)	43 (32.2%)	64 (33.7%)
	Step 4 (medium-dose ICS)	105 (37.4%)	93 (37.1%)	86 (37.9%)	68 (35.8%)
	Step 5 (high-dose ICS)	83 (29.5%)	76 (30.3%)	68 (30.0%)	58 (30.5%)
	p-value		0.730	0.791	0.724
Reliever use, n (%)	Not prescribed	22 (6.3%)	19 (6.3%)	18 (6.8%)	14 (6.5%)
	Less than once a week	194 (55.6%)	168 (55.6%)	147 (55.7%)	114 (53.3%)
	Once or twice a week	90 (25.8%)	80 (26.5%)	70 (26.5%)	60 (28.0%)
	Almost every day	29 (8.3%)	25 (8.3%)	23 (8.7%)	21 (9.8%)
	Every day	14 (4.0%)	10 (3.3%)	6 (2.3%)	5 (2.3%)
	p-value		0.648	0.094	0.175
% Last month adherence, mean (SD)		86.7 (23.3)	87.8 (21.3)	88.0 (21.0)	88.4 (20.8)
	p-value		0.029	0.056	0.084
% Last week adherence, mean (SD)		85.0 (27.2)	85.8 (25.9)	86.7 (25.1)	86.4 (25.5)
	p-value		0.125	0.032	0.198
Inhalation technique, n (%)	Poor (0–1 always)	106 (31.7%)	95 (32.5%)	83 (32.0%)	65 (31.0%)
	Fair (2 always)	81 (24.3%)	65 (22.3%)	56 (21.6%)	48 (22.9%)
	Good (3–4 always)	147 (44.0%)	132 (45.2%)	120 (46.3%)	97 (46.2%)
	p-value		0.082	0.094	0.556

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TABLE 1 (*Continued*) Demographic and clinical characteristics of the participants.

		All (n = 350)	ACQ and exacerbations (n = 303)	EQ-5D (n = 265)	PROMIS-PAIS (n = 215)
ACQ	Not well-controlled (>1.5)	71 (20.9%)	63 (21.3%)	51 (19.5%)	40 (18.9%)
	Intermediate (0.75–1.5)	48 (14.2%)	43 (14.5%)	40 (15.3%)	35 (16.5%)
	Well-controlled (<0.75)	220 (64.9%)	190 (64.2%)	171 (65.3%)	137 (64.6%)
	p-value		0.767	0.328	0.185
Exacerbation, n (%)	No	210 (61.9%)	184 (62.2%)	161 (61.5%)	134 (63.2%)
	Yes	129 (38.1%)	112 (37.8%)	101 (38.5%)	78 (36.8%)
	p-value		0.830	0.728	0.537
EQ-5D, mean (SD)				0.93 (0.11)	
PROMIS, mean (SD)					13.0 (5.7)

p-values assessing differences between the patients included and those not included in each subsample corresponding to the chi-squared test or *t*-test, according to the type of variable.

reliever medication or no exacerbations generally had better symptom control. In the same direction, a lower risk of exacerbations was found in older children, those reporting well-controlled symptoms, and in those who almost never used reliever medication. Better HRQoL over time was observed in patients who reported better adherence and inhalation technique. Additionally, boys and participants with better symptom control generally had better HRQoL.

4.1 Adherence to ICS-based maintenance treatment

The level of adherence to maintenance treatment in ARCA participants is high on average; they reported having administered 88% of the prescribed dose during the previous month, which is above the range of 20%–70% identified by a systematic review (Herndon et al., 2012; Boutopoulou et al., 2018) in children and/or adolescents.

Consistent with our hypothesis, we found that higher adherence was associated with better asthma symptom control in future assessments, despite the inconsistent results reported both by systematic reviews (Gillette et al., 2016; Vazquez-Ortiz et al., 2020), which mainly included cross-sectional studies, and by more recent longitudinal studies (Dima et al., 2019; Vervloet et al., 2020; Vervloet et al., 2022; Sousa-Pinto et al., 2023). Consistently with our finding, a longitudinal study in French and English adults and children with asthma (Dima et al., 2019) showed that patients maintaining high ICS adherence over time have better asthma control. In the same line, a study of the large Nivel Primary Care Database in the Netherlands shows an association between poor ICS adherence and uncontrolled asthma (Papi et al., 2018). Conversely, a United Kingdom study (Vervloet et al., 2020) using the Optimum Patient Care Research Database (OPCRD) found that patients might adjust their ICS based on the current needs without this necessarily impacting later in hospitalizations, emergency visits, outpatient visits, or the need for oral corticosteroids or antibiotics. Additionally, a longitudinal study in patients from 27 countries with ICS plus LABA maintenance treatment pointed out that most patients only use medication when they are not well (Sousa-Pinto et al., 2023). Overall, these findings lead us to incorporate nuances into our hypothesis: the association between adherence and asthma control might be driven by an increased adherence as a reactive response to uncontrolled symptoms, which could eventually lead to increased symptom control over time.

The association found between increased treatment adherence and increased HRQoL over time is also consistent with our hypotheses as it could reflect an individual's overall investment in maintaining their health and well-being through effective asthma management practices. This association was particularly identified with the asthma-specific questionnaire PROMIS-PAIS, likely due to its focused content, which is potentially more responsive to asthma symptoms (Wiebe et al., 2003). Although the specific association of adherence with HRQoL has been less frequently examined, our results are consistent with findings of a systematic review in adolescents (Usmani et al., 2018) and a multicenter, observational, prospective study in Greek adults with variable asthma severity (Exarchos et al., 2022). Additionally, a longitudinal study in Dutch adolescents (Tiggelman et al., 2015) indicated that higher HRQoL at baseline predicted increased medication adherence at follow-up, although good medication adherence did not predict an increase in HRQoL over time. These results line up with our enhanced hypothesis, distinguishing patients with regular adherence who actively integrate treatment into their daily routines, recognizing its importance, from those with "reactive adherence" who strictly follow treatments only when they feel that their asthma is out of control.

Although there is a substantial body of evidence from RCTs (Adams N. et al., 2005; Adams N. P. et al., 2005; Pauwels et al., 2003; O'byrne et al., 2001) showing that ICS-based maintenance treatment reduces exacerbation risks, there is less consistency in its association with adherence to this type of treatment. Our findings indicate a lack of association between adherence and exacerbation occurrence, which were consistent with observations from the abovementioned longitudinal studies in France, the United Kingdom, and the

TABLE 2 Multilevel models of asthma symptom control (linear) and exacerbation occurrence (logistic).

	Asthma symptom control		Exacerbation occurrence	
	Model A	Model B	Model A	Model B
	b (SE)		OR (SE)	
Intercept	0.281 (0.253)[§]	0.069 (0.203)[§]	0.45 (0.60)	0.81 (0.69)
Time (years)	0.000 (0.003)	0.000 (0.002)	0.97 (0.01) ***[§]	0.97 (0.01) ***[§]
ADHERENCE				
Average adherence	0.001 (0.003)	0.001 (0.002)	1.00 (0.01)	0.99 (0.01)
Current fluctuation of adherence	−0.002 (0.002)	−0.002 (0.001)	0.99 (0.00)	0.99 (0.00)
Prior fluctuation of adherence	−0.005 (0.002) **[§]	−0.002 (0.001)[§]	0.99 (0.00)	0.99 (0.01)
INHALATION TECHNIQUE				
Average IT	0.044 (0.040)	0.016 (0.032)	1.21 (0.10)	1.16 (0.10)
Current fluctuation of IT	0.002 (0.036)	−0.009 (0.033)	1.10 (0.12)	1.06 (0.12)
Prior fluctuation of IT	−0.032 (0.040)	−0.046 (0.036)	1.14 (0.13)	1.11 (0.14)
Treatment				
ICS plus LABA	Ref.	Ref.	Ref.	Ref.
ICS	0.120 (0.091)	0.073 (0.074)	1.06 (0.23)	0.97 (0.24)
Sex				
Male	Ref.[§]	Ref.[§]	Ref.	Ref.
Female	0.233 (0.085) **	0.168 (0.067) *	1.06 (0.20)	0.89 (0.21)
Age				
<8 years	Ref.	Ref.	Ref.[§]	Ref.[§]
8–11	−0.097 (0.104)	−0.055 (0.083)	0.44 (0.24) ***	0.42 (0.25) ***
≥12	−0.053 (0.119)	−0.009 (0.094)	0.38 (0.28) ***	0.34 (0.30) ***
Reliever use				
Almost never		Ref.		Ref.[§]
Usually		0.840 (0.063) ***[§]		3.27 (0.23) ***
Exacerbation				
No		Ref.		
Yes		0.354 (0.067) ***[§]		
Asthma symptom control				
Not well-controlled				Ref.[§]
Intermediate				0.42 (0.38) *
Well-controlled				0.47 (0.29) **
ICC (linear); VPC (logistic)	0.2568	0.1641	0.0129	0.0142
Log-likelihood	−1,085.3	−978.8		
AIC	2,200.6	1,991.5		
BIC	2,271.0	2,071.4		
−2 Res Log Pseudo-Likelihood			3,726.66	3,838.27

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TABLE 2 (*Continued*) Multilevel models of asthma symptom control (linear) and exacerbation occurrence (logistic).

	Asthma symptom control		Exacerbation occurrence	
	Model A	Model B	Model A	Model B
	b (SE)		OR (SE)	
Generalized chi-square			678.05	665.65
Generalized chi-square/DF			0.87	0.86

The *p*-values corresponding to each coefficient or OR, provided by the models were marked with asterisks: *($p < 0.05$), **($p < 0.01$), and ***($p < 0.001$).
ANOVA *p*-values for each independent variable were marked with § ($p < 0.05$).

Netherlands (Dima et al., 2019; Vervloet et al., 2020; Vervloet et al., 2022), and a meta-analysis centered on the effect of interventions to improve adherence to ICS-based maintenance treatments, indicating that they may not always correlate with enhanced clinical outcomes (Normansell et al., 2017). Nevertheless, they contrast with a meta-analysis showing the association between treatment adherence and severe asthma exacerbations (Chongmelaxme et al., 2020). On one hand, it is important to highlight that response bias cannot be discarded in our study since interviews were performed immediately after experiencing an exacerbation, which could have made patients feel accountable, i.e., the patient's behavior may be influenced by the expectation of social interactions with healthcare providers (Oussedik et al., 2017). On the other hand, taking into account that almost 70% of the participants in our study received a medium or high ICS dose, some of them may be candidates for a step-up in treatment, as suggested by a United Kingdom large cohort of adult patients in GINA step 3 or 4 of asthma management (Papi et al., 2018).

4.2 Inhalation technique

In our study, 32% of participants reported poor inhalation technique, which is above the proportion of the suboptimal inhalation technique reported by the studies of children and/or adolescents with asthma (8%–22%) identified in a systematic review (Gillette et al., 2016).

Given the recognized importance of both inhalation technique and adherence in impacting actual drug exposure (Global Initiative for Asthma, 2023; Ramos-Goñi et al., 2024), we hypothesized finding a similar association when both factors were analyzed together. Our results focusing on within-person fluctuations of the inhalation technique revealed that when participants temporarily improved their technique, their HRQoL decreased during that same period, but it improved afterward. This is also consistent with our hypothesis distinguishing between regular and reactive behaviors, suggesting similar patterns for inhalation technique and adherence, where a proactive approach to asthma management, even if initially challenging, ultimately contributes to enhanced HRQoL. These fluctuations are likely due to factors changing within patients with asthma over time rather than stable differences between patients, as highlighted in the longitudinal study involving French and English adults and children (Dima et al., 2019).

Three systematic reviews (Kocks et al., 2018; Usmani et al., 2018; Roche et al., 2022) supported that better inhalation technique, analyzed without considering adherence, are consistently associated with exacerbations (Usmani et al., 2018; Roche et al., 2022) and HRQoL (Kocks et al., 2018; Usmani et al., 2018; Roche et al., 2022), but there are less consistent results with asthma symptoms control (Kocks et al., 2018; Usmani et al., 2018; Roche et al., 2022). However, evidence on the relationship between inhalation technique and HRQoL remains limited. For instance, one of the reviews (Engelkes et al., 2015) included one single prospective longitudinal clinical study with a small sample size. Another review (Kocks et al., 2018) referenced only two intervention-focused studies to enhance inhalation technique. The third review (Vazquez-Ortiz et al., 2020) exclusively referenced a cross-sectional study assessing HRQoL, which found no significant outcome differences between patients based on the inhalation technique. This highlights the need for further comprehensive research to fully understand the impact of inhalation technique on various asthma-related outcomes. The lack of a statistically significant association between inhalation technique and the other outcomes of our study deserves further research.

4.3 Frequency of reliever use

Our findings about the association of the frequent use of reliever medications with uncontrolled asthma symptoms and exacerbation occurrence align with those from the Nivel Primary Care Database from the Netherlands (Vervloet et al., 2022), which also observed them. Two studies conducted across European countries (Quint et al., 2022) and Canada (Noorduyn et al., 2022) also reported the association between the use of SABA and exacerbations occurrence. Furthermore, our study revealed an association between frequent reliever use and worse HRQoL, a relationship that has been explored less. A cross-sectional analysis of the study in France and the United Kingdom measuring the impact of asthma (Hernandez et al., 2018) showed statistically significant differences of HRQoL, according to the frequency of reliever medication use; among women, those using reliever medication almost or every day presented the biggest deviation from the reference norms.

Our findings suggest that the frequent use of reliever medication, which potentially reflects a reactive approach to asthma management, negatively impacts HRQoL. This observation ties in with our earlier hypothesis regarding adherence and inhalation technique, where proactive self-management practices are contrasted with reactive behaviors. Such patterns underline the complex dynamics of asthma self-management and emphasize the need for future research to conduct a more in-depth exploration of the within-person fluctuations in reliever use and its impact on HRQoL.

TABLE 3 Multilevel models of health-related quality of life measured with the EQ-5D and PROMIS-PAIS (linear).

	EQ-5D		PROMIS-PAIS	
	Model A	Model B	Model A	Model B
	b (SE)		b (SE)	
Intercept	0.986 (0.044) ***$	0.988 (0.046) ***$	11.264 (2.384) ***$	11.988 (2.397) ***$
Time (years)	0.000 (0.001)	0.000 (0.001)	−0.034 (0.028)	0.038 (0.140)
ADHERENCE				
Average adherence	0.0004 (0.000)	0.0004 (0.000)	0.027 (0.024)	0.031 (0.023)
Current fluctuation of adherence	0.0002 (0.000)	0.0002 (0.000)	0.007 (0.012)	0.010 (0.012)
Prior fluctuation of adherence	0.0004 (0.000)	0.0002 (0.000)	−0.023 (0.012)	−0.009 (0.013)
INHALATION TECHNIQUE				
Average IT	0.002 (0.007)	0.003 (0.006)	−0.624 (0.379)	−0.658 (0.352)
Current fluctuation of IT	−0.015 (0.006) *$	−0.015 (0.006) *$	−0.316 (0.328)	−0.244 (0.324)
Prior fluctuation of IT	0.021 (0.007) **$	0.019 (0.007) *$	−0.231 (0.364)	−0.094 (0.359)
Treatment				
ICS plus LABA	Ref.	Ref.	Ref.	Ref.
ICS	−0.012 (0.016)	−0.011 (0.016)	−0.074 (0.902)	−0.041 (0.847)
Sex				
Male	Ref.$	Ref.$	Ref.$	Ref.$
Female	−0.029 (0.014) *	−0.029 (0.014) *	2.538 (0.824) **	2.457 (0.764) **
Age				
<8 years	Ref.	Ref.	Ref.$	Ref.$
8–11	0.010 (0.017)	0.006 (0.017)	−0.395 (0.979)	0.073 (0.918)
≥12	0.005 (0.020)	0.001 (0.020)	2.383 (1.169) *	2.709 (1.093) *
Asthma symptom control				
Not well-controlled		Ref.$		Ref.$
Intermediate		−0.018 (0.019)		0.305 (1.053)
Well-controlled		0.016 (0.014)		−2.403 (0.825) **
Reliever use				
Almost never		Ref.		Ref.
Usually		−0.012 (0.012)		1.319 (0.646) *
Exacerbation				
No		Ref.		Ref.
Yes		−0.014 (0.011)		0.082 (0.616)
Interaction time * Adherence last month				
Average adherence				−0.001 (0.002)
Current fluctuation of adherence				0.001 (0.001)
Prior fluctuation of adherences				−0.003 (0.001) *$
ICC	0.6161	0.6362	0.5716	0.5090

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TABLE 3 (*Continued*) Multilevel models of health-related quality of life measured with the EQ-5D and PROMIS-PAIS (linear).

	EQ-5D		PROMIS-PAIS	
	Model A	Model B	Model A	Model B
	b (SE)		b (SE)	
Log-likelihood	312.7	304.6	−1,386.4	−1,400.3
AIC	−591.4	−567.3	2838.2	2848.6
BIC	−522.5	−482.3	2907.7	2946.3

The *p*-values corresponding to each coefficient provided by the models were marked with asterisks: *($p < 0.05$), **($p < 0.01$), and ***($p < 0.001$).
ANOVA *p*-values for each independent variable were marked with § ($p < 0.05$).

4.4 Asthma symptom control

The positive long-term association between asthma symptom control and HRQoL found in our study was consistent with a longitudinal study in dyads of asthmatic children and their parents in USA (Li et al., 2017), showing that poorly controlled asthma status was associated with poor HRQoL. Additionally, a systematic review on adolescents (Vazquez-Ortiz et al., 2020) identified poor disease control, exacerbations, and asthma severity as the main factors associated with impaired HRQoL. In contrast, the longitudinal Dutch study in adolescents (Tiggelman et al., 2015) found that higher HRQoL at baseline did not predict changes in asthma control over time. On the other hand, the lower risk of exacerbations among patients with better asthma symptom control observed in our study aligns with the Asthma Care logic process model (Dima et al., 2016) and the GINA guideline (Global Initiative for Asthma, 2023), which position asthma control as directly related to exacerbations.

4.5 Sociodemographic factors

Our research identified gender differences in asthma outcomes, with girls experiencing worse asthma symptom control and HRQoL compared to boys. This finding is supported by literature reviews (Vazquez-Ortiz et al., 2020; Chowdhury et al., 2021; Jenkins et al., 2022) that also show an association of HRQoL and asthma control impairment with the female gender. Additionally, we observed that individuals aged 12 years and older showed a decreased HRQoL. These associations could be attributed to hormonal changes impacting airway inflammation, potential variances in immune responses, and the distinctive psychosocial challenges faced by female subjects and adolescents, as previously explained (de Benedictis and Bush, 2017; Chowdhury et al., 2021; Jenkins et al., 2022). These factors might collectively contribute to worsened asthma symptoms and treatment outcomes, subsequently affecting HRQoL. Nevertheless, the Dutch study in adolescents (Tiggelman et al., 2015) observed an increase in adolescents' HRQoL over time, attributing this to the possibility that they may perceive their illness as less of a concern. Furthermore, we found that a lower risk of exacerbations was associated with a higher age, which could be related to fewer virus-induced exacerbations, since they are more common in younger children (Ramsahai et al., 2019).

4.6 Limitations

Interpreting our findings requires taking into account various limitations. First, we did not consider the interplay of other important factors, such as comorbidities (rhinitis, obesity, and anxiety among others) and environmental triggers. Second, our results do not preclude the potential benefits of a deliberate effort to improve the overall adherence and inhalation technique due to the participation in a study, which could potentially impact their relationship with outcomes and the outcomes themselves. Third, the InTeQ's reliance on a long recall period (previous 6 months) introduces a potential recall bias. Fourth, the measurement of adherence and the inhalation technique is based on the patient or proxy reporting. Thus, future research could benefit from pharmacy claims, performance tests, and smart inhalers for studying these complex relationships.

Finally, our analysis did not differentiate among specific LABA drugs in the ICS fixed-dose combination treatments (Global Initiative for Asthma, 2023) nor between the types of inhaler devices. Unfortunately, our sample size misbalance among the treatments used (712 reports of ICS-salmeterol, 124 ICS-vilanterol, and 69 ICS-formoterol; 226 patients used pMDI vs. 59 using DPI) prevented carrying out stratified analysis to explore the differences. However, the associations of LABA drugs and the type of inhaler device with adherence were not statistically significant (data not shown). Differences were only found between both inhaler devices among the patients presenting good inhalation technique (41.6% with pMDI vs. 60.7% with DPI, $p = 0.002$), as expected, since children are most likely to use pMDI with a spacer. Therefore, the impact of different inhaler devices on the association between inhaler technique and clinical outcomes merits further research.

5 Conclusion

To the best of our knowledge, this is the first longitudinal study specifically conducted in pediatric patients to assess both HRQoL and clinical outcomes (asthma symptom control and exacerbation occurrence), allowing for the evaluation of their longitudinal relationships with two of the main indicators of the quality use of inhalers (i.e., adherence and the inhalation technique). Methodologically, the hierarchical mixed model approach adopted has the advantage of describing how each person changes over time (within-person) and how these changes differ across people (between-person). In addition, conceptually, the

timelines–events–objectives–sources (TEOS) framework (Li et al., 2017) has been applied to operationalize adherence.

Our findings highlight the multifaceted nature of asthma in children and adolescents, getting closer to a comprehensive understanding of the dynamic process of asthma treatment and outcomes over time. It is remarkable how although treatment adherence showed to be excellent, a third of the participants reported a suboptimal inhalation technique, supporting the need of actions for improvement in the asthma management of pediatric population. We found longitudinal associations at the within-person level of the two indicators of quality use of inhalers: for adherence to ICS-based maintenance treatment with symptom control and HRQoL, as well as for the inhalation technique with HRQoL. This reinforces the importance of further examining changes over time alongside the changes across people. Notably, the frequency of reliever use was associated with symptom control, exacerbation occurrence, and HRQoL; this pointed out the need for examining within-person changes in reliever use, which is further than the usually assessed between-person differences. Finally, due to the differences observed between boys and girls, it is especially important to apply a gender perspective in clinical practice and future studies on children and adolescents with asthma.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of clinical research of the Parc de Salut Mar (no 2015/62/12l) and of the participant centers, following national and international guidelines (code of ethics, Helsinki Declaration), as well as legislation on data confidentiality (Spanish Organic Law 3/2018 of December 5 on the Protection of Personal Data and the Guarantee of Digital Rights). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

CL-B: conceptualization, investigation, methodology, project administration, visualization, writing–original draft, and writing–review and editing. OG: conceptualization, methodology, visualization, and writing–review and editing. KM: conceptualization, methodology, visualization, and writing–review and editing. AD: methodology and writing–review and editing. AP: data curation, formal analysis, and writing–review and editing. MC-R: investigation and writing–review and editing. MP-C: investigation and writing–review and editing. LV-N: investigation and writing–review and editing. MG: investigation and writing–review and editing. AB-S: investigation and writing–review and editing. MF: conceptualization, funding acquisition, methodology, project administration, supervision, visualization, and writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. Financial support for this study was provided through grants by the Instituto de Salud Carlos III FEDER: Fondo Europeo de Desarrollo Regional (PI15/00449) and Generalitat de Catalunya (AGAUR2021 SGR 00624, 2017 SGR 452). The following researchers have worked on this manuscript while funded by grants: CL-B (University of Costa Rica OAICE-85-2019) and KM (ISCIII FI16/00071).

Acknowledgments

The authors would like to thank the participants of the study. They also thank Áurea Martín for her support in English editing and proofreading. ARCA Group: MF, KM, CL-B, OG, YP, and ÀP (Hospital del Mar Research Institute); MC-R (Hospital del Mar); MP-C (Centro de Salud la Candelaria); LV-N (Hospital Universitario Parc Taulí); Ines de Mir (Hospital Vall d'Hebron); Gimena Hernandez, Camila Maroni (CAP La Sagrera); AB-S (Centro de Salud Los Castros); Jose Antonio Castillo (Hospital Infantil Universitario Miguel Servet); MG (Centro de Salud Jerez Sur), Olga Cortés (Centro de Salud Canillejas); Eva Tato (Hospital Universitario Araba); Pilar Ortiz, Marta Ortega, Alberto Servan (Centro de Salud Dos de Mayo), María Ángela Carrasco (Consultorio Sevilla la Nueva); AD (Institut de Recerca Sant Joan de Déu); Eric van Ganse (University Claude Bernard Lyon); and Marijn de Bruin (Radboud UniversityMedical Center). The preprint version of this manuscript is available in the medRxiv repository (Lizano-Barrantes et al., 2023b).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1340255/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Clinical Trial
PUBLISHED 28 March 2024
DOI 10.3389/fphar.2024.1377781

OPEN ACCESS

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RECEIVED 28 January 2024
ACCEPTED 07 March 2024
PUBLISHED 28 March 2024

CITATION
Jošt M, Kerec Kos M, Kos M and Knez L (2024), Effectiveness of pharmacist-led medication reconciliation on medication errors at hospital discharge and healthcare utilization in the next 30 days: a pragmatic clinical trial. *Front. Pharmacol.* 15:1377781. doi: 10.3389/fphar.2024.1377781

Effectiveness of pharmacist-led medication reconciliation on medication errors at hospital discharge and healthcare utilization in the next 30 days: a pragmatic clinical trial

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Transitions of care often lead to medication errors and unnecessary healthcare utilization. Medication reconciliation has been repeatedly shown to reduce this risk. However, the great majority of evidence is limited to the provision of medication reconciliation within clinical trials and countries with well-established clinical pharmacy. Thus, this pragmatic, prospective, controlled trial evaluated the effectiveness of routine pharmacist-led medication reconciliation compared to standard care on medication errors and unplanned healthcare utilization in adult general medical patients hospitalized in a teaching hospital in Slovenia. All patients hospitalized in a ward where medication reconciliation was integrated into routine clinical practice were included in the intervention group and received admission and discharge medication reconciliation, coupled with patient counselling. The control group consisted of randomly selected patients from the remaining medical wards. The primary study outcome was unplanned healthcare utilization within 30 days of discharge, and the secondary outcomes were clinically important medication errors at hospital discharge and serious unplanned healthcare utilization within 30 days of discharge. Overall, 414 patients (53.4% male, median 71 years) were included—225 in the intervention group and 189 in the control group. In the intervention group, the number of patients with clinically important medication errors at discharge was significantly lower (intervention vs control group: 9.3% vs 61.9%). Multiple logistic regression revealed that medication reconciliation reduced the likelihood of a clinically important medication error by 20-fold, while a higher number of medications on admission was associated with an increased likelihood. However, no significant differences were noted in any and serious unplanned healthcare utilization (intervention vs control group: 33.9% vs 27.8% and 20.3% vs 14.6%, respectively). The likelihood of serious healthcare utilization increased with the age of the patient, the number of medications on admission and being hospitalized for an acute medical condition. Our pragmatic trial confirmed that medication reconciliation, even when performed as part of routine clinical practice, led to a substantial reduction in the risk of clinically important medication errors at hospital

discharge but not to a reduction in healthcare utilization. Medication reconciliation is a fundamental, albeit not sufficient, element to ensure patient safety after hospital discharge.

Clinical Trial Registration: https://clinicaltrials.gov/search?id=NCT06207500, identifier NCT06207500

KEYWORDS

medication reconciliation, medication error, healthcare utilization, transitions of care, pharmacist, patient discharge, safety

1 Introduction

Hospitalization is a stressful event in a patient's life that poses patients to a generalized risk of adverse health events during hospitalization and after hospital discharge (Krumholz, 2013). Medication errors at transitions of care, often represented by unintentional medication discrepancies, contribute considerably to this risk (Uitvlugt et al., 2022). Unintentional discrepancies occur in approximately half of hospitalized patients upon hospital admission (Cornish et al., 2005; Tam, 2005; Hellström et al., 2012), and they persist to a similar extent at hospital discharge (Knez et al., 2011b; Grimes et al., 2011). Most importantly, medication errors at transitions of care can lead to patient harm. Namely, unintentional discrepancies at hospital admission resulted in an adverse drug event (ADE) in one-fifth of cases even during a short hospital stay (Jošt et al., 2022). Furthermore, discrepancies at hospital discharge, regardless of their intent, were often associated not only with ADEs but also with increased healthcare utilization and hospital readmission (Coleman et al., 2005; Forster et al., 2005; Uitvlugt et al., 2022). Many of these events are preventable.

Medication reconciliation has been introduced to improve patient safety at transitions of care. Medication reconciliation is the process of identifying an accurate list of a person's current medicines and comparing it with the current list in use, identifying any discrepancies, and documenting any changes, thereby resulting in a complete list of medicines, accurately communicated (Anon, 2011). Indeed, medication reconciliation has been repeatedly shown to reduce medication errors at transitions of care, while its impact on more patient-centered outcomes has led to mixed results, also in several well-designed studies (Cebron Zerovnik, and Kos 2019; Cheema et al., 2018; Ensing et al., 2015; Michaelsen et al., 2015; Mueller et al., 2012). While some studies on medication reconciliation performed in isolation or as part of more complex interventions at transitions of care have shown that post-discharge all-cause and medication-related healthcare utilization were substantially reduced (Gillespie et al., 2009; Marusic et al., 2013; Lenssen et al., 2018; Ravn-Nielsen et al., 2018; Snyder et al., 2020; Schnipper et al., 2022), others have not (Phatak et al., 2016; Karapinar-Çarkıt et al., 2019; Lea et al., 2020; Ceschi et al., 2021; Gurwitz et al., 2021; Kempen et al., 2021; Johansen et al., 2022).

Heterogeneity in the outcomes of medication reconciliation studies is expected. Indeed, there is wide variability in the interventions performed, ranging from providing medication reconciliation only at hospital admission and/or discharge to upgrading it with medication review and various post-discharge interventions, such as patient and caregiver engagement through phone calls or post-discharge visits and communication with primary care physicians, pharmacists and nurses (Dautzenberg et al., 2021). In addition, implementing complex interventions such as medication reconciliation is challenging (Gesell et al., 2021). Many factors contribute to successful implementation, and if these factors are not adequately addressed, it may affect the final outcomes (Jošt et al., 2022; Schnipper et al., 2022). Therefore, medication reconciliation should be tailored to the specifics of each healthcare facility, which inherently limits the generalizability of study results. In facilities with limited clinical pharmacy activities, which include those in many Central-Eastern European countries, previously unreported barriers may be present (Režonja et al., 2010; Knez et al., 2011b; Urbańczyk et al., 2023). In addition, the sustainability of an intervention delivered in the tightly controlled environment of a clinical trial is not guaranteed when the intervention is transferred to everyday clinical practice (Ford and Norrie, 2016; Gesell et al., 2021).

The aim of our pragmatic trial involving hospitalized adult medical patients was to evaluate the impact of routine pharmacist-led medication reconciliation on the occurrence of clinically important medication errors at hospital discharge and healthcare utilization within 30 days after hospital discharge.

2 Methods

2.1 Study design and participants

A pragmatic, prospective, controlled clinical trial was conducted in hospitalized adult medical patients. Patients in the intervention group were offered a pharmacist-led medication reconciliation service, while patients in the control group received standard care.

This study was conducted in five general medical wards at the University Clinic of Respiratory and Allergic Diseases Golnik in Slovenia. The patients admitted to this clinic belong to the population of general medical patients, who are most frequently admitted due to acute pulmonary and cardiovascular disorders or diagnostics in pulmonary diseases. Patients were assigned to the intervention or control group according to their admission ward: one ward, where medication reconciliation was implemented in routine clinical practice, served as the *intervention ward*, whereas the remaining four wards served as *control wards*. Despite no formal randomization into the intervention or control group, the patients' ward allocation was random, as it depended primarily on bed availability and was thus not influenced by the conduct of this study. All patients admitted to the intervention ward were included

in the intervention group, while in the control group, patients were randomly selected from among all patients, admitted to the four control wards using Research Randomizer (Urbaniak and Scott, 2011), and followed the temporal dynamics of patient inclusion in the intervention group. Our aim was to include an equal number of patients in both groups.

All adult general medical patients admitted to the study wards were eligible to participate in this study, except those who did not speak Slovenian, were transferred from another ward or were previously included in the same study. Patients who were hospitalized only for diagnostic purposes, patients transferred to another ward or hospital, patients who died during hospitalization, and patients from the control group who were offered medication reconciliation were subsequently excluded from this study. Because of the study design, participants and ward staff were not blinded to treatment assignment.

All procedures performed in this study were conducted in accordance with the ethical standards of the institutional and national research committee (National Medical Ethics Committee in Slovenia, protocol number 0120-223/2019/4) and with the 1975 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. Informed consent was obtained from all patients included in this study. This study is registered at ClinicalTrials.gov (NCT06207500).

2.2 Intervention

Patients in the intervention group were offered a pharmacist-led medication reconciliation service. The service was provided by clinical pharmacists or final year residents in clinical pharmacy working under the supervision of a clinical pharmacist. The service included medication reconciliation at hospital admission and at discharge, coupled with patient counselling. To guarantee uniform execution of the intervention, a standard operating procedure was created, the pharmacists were trained accordingly, and peer-to-peer supervision was performed prior to the start of this study. In brief, at hospital admission and after reviewing all available medical and pharmacy records, the best possible medication history (BPMH) was obtained through interviews with the patients or caregivers. The BPMH was compared with in-hospital therapy to identify discrepancies. All discrepancies were discussed with the treating physician, unintentional discrepancies were reconciled, and intentional discrepancies were documented in the medical records. At hospital discharge, medication reconciliation was performed to ensure that all unintentional discrepancies between a patient's BPMH and discharge medicines were reconciled and that all intentional discrepancies were explained in the discharge letter. In addition, face-to-face patient counselling on discharge medicines and aligned changes was conducted and coupled with written instructions in lay language. At every step, clinical pharmacists worked in close collaboration with the treating physicians, and all the documentation was prepared by the clinical pharmacist and approved by the physician. All the relevant documents were included in the patients' medical records.

Patients in the control group received only written instructions on discharge medicines in the discharge letter, according to standard practice. Patients in both groups may have received clinical pharmacy services such as therapeutic drug monitoring services, medicine's adjustments in poor renal function, and drug interaction assessments.

2.3 Data collection and outcome assessment

Data collection and outcome assessment were performed by research pharmacists, who were clinical pharmacists or final year residents in clinical pharmacy and were not involved in the treatment of the included patients. To ensure standardized data collection and outcome assessment, a standard operating procedure was established, and the pharmacists were trained accordingly before starting their collaboration. In case of uncertainties in outcome assessment, the research pharmacists consulted with each other to reach a consensus.

The data were collected from patients' medical records and study documentation. Patient's comorbidities were assessed by the Charlson Comorbidity Index (Quan et al., 2005; Shebeshi, Dolja-Gore, and Byles, 2021). The reason for a patient's index hospital admission was retrieved from the discharge letter and grouped into acute or planned admissions. For patients in the control group, a BPMH was collected in the same way as in the intervention group. However, the BPMH served only for study purposes and was thus not documented in patients' medical records.

To identify discrepancies at admission, the BPMH was compared to the medication data in the admission documentation. Likewise, to identify discrepancies at hospital discharge, the BPMH was compared to the discharge therapy. After reviewing the complete medical documentation related to the index hospitalization, discrepancies were classified as unintentional, undocumented intentional or documented intentional. A discrepancy was classified as *unintentional* if no medical reason was evident for the undertaken change in therapy, as *undocumented intentional* if a medical reason for the undertaken change in therapy was evident but not documented in the discharge letter, or *documented intentional* if the medical reason for the undertaken change in therapy was evident and documented in the discharge letter. Unintentional discrepancies and undocumented intentional discrepancies were defined as *medication errors,* and their clinical importance was assessed using a 4-point Likert scale ranging from not important, not very important, and very important to life-threatening medication errors. Very important and life-threatening medication errors represented *clinically important medication errors*.

For both groups, data on healthcare utilization up to 30 (±5) days after hospital discharge were collected through patient or caregiver phone interviews. Healthcare visits within 30 days of hospital discharge were defined as any visit to a general practitioner, specialist, emergency department (ED), or hospitalization. These visits were classified as unplanned if sudden health problems required medical attention and planned if the visits were scheduled. Data on mortality due to any reason were also collected 30 days after discharge. For each patient, only the most detrimental outcome was classified.

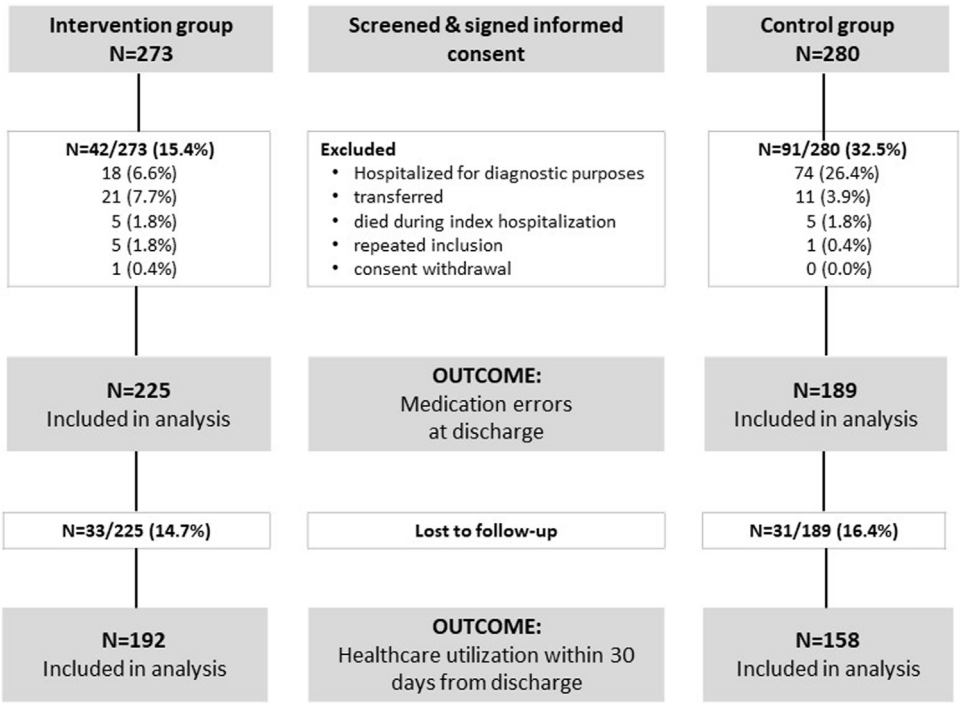

FIGURE 1
Study flow diagram.

The primary study outcome was unplanned healthcare utilization, defined as the occurrence of any unplanned visits or death within 30 days from hospital discharge. Secondary outcomes included the occurrence of clinically important medication errors at discharge and serious unplanned healthcare utilization, defined as the occurrence of any unplanned ED visit, hospitalization or death within 30 days from hospital discharge.

2.4 Sample size calculation and statistical analysis

The literature indicates that between 18% and 67% of patients make an unplanned visit to a healthcare facility within 1 month after hospital discharge (Al-Rashed et al., 2002; Marusic et al., 2013; Snyder et al., 2020; Graebek 2018). Based on the assumption that 30% of the individuals in the control group would require an unplanned healthcare visit, a sample size of 400 patients per group was considered necessary to observe a 30% reduction in these unplanned visits. This calculation assumed a statistical power of 80% and a significance level (α) of 0.05 and took into consideration a potential dropout rate of 10%.

Descriptive statistics were used to describe the baseline characteristics of the participants. A univariable statistical analysis was first performed to compare the intervention and control groups. The chi-square test or Fisher's exact probability test was used for categorical variables, and the nonparametric Mann–Whitney U test was used for continuous variables. Multiple logistic regression models were employed to examine the impact of pharmacist-led medication reconciliation on primary and secondary outcomes. The following covariates were used as potential predictors in the analysis: gender, age, number of medications before admission, comorbidities, type of and reason for admission, and duration of hospitalization. Prior to logistic regression, we ensured that the data met the necessary assumptions for the analysis, including the absence of multicollinearity by using a correlation matrix and variance inflation factor (VIF) methods among predictors. Model fit was evaluated using the Hosmer–Lemeshow goodness-of-fit test. Nagelkerke's R^2 was used to get an insight into the model's explanatory power. The significance of individual variables was analyzed by the Wald statistical test. The results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). All the statistical analyses were performed using the statistical program IBM SPSS Statistics version 28.0. A significance level of $\alpha = 0.05$ was used for all tests.

3 Results

A total of 553 patients were screened and agreed to participate in this study—273 in the intervention group and 280 in the control group. Some patients were subsequently excluded due to reasons arising after hospital admission, resulting in 414 patients remaining for further analysis—225 in the intervention group and 189 in the control group (Figure 1).

The included patients were evenly distributed between genders (53.4% male), most were of older age, with a median age of 71 years

TABLE 1 Patients' baseline characteristics.

	All patients		Intervention group		Control group		*p-value*
	N = 414		N = 225		N = 189		
Gender; male (n, %)	221	53.4%	128	56.9%	93	49.2%	0.119*
Age (years; median, IQR)	71	(63–80)	72	(64–81)	70	(61–78)	0.063 **
Charlson Comorbidity Index (median, IQR)	2	(1–4)	2	(1–3)	2	(1–4)	0.265 **
Number of medications on admission (median, IQR)	7	(4–10)	7	(4–10)	7	(4–10)	0.680 **
Discrepancies on admission (n, %)	358	86.5%	191	84.9%	167	88.4%	0.304*
Admission type; acute (n, %)	317	76.6%	202	89.8%	115	60.8%	**<0.001***
Reason for admission (n, %)							
Infection	125	30.2%	87	38.7%	38	20.1%	**<0.001***
Respiratory disease	112	27.1%	42	18.7%	70	37.0%	
Heart disease	74	17.9%	46	20.4%	28	14.8%	
Malignancy	58	14.0%	24	10.7%	34	18.0%	
Other	45	10.9%	26	11.6%	19	10.1%	
Duration of hospitalization (days; median, IQR)	7	4%–10%	6	4–9	7	6–11	**<0.001****

Abbreviations: IQR, interquartile range; significant *p* values are marked in bold.
*Chi square test; ** Mann–Whitney U test.

TABLE 2 Medication errors and healthcare utilization at hospital discharge and within 30 days from discharge.

	All patients		Intervention group		Control group		*p-value*
Patients with discrepancies at discharge	N = 414		N = 225		N = 189		
Any discrepancy (n, %)	405	97.8%	218	96.9%	187	98.9%	0.154 *
Medication error (n, %)	256	61.8%	75	33.3%	181	95.8%	**<0.001** *
Clinically important medication error (n, %)	138	33.3%	21	9.3%	117	61.9%	**<0.001** *
Discrepancies per patient at discharge							
Any discrepancy; median (IQR)	4	(2–6)	3	(2–5)	5	(3–8)	**<0.001** **
Medication error; median (IQR)	1	(0–3)	0	(0–1)	3	(2–6)	**<0.001** **
Clinically important medication error; median (IQR)	0	(0–1)	0	(0–0)	1	(1–2)	**<0.001** **
Healthcare utilization within 30 days from discharge	N = 350		N = 192		N = 158		
Unplanned healthcare utilization (n, %)	109	31.1%	65	33.9%	44	27.8%	0.227 *
Serious unplanned healthcare utilization (n, %)	62	17.7%	39	20.3%	23	14.6%	0.160 *
• Death[a]	16	4.6%	10	5.2%	6	3.8%	
• Hospitalization[a]	32	8.9%	17	8.9%	14	8.9%	
• Emergency department visit[a]	15	4.3%	12	6.3%	3	1.9%	

[a]Most severe outcome.
*Chi square test; ** Mann–Whitney U test.
Significant *p* values are marked in bold.

(interquartile range (IQR) 63-80), patients had a median Charlson Comorbidity Index of 2 (IQR 1-4) and a median intake of 7 medications on admission (IQR 4-10). There were no differences between groups (Table 1). In the intervention group, more patients (89.8%) were admitted for an acute health condition than in the control group (60.8%; $p < 0.001$). Additionally, the reason for admission differed between the groups, with more patients in the intervention group admitted due to infection and

TABLE 3 Multiple logistic regression results.

Covariates	Outcome					
	Clinically important medication error at discharge		Unplanned healthcare utilization within 30 days of discharge		Serious unplanned healthcare utilization within 30 days of discharge	
	Nagelkerke's R^2 = 0.465; *P* = 0.535*		Nagelkerke's R^2 = 0.087; *P* = 0.119*		Nagelkerke's R^2 = 0.209; *P* = 0.740*	
	OR (95% CI)	*P value*	OR (95% CI)	*P value*	OR (95% CI)	*P value*
Gender (male vs. female)						
Female	Reference					
Male	0.969 (0.563-1.666)	0.909	1.282 (0.783-2.100)	0.323	1.555 (0.827–2.925)	0.171
Study group						
Control group	Reference					
Intervention group	0.050 (0.027–0.095)	**<0.001**	1.324 (0.791–2.216)	0.285	1.464 (0.762–2.815)	0.253
Age (years)	0.996 (0.973–1.019)	0.737	1.013 (0.993–1.034)	0.208	1.033 (1.003–1.064)	**0.031**
Charlson Comorbidity Index	1.044 (0.891–1.223)	0.596	1.106 (0.954–1.281)	0.183	1.188 (0.999–1.413)	0.052
Number of medications on admission	1.173 (1.092–1.259)	**<0.001**	1.049 (0.987–1.116)	0.125	1.102 (1.020–1.190)	**0.013**
Admission type						
Planned	Reference					
Acute	1.056 (0.545–2.048)	0.871	1.889 (0.918–3.888)	0.084	3.106 (1.133–8.517)	**0.028**
Reason for admission		0.314		0.874		0.300
Infection	Reference					
Malignancy	0.959 (0.356–2.584)	0.937	0.801 (0.338–1.896)	0.614	1.628 (0.486–5.456)	0.429
Heart disease	1.635 (0.475–5.632)	0.436	0.972 (0.301–3.140)	0.962	3.397 (0.729–15.835)	0.119
Respiratory disease	1.985 (0.700–5.627)	0.197	0.868 (0.338–2.226)	0.768	0.859 (0.219–3.371)	0.827
Other	0.926 (0.362–1.059)	0.881	1.141 (0.478–2.720)	0.766	1.488 (0.420–5.269)	0.538
Duration of hospitalization (days)	1.020 (0.983–1.059)	0.290	1.027 (0.993–1.063)	0.118	1.026 (0.986–1.067)	0.202

Abbreviations: OR; odds ratio; CI; confidence interval
Significant p values are marked in bold. *Hosmer-Lemeshow test

heart disease ($p < 0.001$). The length of hospital stay was shorter in the intervention group (6 days vs 7 days; $p < 0.001$).

3.1 Medication errors at hospital discharge

The majority of patients (97.8%) had at least one discrepancy at hospital discharge, with no difference between the intervention and control groups (Table 2). However, in the intervention group, significantly fewer patients had at least one medication error at discharge (75/225; 33.3% vs 181/189; 95.8%; $p < 0.001$), with a significantly lower number of medication errors per patient than in the control group (median 0, IQR 0-1 vs median 3; IQR 2-6; $p < 0.001$). Most importantly, a significant difference was also observed for clinically important medication errors, with 9.3% (21/225) of patients in the intervention group and 61.9% (117/189) in the control group ($p < 0.001$) having these types of errors. Some examples of clinically important medication errors are presented in Supplementary Table S1. Patients in the intervention group had significantly fewer clinically important medication errors per patient (median 0, IQR 0-0) than patients in the control group did (median 1, IQR 1-2; $p < 0.001$). Furthermore, the intervention considerably reduced the risk of clinically important medication errors by 20-fold, as shown by the multiple logistic regression model (OR 0.050, 95% CI 0.027–0.095; $p < 0.001$; Table 3). In contrast, the number of medications on admission had the opposite effect, albeit to a lesser extent (OR 1.173, 95% CI 1.092–1.259; $p < 0.001$).

3.2 Healthcare utilization within 30 days from hospital discharge

Overall, unplanned healthcare utilization within 30 days of discharge was noted in approximately one-third of patients, with no significant differences between the intervention (65/192: 33.9%)

and the control (44/158: 27.8%) groups (p = 0.227; Table 2). Serious unplanned healthcare utilization occurred in 20.3% (39/192) of patients in the intervention group and in 14.6% (23/158) of patients in the control group, with no difference between groups (p = 0.160). Unplanned hospitalizations occurred in 8.9% of patients in both groups, while 5.2% (10/192) and 3.8% (6/158) of patients died in the intervention and control groups, respectively.

According to the multiple logistic regression model, no significant associations were found between the intervention and other variables with unplanned healthcare utilization within 30 days from discharge. On the other hand, serious unplanned healthcare utilization was associated with increasing age (OR 1.033, 95% CI 1.003–1.064; p = 0.031), a greater number of medications on admission (OR 1.102, 95% CI 1.020–1.190; p = 0.013) and admission for an acute health condition (OR 3.106, 95% CI 1.133–8.517; p = 0.028), while the intervention had no significant effect (Table 3).

4 Discussion

The current pragmatic, prospective clinical trial in adult medical patients described a remarkable, 20-fold reduction in the risk of clinically important medication errors at hospital discharge through the provision of pharmacist-led medication reconciliation within routine clinical practice. However, our study was unable to demonstrate that this improvement translated into a reduction in unplanned healthcare utilization within the first month of hospital discharge.

The 414 included patients were older aged (median age >70 years), had comorbidities (median Charlson Comorbidity Index score of 2) and were treated with polypharmacy (median of 7 medications on admission), with no differences between groups. However, significantly more patients in the intervention group (89.8%) were hospitalized for an acute health condition, most commonly for infection or heart disease, than in the control group (60.8%). Despite the broad inclusion criteria of the present study, the included patients were representative of the population at high risk for medication errors, rehospitalization and mortality (Gleason et al., 2010; Allaudeen et al., 2011; van Walraven, 2014; Alassaad et al., 2015).

As expected, almost all patients experienced a change in pharmacotherapy at hospital discharge, exposing them to a risk of discrepancies. Patients who underwent medication reconciliation had a significantly lower median number of discrepancies (intervention vs control group: 3 vs 5), medication errors (intervention vs control group: 0 vs 3) and clinically important medication errors (intervention vs control group: 0 vs 1; all $p < 0.001$), all of which were assessed by independent observers. Moreover, the proportion of patients with at least one clinically important medication error at hospital discharge was 6-fold lower in the intervention group (9.3%) than in the control group (61.9%; $p < 0.001$), and, after adjustment for other patient and hospitalization characteristics, patients in the intervention group benefited from a 20-fold reduction in the risk of a clinically important medication error (multiple logistic regression, Table 3). Our results are consistent with those of previous studies that have repeatedly shown that pharmacist-led interventions reduce medication discrepancies and medication errors at transitions of care and are among the ones showing the greatest impact (Nickerson et al., 2005; Mueller et al., 2012; Ensing et al., 2015; Michaelsen et al., 2015; Cheema et al., 2018; Lipovec et al., 2019).

However, the reduction in medication errors at discharge was not accompanied by decreased healthcare utilization. Approximately one-third of patients had an unplanned healthcare visit or died within 30 days of discharge; there was no significant difference between the intervention group and the control group (33.9% vs 27.8%, $p > 0.05$), and there was no association with other patient or hospitalization characteristics (multiple logistic regression, Table 3). Moreover, there were no differences between the groups in terms of serious unplanned healthcare utilization, including ED visits, hospitalization or death (intervention vs control group: 20.3% vs 14.6%, $p > 0.05$); however, the likelihood of serious unplanned healthcare utilization increased with patient age, number of medications at admission and being hospitalized hospitalization for an acute medical condition (multiple logistic regression, Table 3).

Patient enrolment began in October 2019. However, it was temporarily halted due to the declaration of the coronavirus disease 2019 (COVID-19) epidemic in Slovenia on 12 March 2020 and finally ended with the second declaration of the epidemic on 18 October 2020, after inclusion of only 50% of the planned patients. Consequently, the planned sample size of 800 patients was not reached, which led this study to be underpowered to detect the initially expected difference in unplanned healthcare utilization. However, the current results do not indicate a difference between the groups, and our observations would probably not be affected by increasing the sample size. In some studies, pharmacist-led medication reconciliation reduced healthcare utilization, prehospitalization or ED visits and other outcomes (Gillespie et al., 2009; Marusic et al., 2013; Ravn-Nielsen et al., 2018; Snyder et al., 2020), while our study is one of numerous others that failed to demonstrate this (Graabaek et al., 2019; Karapinar-Çarkıt et al., 2019; Lea et al., 2020; Ceschi et al., 2021; Kempen et al., 2021; Johansen et al., 2022). No distinct characteristic, such as the inclusion of high-risk patients, the integration of medication reviews within the intervention or distinct post-discharge activities, distinguished successful from unsuccessful studies.

The inconsistent results described in our study, which showed a large effect of medication reconciliation on the reduction of clinically important medication errors but no effect on healthcare utilization, are disappointing. Indeed, healthcare utilization is an important outcome that needs to be considered when introducing new services. However, in addition to medication errors, healthcare utilization is influenced by numerous other factors, such as age, the number of medications taken at admission and the reason for admission, as in the present study. Furthermore, only a portion of healthcare utilization is medication related (Ravn-Nielsen et al., 2018), and only a portion is preventable (Jencks, Williams, and Coleman, 2009; van Walraven, 2014). For example, it is estimated that only one in five 30-day readmissions is medication related (Ravn-Nielsen et al., 2018) and that only 40% of these readmissions could be prevented (van Walraven, 2014; El Morabet et al., 2018; Meurs et al., 2021; Uitvlugt et al., 2022). Therefore, medication reconciliation interventions may only partially change overall healthcare utilization, even if they focus on more stringent outcomes such as medication-related hospitalizations.

Nevertheless, our results clearly showed that the medication reconciliation service, as provided in the current study and within

routine clinical practice, was effective at reducing the occurrence of clinically important medication errors at hospital discharge. The high rate of more than 60% of patients with clinically important medication errors in the control group, with some patients being discharged with up to 10 clinically important medication errors, requires, in our opinion, the implementation of medication reconciliation as a fundamental, albeit not sufficient, element to ensure patient safety. Finally, we believe that the insights gained in our study can significantly contribute to the development, implementation and delivery of seamless care on a national level. This contribution becomes even more crucial following the national reimbursement of pharmacist-led seamless care programs in 2023.

4.1 Limitations and strengths

One of the major strengths of our study is that we evaluated the benefits of a pharmacist-led medication reconciliation intervention in routine clinical practice. The high rate of correction of medication errors at discharge in the intervention group suggested good integration of the service into ward routines, although this was not formally assessed. As we have described in our previous research (Knez et al., 2011a; Jošt et al., 2022), the integration of new pharmacy services can be challenging (Schnipper et al., 2022), particularly in settings that have only recently introduced clinical pharmacy. As most of the research on medication reconciliation comes from countries with a long tradition of clinical pharmacy (Anderson et al., 2019), our findings should be very informative for many settings in Central-Eastern Europe. The pragmatic design of our trial with broad patient inclusion criteria (Zwarenstein et al., 2008) allowed the inclusion of patients who are usually excluded from studies evaluating pharmacist-led interventions (Ravn-Nielsen et al., 2018; Graabaek et al., 2019; Karapinar-Çarkıt et al., 2019; Kempen et al., 2021; Johansen, Halvorsen, Svendsen, et al., 2022), thus providing evidence of the benefits of medication reconciliation for the general population of hospitalized medical patients. Notably, outcome assessment was performed by independent observers who were not included in the service provision. Although the observers were not blinded to patient allocation, they were trained according to standard operating procedures to minimize the risk of bias.

The lack of randomization is an important limitation of the present study and was dictated by its primary aim. Specifically, our aim was to assess the benefit of medication reconciliation conducted as part of routine clinical practice. Thus, randomization at the patient and cluster levels could not be performed because it would lead to cross-contamination and inability to integrate services into routine clinical practice, respectively. Although the allocation of patients to wards was random *per se*, as it depended primarily on bed availability and was therefore not influenced by the conduct of this study, the lack of randomization may have led to bias. As measured biases, e.g., in baseline patient characteristics, were accounted for by conducting multivariable analyses, unmeasured bias due to differences in ward practices beyond the provision of medication reconciliation could not be evaluated. Additionally, as mentioned above, our study was not sufficiently powered for the primary outcome of unplanned healthcare utilization because of premature termination of patient recruitment due to the COVID-19 epidemic. The effect of medication reconciliation on overall healthcare utilization was probably overestimated because studies with larger effects were selected for sample size calculations. Nonetheless, this study demonstrated the high validity of medication reconciliation, as carried out in our study, which is a prerequisite for its implementation in more complex, interprofessional and transmural interventions to further improve patient safety.

5 Conclusion

This pragmatic trial confirmed that pharmacist-led medication reconciliation reduced the risk of clinically important medication errors at hospital discharge by 20-fold. Notably, this effect was achieved while providing medication reconciliation within routine clinical practice and in a country where clinical pharmacy services are relatively new, in contrast to countries with long-standing tradition of clinical pharmacy. However, the provided service did not lead to a reduction in healthcare utilization within 30 days of discharge. Since various factors beyond medication errors contribute to post-discharge healthcare utilization, the medication reconciliation process employed in this study should be regarded as a crucial, but not sufficient, element to guarantee patient safety.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

MJ: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Writing–original draft, Writing–review and editing. MKK: Conceptualization, Data curation, Methodology, Supervision, Validation, Visualization, Writing–review and editing. MK: Conceptualization, Data curation, Formal Analysis, Methodology, Supervision, Validation, Writing–review and editing. LK: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing–review and editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. The authors acknowledge the financial support from the Slovenian Research Agency (research core funding No. P1-0189 and P-0360).

Acknowledgments

We thank all the patients and ward staff who agreed to participate in our pragmatic trial. In addition, we thank the physicians in the intervention ward for their acceptance, support and participation in pharmacy-led medication reconciliation as part of routine clinical practice. Our trial could not have been conducted without the dedicated and enthusiastic work of the pharmacists. Therefore, we thank all clinical pharmacists at the Golnik Clinic for their careful implementation and performance of the intervention, the pharmacy students for collecting the data in the control group, and the clinical pharmacy residents for their extensive work in collecting the data and evaluating all the results.

Conflict of interest

LK has received a speaker honourarium from MSD, Pfizer and Roche. MJ received a speaker honourarium from Shire and Takeda.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1377781/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 09 April 2024
DOI 10.3389/fphar.2024.1350717

OPEN ACCESS

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RECEIVED 05 December 2023
ACCEPTED 26 March 2024
PUBLISHED 09 April 2024

CITATION
Kardas P, Kwiatek A, Włodarczyk P, Urbański F and Ciabiada-Bryła B (2024), Statins use amidst the pandemic: prescribing, dispensing, adherence, persistence, and correlation with COVID-19 statistics in nationwide real-world data from Poland.
Front. Pharmacol. 15:1350717.
doi: 10.3389/fphar.2024.1350717

Statins use amidst the pandemic: prescribing, dispensing, adherence, persistence, and correlation with COVID-19 statistics in nationwide real-world data from Poland

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Background: Adherence to medications presents a significant challenge in healthcare. Statins, used in primary and secondary prevention of cardiovascular disease, are of particular importance for public health. The outbreak of the COVID-19 pandemic resulted in additional healthcare system-related barriers impeding the execution of therapies. This study aimed to assess the use of as well as adherence and persistence to statins in a national cohort of 38 million of Polish citizens during pandemic.

Methods: A retrospective analysis of prescription and dispensation data for all statins users from the national payer organization covering the years 2020–2022 was conducted. Medication adherence was assessed using the Medication Possession Ratio, for persistence the 30-day cut-off was accepted. National data on COVID-19 cases and COVID-19 related deaths were obtained from ECDC.

Results: The analysis identified 7,189,716 Polish citizens (approximately 19% of Polish population) who were dispensed at least 1 pack of statins within the study period. Over that time, there was a continuous significant increasing trend in prescribing and dispensing of statins. Despite a total increase of 18.9% in the number of prescribed tablets, the percentage of tablets dispensed remained similar, averaging 86%. Overall percentage of adherent patients was 48.2%. For a random sample of 100,000 patients, the mean period of continuous therapy in 2022 was 6.2+/- 5.3 months. During the lockdown period, the mean number of prescribed and dispensed tablets was lower by 6.8% and 5.9%, respectively ($p < 0.05$). However, fluctuations in the number of COVID-19 cases or COVID-19-related deaths per week had no major impact on the prescribing and dispensing of statins.

Conclusion: Over the time of pandemic, there was a continuous increase in the number of statin tablets prescribed and dispensed in Poland. This suggests that, despite the potential limitations posed by COVID-19, access to statins remained easy, which may be attributed to the mass-scale implementation of the national e-prescription system. However, it is crucial to realise that approximately 1/7 of

prescribed statin doses were never dispensed, and the overall levels of adherence and persistence were low. This underscores the necessity for concerted efforts to change this scenario in Poland.

KEYWORDS

statins, COVID-19 pandemic, adherence, persistence, prescribing, dispensation, Poland, real-word data

1 Introduction

Despite the outstanding progress medicine has made in the last decades, cardiovascular diseases still account for a large portion of morbidity and mortality. In Poland, over 40% of total deaths are attributed to cardiovascular disease, with atherosclerotic cardiovascular disease (ASCVD) ranking as the leading cause of mortality (Główny Urząd Statystyczny, 2020). Various forms of hyperlipidaemias, and particularly those leading to elevated levels of low-density lipoprotein cholesterol (LDL-C), are considered a significant causal risk factor for the development of ASCVD. Therefore, the key to primary and secondary prevention is to decrease LDL-C levels by lipid-lowering therapies. The currently applicable European as well as Polish guidelines on dyslipidaemia management recommend long-term, usually lifelong therapies with lipid-lowering drugs in order to reduce the cardiovascular risk (Mach et al., 2020; Szymański et al., 2022). Despite new drugs that have emerged over the last years, statins play a cardinal role in effective management of this problem, owing to the extensive evidence of their effectiveness in both primary and secondary prevention (Author Anonymous, 1994; Collins et al., 2003). Consequently, they are of absolutely fundamental importance to public health, representing one of the most often prescribed groups of drugs (De Vera et al., 2014; Fuentes et al., 2018).

Unfortunately, the effectiveness of statins is negatively affected by suboptimal execution of therapy in real-life settings. Patients fail to adhere to the treatment in different ways, corresponding with all three phases of adherence as defined by the ABC terminology (Vrijens et al., 2012). Namely, they 1) do not initiate the treatment (which holds the name of "primary non-adherence"); 2) poorly execute their daily therapy (which typically is referred to as "poor adherence", however, according to ABC taxonomy, should be rather called "poor implementation"); and 3) discontinue the therapy, revealing poor persistence.

All these ways of behaviour have negative consequences. Non-adherence and non-persistence with statins lead to ineffectiveness in LDL-C level reduction in both primary and secondary prevention (Shalev et al., 2014). Consequently, they significantly elevate the risk of fatal and nonfatal cardiovascular events, as well as mortality. A systematic review of studies indicates an increased CVD risk ranging from 1.22 to 5.26, and mortality risk ranging from 1.25 to 2.54 among non-adherent individuals. Non-persistent individuals, on the other hand, face an elevated risk of CVD ranging from 1.22 to 1.67, and mortality risk ranging from 1.79 to 5.00 (De Vera et al., 2014). Non-adherence and non-persistence with statin therapy also has an impact on hospitalization costs and other CVD-related costs (Bansilal et al., 2016).

Of importance is the fact that there are some objective thresholds that allow for obtaining a full benefit of statin therapy. Namely, the most consistent benefits were observed at an adherence level of at least 80%. In primary prevention cohorts, clinical benefits usually occurred after 1 year of continuous therapy, whereas longer duration of treatments were associated with additional improvements in outcomes (Simpson and Mendys, 2010; Deshpande et al., 2017).

Medication adherence is affected by a number of factors. A useful model created by the World Health Organization (WHO) categorizes them into five distinct clusters that encompass health system, therapy, condition, patient, and socioeconomic factors World Health Organization (2003). The last few years were characterised by a strong effect of an element that penetrated to several of these clusters, namely, the COVID-19 pandemic. Not only did it exert a major impact on morbidity and mortality (accounting for nearly 18% of total deaths in Poland in 2021 (Statistics Poland, 2021)), but it also had both direct and indirect effect on adherence, seriously limiting access to healthcare services. Additionally, it negatively affected economies and daily life of citizens due to lockdowns, social distancing, remote mode of work, etc. (Ágh et al., 2021; Kardas et al., 2021; Agh et al., 2023).

Medication adherence can be assessed using a variety of measurement techniques. For instance, the implementation phase can be evaluated through dedicated questionnaires, urine and blood tests to detect drug presence, or electronic drug monitors. In the case of persistence and discontinuation, pharmacy claims data and insurers' databases are commonly utilized. Of course, each of these methods has its limitations. However, depending on the specific aspect of interest, many of them are employed in current research. Unfortunately, their utilization in clinical practice is much less common. As a result, in many countries, including Poland, adherence is not systematically monitored (Kardas, 2024).

Interestingly, just before the outbreak of COVID-19 pandemic, the e-prescription system was introduced on the mass scale in Poland. Polish e-prescriptions contain details of patient characteristics such as name, date of birth, and national identification number (but not clinical indications), as well as the qualitative and quantitative characteristics of prescribed drugs. Once authorized by the prescriber, they are stored in a centralized database, where their status changes in case of partial or complete dispensation. Therefore, this allowed for comparison of prescribing and dispensing data in an unprecedentedly precise way. Taking advantage of this opportunity, this study was aimed to examine the use of statins in Poland during the pandemic, with the particular focus on exploring the prescribing and dispensing patterns, medication adherence, persistence, and their relationship with COVID-19 statistics.

2 Methods

This retrospective analysis was based on data from e-prescriptions issued and dispensed in Poland between 2020 and 2022. As the nationwide e-prescription system was launched on 8 January 2020, the analysis period for prescription and dispensation was confined to 8 January 2020 to 31 December 2022, allowing access to the complete dataset.

2.1 Source data

The data used in this study was retrieved from the databases of e-Health Centre (Polish: Centrum e-Zdrowia), a governmental institution responsible for managing the Polish national eHealth system, including a nationwide e-prescription system. Each individual record contained information on the date of prescription, details of the prescribed drug (such as the trade name, dose, number of packs, etc.), date of dispensation (if it took place), as well as details of the drug dispensed. The basic patient characteristics (i.e., age and sex) were also recorded, however, no clinical data were collected or analysed. For the analysis of the cohort, patients were included with their first statin dispensation. Original prescription and dispensation data were presented with weekly granularity, and expressed in units of tablets. The percentage of tablets dispensed was also calculated in a similar way. When applicable, the data were further recalculated using a 30-tablet pack as the standard unit.

The primary focus of this analysis were statins, i.e., lipid-modifying agents being HMG CoA reductase inhibitors. It included both drugs formed from a single chemical compound, as well as fixed-dose combination of lipid-lowering medications, whereas fixed-dose drugs containing statins and non-lipid-lowering drugs were not taken into consideration. Other lipid-lowering drugs, such as ezetimibe or fibrates, were not considered.

Consequently, the analysis covered patients fulfilling the following inclusion criteria.

1. Patients prescribed drugs corresponding with one of the codes of the Anatomical Therapeutic Chemical (ATC) classification provided below:
   a) statins (ATC code: C10AA)
   b) fixed combinations of statins and other lipid-modifying agents (ATC codes: C10BA01 - C10BA09, C10BA11 and C10BA12)
2. Patients dispensed at least one pack of such a drug within the analysed period.

No exclusion criteria were employed.

Of a note is that the Polish regulations support prescribing and dispensing of the drugs in original packs, as manufactured. However, packs differ in size, most often containing either 28, or 30 tablets in the pack, or multiplicity of these numbers. Adopting one tablet as the basic unit for this analysis allowed for avoiding a potential bias resulting from various sizes of packs. Moreover, Polish legislation permits generic substitution, and thus a drug specified in a prescription may be substituted by another drug with the same active compound and potency. Therefore, for the purpose of this analysis, all the drugs containing statins and corresponding to one of the above-listed ATC codes were considered as interchangeable, and the daily dose was one tablet, regardless of the compound and dosage prescribed.

The outbreak of the COVID-19 occurred in December 2019, whereas the first Polish COVID-19 case was reported on 4 March 2020. The World Health Organization announced the COVID-19 pandemic on 11 March 2020, and declared its end on 5 May 2023 (United Nations News, 2024). Hence, the timeframe included in this analysis, spanning from January 2020 to December 2022, was entirely impacted by the pandemic.

For the purpose of this analysis, national data on COVID-19 cases and COVID-19-related deaths were obtained from the publicly available databases of the European Centre for Disease Prevention and Control (ECDC), with weekly granularity applied (ECEC Data on the daily number of new reported COVID-19 cases and deaths by EU/EEA country, 2024).

During the COVID-19 pandemic in Poland, there were three lockdowns: the first one from 14 March to 31 May 2020, the second from 7 November to 28 December 2020, and the last one from 20 March to 26 April 2021. These periods correspond with weeks 12–22 and weeks 46–52 of the year 2020, as well as weeks 12–16 of the year 2021. Therefore, out of the 156 weeks studied, 23 were considered to be lockdown periods.

According to the national statistical office (Statistics Poland), the population of Poland (in thousands of inhabitants, as of December 31) was 38,089, 37,908 and 37,766 for years 2020, 2021 and 2022, respectively (Główny Urząd Statystyczny, 2020).

2.2 Adherence and persistence definitions

Adherence and persistence were computed for each patient over the study duration, being two key complementary parameters describing long-term drug taking.

Adherence was defined as the degree to which a patient adheres to the prescribed medication regimen. Medication adherence was assessed using the Medication Possession Ratio (MPR), which represents the proportion of days for which medication was supplied in relation to the total days of the intended treatment. Assuming that statin therapy is typically lifelong, the analysis period for each patient was defined from the day of dispensation of the first statin prescription until 31 December 2022. Patients with an MPR below 0.80 (indicating that they possessed medication for less than 80% of the prescribed treatment period) were classified as non-adherent.

Persistence, on the other hand, measured whether patients continued to refill their statin prescriptions during the analysis period. Non-dispensation was defined as a failure to collect a medication within 30 days after the supply dispensed based on the preceding e-prescription had run out. Consequently, non-persistence was deemed to occur when a patient refrained from refilling their statin medication for a period exceeding 30 days.

2.3 Statistical analysis

Statistical analysis involved descriptive statistics of both prescribing and dispensing, as well as the percentage of drugs dispensed (compared to drugs prescribed). All the data were

expressed with weekly granularity. The Shapiro-Wilk W test was used to study the normal distribution of continuous variables. If the assumption of normality was met, then means were used in subsequent stages of the analysis. Otherwise, medians were used.

Categorical variables were expressed as proportions and compared between relevant groups using the $\chi 2$ test. To compare the average percentage of statin tablets dispensed for every out of three studied years, the Kruskal–Wallis test was used. The p-value of less than 0.05 was considered significant. Statistical calculations were made with the use of Statistica 13.1 software (TIBCO Software Inc.).

2.4 Ethical issues

The source data were fully anonymised. Similarly, all the findings were reported in an aggregated manner, and no individual data were disclosed. Therefore, in accordance with the policy of the Ethics Committee of the Medical University of Lodz, the study did not require ethical approval.

3 Results

3.1 General data

Throughout the entire analysed period, there were more and more new individuals who were dispensed statins, and thus satisfied the inclusion criterion. They were added to the analysed cohort with a steady mean pace of 2,794 per day. In total, between 1 January 2020 and 31 December 2022, as many as 7,189,716 Polish citizens (i.e., approximately 19% of the Polish population) were dispensed at least one pack of statins. Out of this number, 695,636 died in the analysed period. The mean age of these individuals ± standard deviation (SD), calculated on 31 December 2022 or the day of their death, was 67.6 ± 12.3 years. In the group discussed, 55.4% were females and 44.4% were males (gender data was missing for 0.2%).

3.2 Statins prescribed and dispensed

Between 8 January 2020 and 31 December 2022, 4,681,614,262 statin tablets were prescribed, and 4,010,716,658 dispensed in Poland. If recalculated as typical 30-tablet packs, these numbers translate into 156,053,809 (52,017,936 per year, on average) packs prescribed, and 133,690,555 (44,563,518 per year) packs dispensed.

The quantities of prescribed and dispensed statins were subject to weekly and seasonal variation, going in parallel for both these parameters. What is noteworthy is, e.g., a sharp drop in the quantity of prescribed and dispensed drugs within the last 2 weeks of each year, with a subsequent sharp rise in the first weeks of the following year. Nevertheless, a continuous rising trend was observed for both these parameters along the entire analysed period (Figure 1). Consequently, when studying the trends of these data, it may be observed that the weekly number of prescribed tablets of stains increased between 8 January 2020 and 31 December 2022 from 27,418,954 to 32,601,689, i.e., by 18.9%, and the number of dispensed tablets from 23,133,631 to 28,285,831, i.e., by 22.3%, which in both cases reflected a significant change ($p < 0.05$). Similar trends were observed for both the weekly numbers of prescribed and dispensed statin tablets per thousand of inhabitants, which increased within the analysed period from 652.4 to 1000.4, and from 445.1 to 817.1 tablets/week per 1000 inhabitants for prescribed and dispensed statins, respectively ($p < 0.05$). Figure 2 shows annual trends of weekly number of statin packs dispensed per 1000 citizens.

3.3 The percentage of dispensed statins

Despite these changes, the percentage of statin tablets dispensed was very stable. Linear regression proved a mean weekly increase of this parameter by 0.016%, leading to a statistically insignificant change of this percentage from 84.9% to 87.4% ($p > 0.05$) along the entire studied period. The mean percentage of statin tablets dispensed for every out of three studied years was in consequence very similar at approximately 86% (mean: 86.1 ± 4.9%, range: 85.9 ± 4.0% for 2022–86.4 ± 3.8% for 2021), and the observed differences were insignificant ($p > 0.05$).

As illustrated in Figure 3, weekly fluctuation of the percentage of dispensed statin tablets showed clear repeatable characteristics. The highest values came with last weeks of the year (particularly in weeks 51–53), followed by a sharp drop in a few first weeks of the next year. More granular analysis revealed some additional information. For example, in the year 2020, there was a significant rise in week 14, preceding the Easter holiday, during the first lockdown, whereas a considerable decline was observed in week 18, which ended with the May long weekend (in Poland, 1st and 3rd of May are national holidays), preceded by an increase in week 17, etc. Data aggregated for trimesters proved some stable annual trends. The mean percentage (± SD) of statin tablets dispensed in the first trimesters of the years analysed (82.07 ± 3.82%) differed from those of the third and fourth trimesters (87.40 ± 1.49% and 87.52 ± 2.59%, respectively; $p < 0.05$).

3.4 Adherence and persistence

Overall adherence calculated for the entire analysis period was low: the mean MPR was 70.2 ± 37.3%. The percentage of adherent patients was low at 48.2% (and even lower at 38.7%, if the threshold of possession of ≥ 90% of doses was used).

For a random sample of 100,000 patients, who were statin users before 1 January 2022, persistence was assessed for the period between 1 January and 31 December 2022. Figure 4 presents a Kaplan-Meier curve of persistence to statin therapy in that sample, and shows that at month 12 persistence was 40.0%, with the mean period of continuous therapy of 6.2 ± 5.3 months.

3.5 Effect of the COVID-19 pandemic and the related lockdown

Figure 5 illustrates weekly numbers of COVID-19 cases, COVID-19-related deaths and the percentages of statins

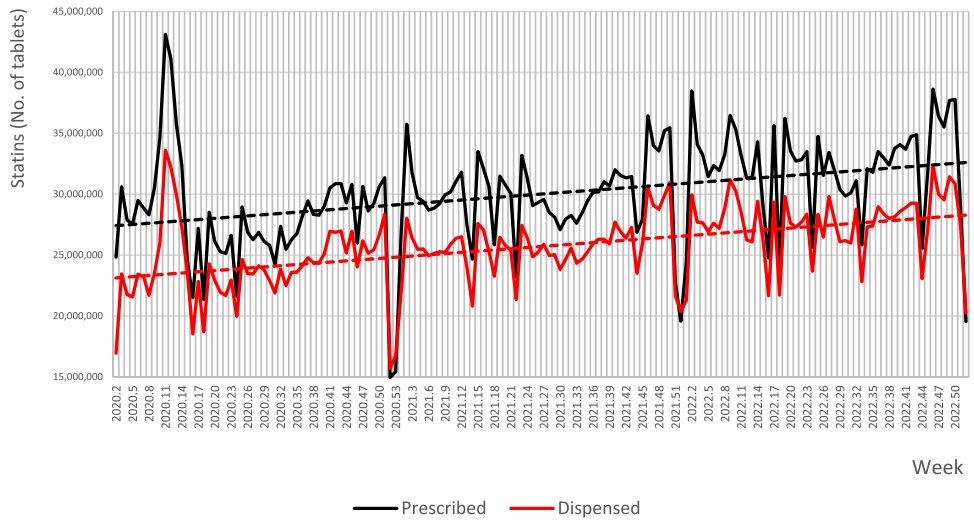

FIGURE 1
Weekly numbers and longitudinal trends of prescribed and dispensed statins in Poland from 8 January 2020 to 31 December 2022. Note: dotted lines represent trend lines.

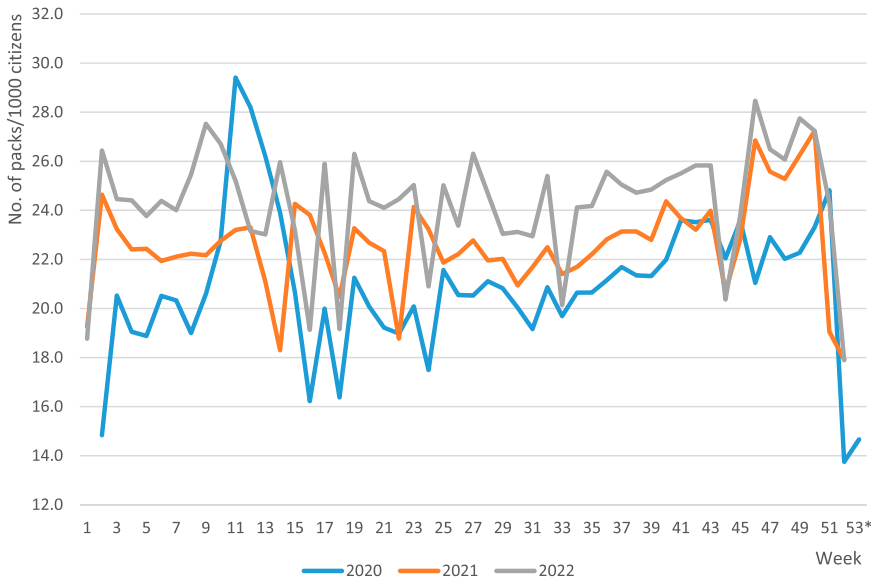

FIGURE 2
Annual trends of weekly number of statin packs dispensed per 1000 citizens of Poland from 8 January 2020 to 31 December 2022. Note: Standard 30-tablet packs were the basis for calculation. *week 53 applicable to year 2020 only.

dispensed in Poland during the period of pandemic. The correlation analysis revealed a statistically significant but weak positive relationship between the number of COVID-19 cases and the quantity of statin tablets dispensed ($p < 0.05$). Similar correlation was observed for the number of statin tablets prescribed, however it was insignificant. No correlation was observed between weekly COVID-19 death counts and the number of prescribed or dispensed statins. Similarly, the percentage of dispensed statins showed no correlation with either the number of COVID-19 cases or deaths.

As regards the non-lockdown period, the correlation analysis demonstrated a statistically significant ($p < 0.05$) weak positive relationship between the number of COVID-19 cases and the quantity of dispensed tablets, however, not for prescribed tablets. Nevertheless, during the lockdown period, the mean number of prescribed and dispensed tablets was lower by 6.8% and 5.9%, respectively, compared to the non-lockdown period (in both cases, the differences being statistically significant, $p < 0.05$). On the other hand, the mean percentage of tablets dispensed during the lockdown period was slightly higher than that during the non-

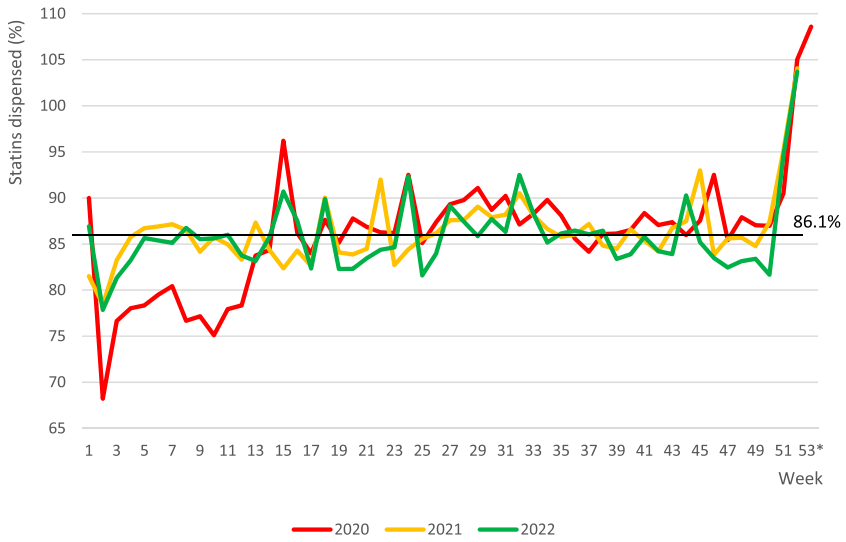

FIGURE 3
Fluctuations in the percentage of dispensed statins in Poland from 8 January 2020 to 31 December 2022. Note: horizontal line represents the mean value for entire period of analysis. *week 53 applicable to year 2020 only.

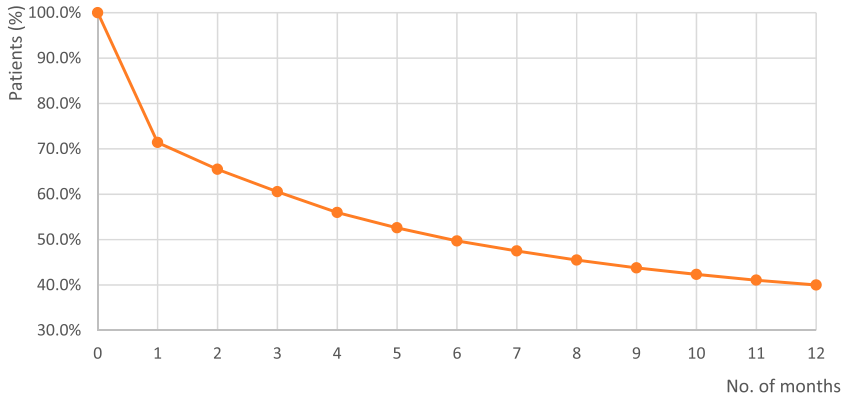

FIGURE 4
Kaplan-Meier curve of persistence with statin therapy of a random group of 100,000 Polish patients. Note: The time covered by this analysis was 1 January–31 December 2022; Base: a randomly selected cohort of 100,000 individuals who were statin users before 1 January 2022.

lockdown period (median ± SD: 86.3 ± 5.3% and 85.8 ± 4.9%, respectively, $p > 0.05$). A comparison of the weeks in 2020 and 2021 in which there were lockdowns with their corresponding "open" weeks in 2022 revealed that the percentage of dispensed tablets was higher during both the first and the second lockdown periods than outside them. In contrast, during the third lockdown period, the mean percentage of dispensed tablets was lower than outside it. However, in all these three cases, no statistically significant differences were found ($p > 0.05$).

4 Discussion

Due to high prevalence of ASCVD in Poland, statins play a pivotal role in public health. Good access to these drugs, and their continuous use by patients is of utmost importance for both primary and secondary prevention. This is particularly true given the rapidly aging Polish population, a factor that could further contribute to the increased incidence of ASCVD. Unfortunately, the recent outbreak of the COVID-19 pandemic created unfavourable conditions for maintenance of long-term therapies (Ágh et al., 2021; Kardas et al., 2021). Hence, as the first study of its kind to investigate statin use in Poland during the pandemic, this research yields doubly interesting results. It not only illustrates general aspects of prescribing, dispensing, adherence, and persistence with these drugs but also explores potential correlations with COVID-19 statistics. In fact, this research presents a comprehensive analysis of real-world data on a drug class of paramount importance. Using a nationwide database encompassing 38 million Polish citizens, the study provides robust evidence that will inform future preventive and corrective interventions.

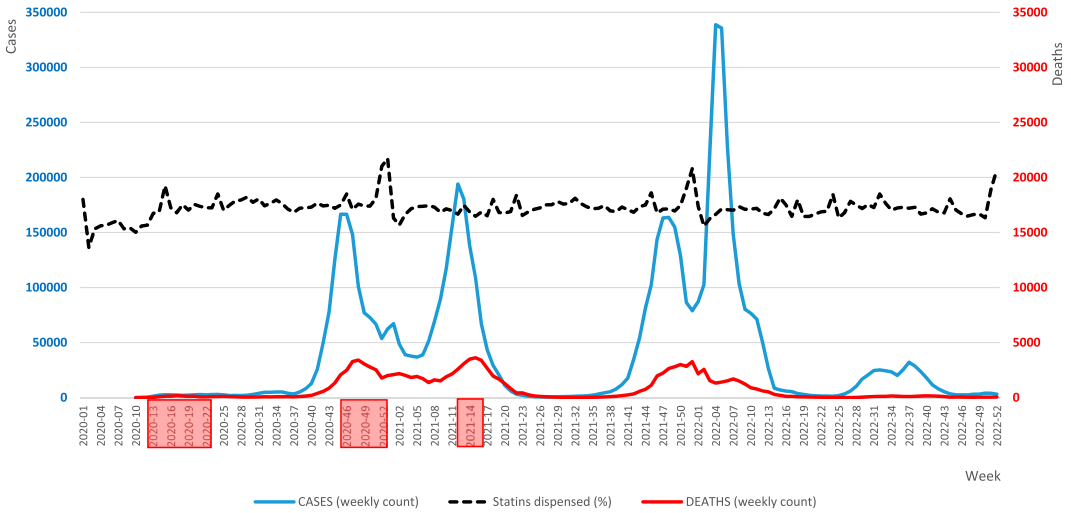

FIGURE 5
Weekly numbers of COVID-19 cases, COVID-19-related deaths and the percentage rates of statins dispensed in Poland during the pandemic period. Note: The analysed period spans from 8 January 2020 to 31 December 2022. The dotted line, illustrating the percentage of dispensed statins, is for illustrative purposes only and does not come with a scale. Lockdowns are indicated by red boxes along the timeline.

An interesting observation of our study pertains to the consistent annual fluctuations in prescribing and dispensing of statins. The remarkable repeatability of trends in specific years is noteworthy. Towards the end of the year, there is a substantial drop in the number of both prescribed and dispensed tablets, which lasts till the first weeks of the new year. Similar observations have been described in another study performed during the COVID-19 pandemic in Italy (Olmastroni et al., 2020). It reflects the typical trend among patients who devoted less attention to management of their chronic asymptomatic conditions in the last days of the year and the first days of the new year. It is highly likely that this phenomenon was also related to the limited access to healthcare providers at that time. In the Italian study, a remarkable drop in dispensed statins was observed in August, which most probably corresponded to the traditional summer holiday period in this country. In Poland, this trend was not observed, however, altered dispensation was identified in other periods, i.e., various holidays such as Easter and the May long weekend.

Interestingly, there were distinct annual fluctuations in the percentage of dispensed tablets. The most notable variation, marked by peak values, occurred in the last weeks of the year, specifically in weeks 51–53, followed by a sharp decline in the initial weeks of the following year. These trends can be ascribed to the uncertainty surrounding the availability and pricing of medications in the coming year, combined with a potential hesitation to leave health issues unresolved from the previous year that was observed among those who had committed to therapy.

Despite these fluctuations, a continuous rising trend in both prescribing and dispensing was identified. To some extent, it could be explained by the demographics of the Polish population, being slowly modified by the aging process. However, it does not fully justify a nearly 20% rise in the quantity of statin tablets prescribed and dispensed within 3-year period covered by our analysis. Perhaps, it rather reflects better saturation of the national population with lipid-lowering therapies, occurring despite the unfavourable COVID-19 conditions.

In spite of the overall rise in prescribing and dispensing, the percentage of dispensed statins was very stable in our analysis. Throughout the entire 3-year period of the analysis, it approximated 86%. When interpreting this figure, it should be noticed that a small portion of these prescriptions were those issued for the first time to patients supposed to initiate statin treatment, whereas a majority were prescribed to the established users. Therefore, it is striking that in our nationwide cohort, every seventh prescription for statin was never filled in. Our previous study based on the data coming from the pilot implementation of e-prescriptions in Poland, which took place in 2018, demonstrated an even higher overall level of non-dispensation (20.8%), with prescriptions for statins not dispensed in 17.9% of cases (Kardas et al., 2020). This result is similar to that observed in the current study on the COVID-19 pandemic. Thus, the problem seems to be persistent, and definitely not related to the pandemic only. Of interest is the fact that in a 2021 analysis including six classes of drugs, performed in the neighbouring country of the Czech Republic (Bruthans et al., 2023), primary non-adherence was most prevalent (5.7%) for lipid-lowering drugs, underscoring statins as particularly prone to poor adherence. Indeed, our results coming from the analysis of real-world data of national cohort prove that non-adherence to statins is prevalent in Poland. In our study, the overall adherence calculated for the entire analysis period was low at MPR = 70.2 ± 37.3%, despite the fact that a large part of analysed patients entered the cohort over the way, i.e., was followed for a much shorter time than 3 years. Moreover, only 48.2% of these patients satisfied typical definition of adherence (i.e., MPR ≥ 80%). All of this must be interpreted in the context of the structure of the Polish healthcare system, which is universal and provides access to essential medications like statins with minimal co-payments (typically ranging from 1 to 5 euros per pack) or free of charge for individuals aged 75 and older.

Suboptimal adherence can diminish the potential benefits of lipid-lowering therapies, and lead to substantial increase in healthcare expenditures. Nevertheless, studies uniformly report alarmingly high levels of non-adherence with statins, in some cases reaching even higher

than those observed in the present study. Various deviations from advised therapy may stand behind this problem. A study in older adults identified 4 distinct trajectories of statin use, out of which 3 accounted for non-adherence: gradual decline (16.8%), gaps in adherence (17.2%), and rapid discontinuation (7.8%), with only 58.2% of patients presenting high or nearly perfect adherence (Vadhariya et al., 2019). Not surprisingly, a recent meta-analysis proved suboptimal lipid management across Europe, and found adherence to lipid-lowering therapies to range between 46% and 92% (Barrios et al., 2021). In patients discharged with acute coronary syndromes in China, 72% adhered to statin therapy after 6 months only (Xie et al., 2017). Studies assessing patients newly prescribed statins found adherence to be extremely low in some cases, with 27% of men and 19% of women being adherent at 1-year only (Olmastroni et al., 2020; Ofori-Asenso et al., 2018a). Studies assessing adherence in a longer perspective provide equally striking results. A meta-analysis of data of more than 3 million older statin users in 82 studies proved that at 1-year follow-up, 59.7% (primary prevention 47.9%; secondary prevention 62.3%) of users were adherent, whereas at 3 and ≥10 years, 55.3% and 28.4% of users were adherent, respectively (Ofori-Asenso et al., 2018a). Recent studies echo comparable findings: the mean proportion of days covered (PDC) with statins at the conclusion of a 3.75-year period was 84% in Germany (Koenig et al., 2023). In Australia, the proportion of adherent individuals was 51% after 5 years (Talic et al., 2022), while in Taiwan, among patients who initiated statins post-hospital discharge for new-onset ASCVD, only 42% demonstrated adherence at the end of the seventh year (Chen et al., 2019).

It is noteworthy, however, that the studies cited above presented statistics on statin use from the pre-pandemic era. In contrast, our study, spanning the COVID-19 pandemic period, offers additional insights into statin use amid challenging conditions. It reveals that during the pandemic, Polish patients exhibited adherence and persistence levels comparable to those observed in studies conducted in other countries, outside pandemic scenarios.

In our study, persistence at month 12 was 40.0%, with the mean period of continuous therapy of 6.16 ± 5.31 months within the analysed period of 12 months. These results were very similar to those obtained in a study assessing a wide cohort (N = 613,654 patients) of new statin users prior to the COVID-19 pandemic, in which the percentage of persistent patients was 23.1% among men, and 15.8% among women, if the threshold of 30 days was used (Olmastroni et al., 2020).

Persistence with statins is generally very poor. Multiple studies from various locations report high percentage of new statin users who discontinue their treatment even within the first year after initiation, from 23.9%, on average, in meta-analysis of 82 studies (Ofori-Asenso et al., 2018a) up to 39% in Japan (Tomida et al., 2023), and 44.7% in Australia in recent reports (Ofori-Asenso et al., 2018b). Among patients with high-risk of CV events who newly initiated statin therapy in USA, median time to statin discontinuation was approximately 15 months (Lin et al., 2016). Among Scottish patients who initiated statin use for the secondary CVD prevention, 12% discontinued it within 1.5 years since initiation, and 19% within 3.5 years (Thalmann et al., 2023). In a longitudinal nationwide study assessing long-term persistence with statin therapy in Finland, only 43.9% were using statins up to the end of the 10th year of observation (Helin-Salmivaara et al., 2008). In a recent German analysis of lipid-lowering drugs use, at 12, 24 and 36 months after initiation the level of discontinuation was 60.8%, 73.8% and 79.4%, respectively (Lin et al., 2016). Interestingly, discontinuation is not limited to new users. Quite the contrary, in a nationwide study conducted among elderly Danes, approximately 19% of long-term statin users discontinued therapy within 2 years (Morotti et al., 2019).

On the other hand, an unexpected finding of this study is that the pandemic neither stopped new patients from initiating their statin therapy, nor the other patients from continuing it. Just the contrary, new individuals continuously initiated statin therapy, and the overall number of statin tablets prescribed and dispensed over the analysis period was continuously rising (see Figure 1). Indirectly, it confirms good access to medical services during the COVID-19 pandemic in Poland. Interestingly, the pandemic in a sense promoted statin use, as its exacerbation had a positive effect on the statin use: the higher the number of COVID-19 cases was, the higher were the numbers of statins prescribed (NS) and dispensed ($p < 0.05$). Although during the lockdown period, the mean number of prescribed and dispensed tablets was lower by 6.8% and 5.9%, respectively, as compared to non-lockdown periods ($p < 0.05$), the percentage of dispensed tablets showed the opposite, yet a non-significant tendency.

When interpreting these results, it should be emphasised that in Poland prescription drugs cannot be ordered in online pharmacies, and home delivery of such medications is not available. Such limitations created objective barriers to adherence at the pandemic peak, and particularly during lockdowns. However, our data prove that despite expectations, these factors did not constitute major obstacles to adherence during the COVID-19 pandemic.

The overall effect of the COVID-19 pandemic on adherence to chronic therapies seems to be ambiguous. As illustrated by the systematic review, a lot of chronic treatments were interrupted or negatively affected by the pandemic, due to various factors, such as fear of infection, lowered access to healthcare facilities, and unavailability of medicines. However, other therapies remained relatively unaffected, primarily because of the increased use of e-health tools and telemedicine (Olmastroni et al., 2020). Analysis of a large pharmacy claims database (over 250 million patients) found that most of American patients were able to access chronic medications in the early months of the COVID-19 pandemic, yet they were still more likely to discontinue their therapies than in the previous months. Moreover, at the time of the pandemic, there were fewer new patients who started taking their chronic medications (Clement et al., 2021). A study performed in Uganda found that risk of running out of antiretroviral drugs among HIV patients increased from 5% before the lockdown to 25% (Wagner et al., 2021).

Studies that looked specifically at adherence to stains during the pandemic yielded equally equivocal results. A few of these studies have been performed in Italy, a country heavily affected by the first wave of COVID-19. When comparing 2020 to the previous year, one study found that in the Pescara region, the adherence did not change much, unlike the persistence which dropped significantly (Romagnoli et al., 2022). Another study conducted in Lombardy identified an increase in PDC in March and April 2020, with a sharp decrease in May and June 2020. However, only a negligible decrease (−2.22%) in the total quantity of packs of lipid-lowering drugs dispensed in 2020 was observed (Casula et al., 2022). Another study found just a small rise in the proportion of failed refills of lipid-lowering drugs in April and May 2020 (42.4% and 42.5%,

respectively *versus* 38.6% in the pre-COVID-19 period) (Degli Esposti et al., 2020). A Japanese study addressing the same issue identified no clinically meaningful difference in PDC between periods before and during the pandemic, despite a temporary decline in physician visits (Osawa et al., 2021). Finally, a study performed in Malesia observed a positive effect of lockdown on medication adherence with statins, which could be related to relaxed restrictions on medication prescriptions and larger quantities of medications supplied to patients due to the COVID lockdown, as well as the important role that telemedicine and mail-order pharmacies played during the pandemic period (Sim et al., 2023).

Finally, it needs to be acknowledged that this study has several limitations. Firstly, due to the use of prescription and dispensation data, the study could not assess the extent to which prescribed medications were actually used by patients. It was not possible to monitor daily variations of patient adherence to treatment either. Secondly, we do not have information regarding the extent of prescriber-initiated discontinuation of statins, discontinuation related to adverse effects, etc. Additionally, this study was not focused on factors affecting adherence. Some studies found adherence and persistence to statins to be related to patient and therapy characteristics, e.g., persistence was significantly higher in men than in women (Olmastroni et al., 2020), those taking higher number of prescribed medications (Morotti et al., 2019), and in patients prescribed high-intensity statin therapies (Rezende Macedo do Nascimento et al., 2020; Svensson et al., 2022; Koenig et al., 2023). What also matters are economic parameters, e.g., adherence to preventive statin therapy dropped with decreasing income (Wallach-Kildemoes et al., 2013); whereas increased co-payment either led to reduced use of statins, or their discontinuation (Seaman et al., 2021). A higher percentage of adherent patients was observed among users of generic statins vs. brand-name drugs (Gao et al., 2021). Moreover, when interpreting results of studies on adherence and persistence, one needs to consider various thresholds of discontinuation applied by their authors, ranging from 30 up to 270 days even (Helin-Salmivaara et al., 2008; Morotti et al., 2019; Ofori-Asenso et al., 2018a). This factor may have profound consequences for study results. For example, in one study 73.3% of the initiators continued statin therapy at the end of the first year with a 270-day gap between prescriptions used as a cut-off, whereas the proportions for 180-day and 90-day gaps were 69.0% and 56.7%, respectively (Helin-Salmivaara et al., 2008).

Nevertheless, our study has various strengths. First of all, the research was conducted on a large national database including 38 million citizens, which was feasible due to the electronic prescribing system introduced on the national level just before the outbreak of the COVID-19 pandemic. Moreover, national prescription and dispensation database offers precise and reliable data as, serving as the basis for reimbursement for pharmacies, they are carefully revived.

Results of this study indicate an urgent need to improve medication adherence to statins since these are drugs of the utmost importance for public health. Several interventions of proven effectiveness are available to change this scenario (Reston et al., 2020; Krüger et al., 2018). Unfortunately, current use of such adherence-enhancing interventions is more than limited, not only in Poland. Systematic search across Europe identified 13 reimbursed interventions in nine countries only (Ágh et al., 2021). Therefore, it is strongly recommended to enhance the implementation of initiatives and tools that support patients in regular drug intake. This recommendation is primarily directed towards the national regulator and payer organization, the National Health Fund. In particular, offering relevant support to prescribers, such as automated digital alerts facilitating timely prescribing of refills, appears to be an effective solution that may ensure unbroken continuity of therapy.

5 Conclusion

To the best of our knowledge, this is the first study focused on examining real-world adherence and persistence among Polish patients during the pandemic. According to its results, over the 3 years of the COVID-19 pandemic in Poland, there was a continuous increase in the number of statin tablets prescribed and dispensed. This suggests that, despite the potential limitations posed by the pandemic, access to statins remained easy, which may be attributed to the mass-scale implementation of the e-prescription system that became the compulsory prescribing mode at the beginning of 2020. However, it is crucial to realise that approximately one-seventh of prescribed statin doses were never dispensed, and the overall levels of adherence and persistence were low. This underscores the necessity for concerted efforts to change this scenario in Poland.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Dataset belongs to public payer organisation. Requests to access these datasets should be directed to przemyslaw.kardas@umed.lodz.pl.

Author contributions

PK: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing–original draft, Writing–review and editing. AK: Conceptualization, Data curation, Investigation, Methodology, Software, Validation, Visualization, Writing–review and editing. WP: Data curation, Investigation, Methodology, Software, Validation, Writing–review and editing. FU: Investigation, Methodology, Supervision, Validation, Writing–review and editing. BC-B: Data curation, Formal Analysis, Investigation, Methodology, Software, Validation, Visualization, Writing–review and editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 10 April 2024
DOI 10.3389/fphar.2024.1379700

OPEN ACCESS

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RECEIVED 31 January 2024
ACCEPTED 20 March 2024
PUBLISHED 10 April 2024

CITATION
Larsen RE, Hole K, Selle ML, Johannessen Landmark C, Krogstad T and Holm LB (2024), Access to a tailored mobile application enhances medication adherence among young users of antidepressants. *Front. Pharmacol.* 15:1379700. doi: 10.3389/fphar.2024.1379700

Access to a tailored mobile application enhances medication adherence among young users of antidepressants

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Introduction: Patients' adherence to antidepressants is generally reported to be poor. This study examined whether users of selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) enhance medication adherence following access to a mobile application (app) tailored for this patient group. The study addresses the implementation phase of medication adherence.

Methods: The study was a single group pre-post intervention design. Data were collected using the validated OsloMet Adherence-to-medication Survey tool (OMAS-37) before and after app access. Pre-app access survey (Survey 1) was conducted via social media and online newspapers, encompassing 445 SSRI/SNRI users aged 18 years and above. Post-app access survey (Survey 2) was sent to 103 SSRI/SNRI users from Survey 1. Wilcoxon Signed Rank Test compared pre- and post-intervention adherence measurements. Pearson's chi-square tests and Fisher's exact tests compared study population categories.

Results: Forty-two SSRI/SNRI users, median age 26 (IQR 17), 93% identifying as female, used the app while using the same antidepressant during the 2-month period between gaining access to the app and Survey 2. There was a statistically significant reduction in non-adherence score post-app access ($z = 3.57$, $n = 42$, $p < 0.001$) with medium effect size ($r = 0.39$), indicating enhanced adherence. Total non-adherence score decreased by 39% from pre-to post-access, and there was a 12% decrease in users scoring equivalent with poor adherence (score <2) post-access. Twenty-nine of 37 non-adherence causes improved, with three showing statistical significance. Of 42 responders, 50% (n = 21) indicated using the app one to two times, while 50% (n = 21) more than three times. Approximately 69% (n = 28) found it useful, and 43% (n = 18) felt safer in their use of antidepressants after access to the app. No significant preference was observed for the app over alternative sources of information.

Discussion: Enhanced medication adherence was observed among antidepressant users following access to the tailored app. Further studies are warranted to evaluate the app applicability to a broader range of antidepressants users or other patient groups, encompassing those in the initiation phase of

medication adherence. The app is intended as an easily accessible supplement to the information and advice provided by prescribing physicians and dispensing pharmacists.

KEYWORDS

SSRI, SNRI, OMAS-37, antidepressants, medication adherence, mHealth, mobile apps

1 Introduction

Patients' adherence to medication is often inadequate (World Health Organization, 2003; Foley et al., 2021), and there are numerous studies concerning factors impacting medication adherence (Cheen et al., 2019; Gast and Mathes, 2019). Reasons for non-adherence are complex and vary both among individual patients and within each patient over time (World Health Organization, 2003; Horne et al., 2019). For instance, these variations could be dependent on whether the medication regimen has recently been initiated or has been in place for an extended period, and the rationale behind a patient's use of the medication (Horne et al., 2019). Given the influential effect of how long a patient has used a medication, the definition of medication adherence consists of three phases: the initiation phase (from prescribing to first dose), implementation phase (from first dose to discontinuation), and discontinuation (last dose). Alternatively, the initiation phase, implementation phase, and persistence phase - wherein persistence refers to the duration between the initiation and the last dose, which immediately precedes discontinuation (Vrijens et al., 2012; De Geest et al., 2018). In a clinical setting with patients who are non-adherent, it is crucial to ascertain the reasons for non-adherence, including the rationale behind a patient's medication use, and to devise interventions accordingly. In their evidence-based guideline on medication adherence (2023), the National Institute for Health and Care Excellence (NICE) in the UK designates a key principle for interventions. According to NICE, while the improvement of adherence is feasible, there is no one-size-fits-all intervention suitable for every patient. The institute strongly advocates for personalized interventions tailored to address the unique adherence challenges faced by each individual (National Institute for Health and Care Excellence, 2019). Although individual adherence interventions are considered ideal, it might be more cost effective with interventions tailored for specific patient groups. Such an intervention could be used as an adherence-enhancing tool, for instance as a part of individual intervention guidance by health personnel. In this way, it could serve as a resource-saving measure, providing healthcare personnel with a quality-assured tool to offer specific patient groups as a supplement to individual counseling. In our previous study utilizing the validated OsloMet Adherence-to-medication Survey tool, OMAS-37, we revealed that patients using medication for Mental health disorders (MHD) were among the most non-adherent. This finding is supported by previous studies reporting poor adherence to medication for MHD-patients (Semahegn et al., 2020; Lassen et al., 2024). These patients could benefit significantly if such a tailored intervention provided an effect on adherence. The benefits include improved quality of life due to improved treatment outcomes and a reduced burden from adverse drug reactions. In our previous study we found that the five main causes of non-adherence for this patient group were "Forgot to take the medication", "Having used the same type of medication before without them having good/satisfactory effect", "Feeling better", "Fearing adverse drug reactions" and "Having difficulties taking the medication to specific hours". Therefore, addressing these causes would be important topics in a tailored intervention for this patient group. To be able to provide tailored information on for instance adverse drug reactions, medications for mental health disorders need to be narrowed down to a specific medication group. Among the psychiatric disorders, depression is the leading cause of disability (Abate et al., 2018). The recommended first-line pharmacological treatment for depression is second generation antidepressants, where selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) are widely used (Kennedy et al., 2016; Qaseem et al., 2016; National Institute for Health and Care Excellence, 2022). According to the Norwegian National Institute of Public Health (NIPH), 7% of the population was prescribed at least one antidepressant in 2021. The proportion was higher among women and the older population: in 2021, 9% of women and 11% of those over 65 years old were prescribed at least one antidepressant (NIPH, 2022). An intervention tailored to enhance adherence among SSRI/SNRI users could consequently have a significant impact on a large number of individuals. Developing this intervention as a mobile application, referred to as app, would facilitate easy accessibility as smartphones are ubiquitous. Although previous systematic reviews display mixed evidence regarding the benefits of mobile health (mHealth) interventions on adherence to medication, over all these interventions seem to be beneficial (Anglada-Martinez et al., 2015; Hamine et al., 2015). The aim of this study was to examine whether access to an app specifically tailored for this patient group would improve self-reported medication adherence among patients using SSRI/SNRI medication.

2 Materials and methods

2.1 Study design and data collection

The study was designed as a single group pre-post intervention study. The data were collected using two OMAS-37-incorporated e-surveys: Survey 1 was conducted prior to the respondents' access to an app, followed by Survey 2 conducted approximately 2 months after they gained access to the app. The study addressed individuals that were actively using medication, indication their presence in the implementation phase of adherence to medication (De Geest et al., 2018).

2.1.1 The OMAS-37 incorporated e-surveys: Survey 1 and Survey 2

OMAS-37 is a validated adherence assessment tool (Larsen et al., 2022) that comprises 37 causes of non-adherence. The tool enables the calculation of individual responders' non-adherence score on a

scale from 0 to 111, with an increasing score indicating reduced adherence. Additionally, the tool facilitates the calculation of cause-specific adherence scores, providing insight into the most prominent causes for non-adherence. Alongside OMAS-37, both e-surveys encompassed questions regarding demographics and medication usage. In addition, respondents were asked to indicate the medical conditions for which they received medication within the last 12 months. The respondents were given the choice to select one or more medical-condition groups from a list of 24 choices, selected from The Norwegian Medicines Manual for Health Personnel (NMM, 2023) in addition to the options "other" and "do not know/do not want to tell/not applicable". Predefined inclusion criteria for Survey 1 were using medication and being 18 years or older. Incorporated adaptive features excluded respondents not meeting the predefined inclusion criteria. Furthermore, the adaptive features of Survey 1 allowed users who checked off using medication for mental health disorders to be asked whether they used antidepressants for the treatment of depression. Those who responded affirmatively were further questioned about the specific type they used and could choose from a list of marketed SSRI/SNRI medications in Norway in addition to the options "none of these" and "do not know/do not want to tell/not applicable". Those who reported using medication from this medication list were asked if they were interested in testing an app and provided with information about the study. Those who agreed were prompted to input their email addresses for further contact regarding consent and access to the app. To ensure anonymity, the responses to Survey 1 were sent directly to and stored in a secure server for sensitive data, TSD - Services for sensitive data (University of Oslo, 2024). Survey 2 closely resembled Survey 1, with the exception of the questions: whether they used antidepressants, if they wanted to participate in the study, or about leaving their email address. In Survey 2, the first question asked the respondents to provide a unique code they received in the same email as the online hyperlink to Survey 2. This was done to enable pairing of each respondent's pre- and post-access responses without asking for personal information. Respondents in Survey 2 were also asked whether they were still using the same antidepressant as they did approximately 2 months ago, to ensure that they still belonged to the target group. Questions regarding the usage and usefulness of the app were also added, including one question comparing the app to information provided by sources other than a physician or pharmacist. Participants were asked to rate on a scale from 1 to 10, where 1 indicates a strong preference for other methods of obtaining information about medications (excluding physicians and pharmacists), and 10 indicates a strong preference for a quality-assured app like the one they were given access to. To ensure completeness of responses in both Survey 1 and Survey 2, all checkbox questions were mandatory. Prior to submission, respondents were afforded the option to navigate back to prior pages by selecting "Previous page".

2.1.2 The app

A web app was made specifically for the study in the non-code app builder Glide (Glide, 2023). Access was given by sending the respondents the app hyperlink/QR-code via email. The app content was tailored for individuals who had been prescribed SSRI/SNRI for depression by a physician and were actively using the medication. The content was developed based on the five main causes of non-adherence for users of medication for Mental Health Disorders identified in our previous study. An illustration depicting the content of the app can be found in the Supplementary Material. The information was given in accordance with Norwegian guidelines from the National Online Portal for Health Services in Norway and the Norwegian Directorate of Health. Quality-assured information was provided by entities like the national network of four regional medicines information and pharmacovigilance centers in Norway and the Norwegian Pharmaceutical Product Compendium. The information was conveyed in a manner designed to motivate good adherence and instill greater confidence regarding medication use. The app content was quality-assured by a resource group consisting of a physician (specialization in psychiatry and clinical pharmacology), a postdoctoral psychologist, and four pharmacists with clinical experience: a professor, two associate professors, and a post doctor scientist. Additionally, the resource group included three members from the intended target group, one female and two males. The app underwent three successive releases for quality assurance by the resource group, where each version was reviewed, revised, and then followed by release and subsequent review of a new iteration. After the third version, no major comments were made. Following the revision, the resource group evaluated the app by employing the user version of the mobile Application Rating (uMARS) (Stoyanov et al., 2016) to assess the app. Based on uMARS the app quality mean score was 4.3 out of 5. Response rate was 78%, which included the three members from the target group. The app was ultimately named ADA (AntiDepressantsApp).

2.1.3 Data collection

Recruitment for Survey 1 was carried out by distributing invitations, each containing a hyperlink to Survey 1, through social media and 15 online newspapers during July to October 2023. On Facebook, the invitation was directed to individuals living in Norway, aged 18 years or older and using medication. The invitation was posted on one of the researcher's Facebook-page and Messenger-account with encouragement to share the invitation. Furthermore, the invitation was posted on large Norwegian Facebook groups that encompassed both health related and non-health related subjects. Paid advertising was used on Snapchat, in 14 online newspapers and in an online magazine for the Mental Health Council, to recruit adults aged 18 or older who used antidepressants.

All communication with participants who provided their email addresses in Survey 1 occurred through a dedicated study email account. This communication included providing study information, seeking, and receiving consent, delivering the app access hyperlink/QR-code and hyperlink to Survey 2. In addition, approximately 1 week after the app hyperlink/QR-code was sent, the recipients were sent an email reminder to utilize it. The hyperlink to Survey 2 was sent around 2 months after delivering app access. The data from Survey 2 were collected from September 2023-January 2024.

2.2 Sample size determination

Sample size was calculated based on a two-sided paired *t*-test, using a 5% significance level, 80% power and a standard deviation (SD) of 9. SD was based on our previous OMAS-37 study. To detect

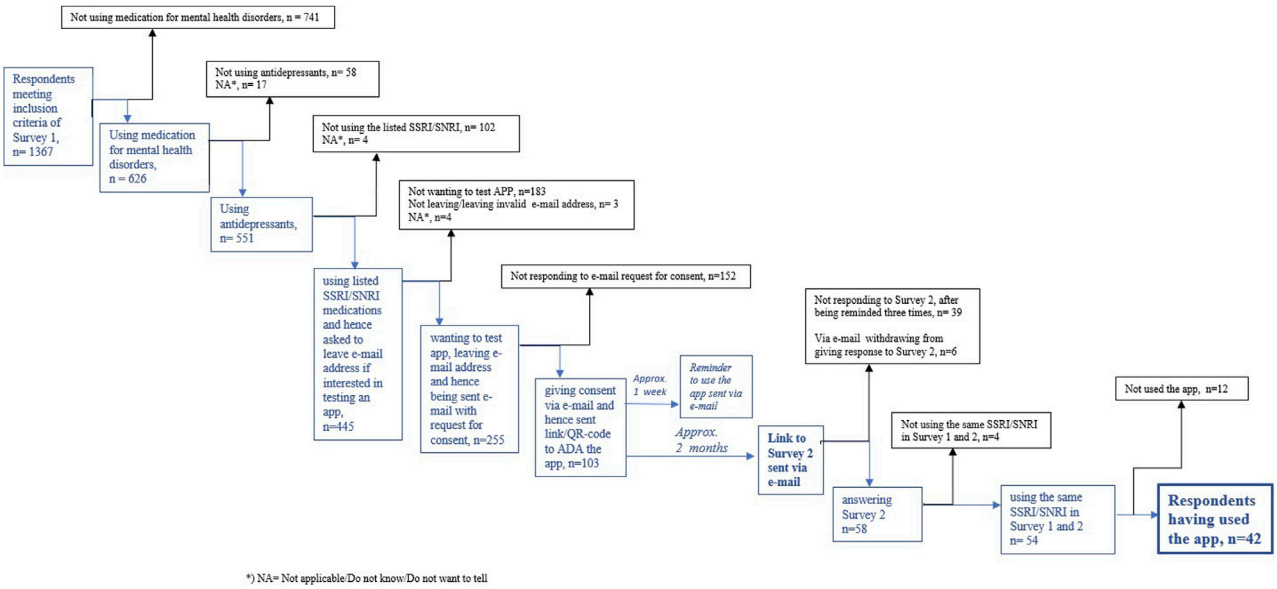

FIGURE 1
Respondents' flowchart.

a change of 3.5 points using a paired design, 62 participants were needed.

2.3 Statistical methods

General features of the study population were described using medians, interquartile range (IQR), numbers and percentages. SSRI/SNRI users were divided into those who did not want to use the app, referred to as non-app users, and those who did use the app and continued to use the same antidepressant after 2 months, referred to as app users. Predefined groups of categorical features were compared between the non-app users and app-users using Pearson's chi-square test. Fisher's exact tests were performed when the sample size of the selected groups was too low for Pearson's chi-square tests. Pre- and post-intervention adherence measurements were compared using the non-parametric Wilcoxon Signed Rank Test. The same test was used *post hoc* for comparing pre- and post-non-adherence scores for each of the specific causes of non-adherence. Despite performing power calculations based on a parametric test (paired *t*-test), we decided to perform a non-parametric test comparing pre- and post-intervention measurements since the conditions of the *t*-test were not fulfilled (normal assumption). OMAS-37 differentiates between a statistical cut-off score for good versus poor adherence by a threshold of 10 points, and a clinical cut-off score by a threshold of two points (Larsen et al., 2022). In this study, the clinical cut-off score of two was utilized, suggesting that a score of 1or 0 indicates good adherence. All data were analyzed by SPSS Statistics version 27, R version 4.3.0, and Microsoft 365 Excel version 2,208. The selected significance level alpha was 0.05. The results are reported in accordance with the ESPACOMP Medication Adherence Reporting Guideline (EMERGE) (De Geest et al., 2018).

3 Results

3.1 Selection and demographic characteristics of respondents

3.1.1 Demographic and medication profile

Survey 1 was answered by 1,367 respondents, of whom 445 indicated that they were using SSRI/SNRIs and were therefore asked to participate in the subsequent study (Figure 1). A total of 103 respondents gave their consent and were given access to the app. Approximately 2 months later, these respondents were sent Survey 2. Of the 58 respondents who completed Suvery 2, 42 were using the same SSRI/SNRI medication during the approximatley 2-month period between answering the two surveys, while also using the app. The demographics (Table 1) revealed that the 445 respondents who reported using SSRI/SNRIs were significantly younger, with a median age of 26 years (IQR 17), compared to the total sample of 1,367, which had a median age of 47 years (IQR 31). The subgroup of SSRI/SNRI users who were using the app (n = 42), had the same median age as the SSRI/SNRI users who did not use the app (n = 403). Male participation was low across all three groups, with 15% for the total sample, 10% for the non-app users, and 5% for the app users.

There were no statistical differences between the app-users and the non-app users in education, number of medical conditions or medication usage. A greater proportion of the non-app users (38%) had one to two conditions compared to the app users (29%), and a greater proportion of the app users (38%) had more than five conditions compared to the non-app users (28%).

3.1.2 Recruitment of app users

The timeline of Survey 1 recruitment, received email addresses, consents, and app access dispatches is shown in Figure 2. The final participant received app access on 5 November 2023.

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TABLE 1 Demographics of the total respondents of Survey 1, the SSRI/SNRIs group not using the app, and SSRI/SNRI group using the app.

Sample		Total *n* = 1367 (100%)	Using listed SSRI/SNRI and not app, *n* = 403 (100%)	Using listed SSRI/SNRI and app, *n* = 42 (100%)
Age in years	Median	47.0	26.0	26.0
	IQR	31.0	17.0	17.0
	Young 18–44 years	647 (47)	330 (82)	39 (93)
	Middle aged 45–65 years	535 (39)	56 (14)	3 (7)
	Young-elderly 66–79 years	163 (12)	15 (4)	0 (0)
	Elderly-Elderly 80–89 years	22 (2)	2 (<1)	0 (0)
Gender	Female	1141 (84)	353 (88)	39 (93)
	Male	206 (15)	41 (10)	2 (5)
	Other	16 (1)	9 (2)	1 (2)
	NA*	4 (<1)	0 (0)	0 (0)
Education level	K-12 education		277 (69)	30 (71)
	Postsecondary education		120 (30)	12 (29)
	NA**		6 (1)	0 (0)
Number of selected medical condition groups	1–2		153 (38)	12 (29)
	3–4		138 (34)	14 (33)
	5 or more		112 (28)	16 (38)
Years of regular medication use	0–1		49 (12)	5 (12)
	2–5		126 (31)	16 (38)
	6 or more		225 (56)	16 (50)
	NA*		3 (1)	0 (0)
Number of daily medications	1–2		203 (50)	21 (50)
	3 or more		197 (49)	21 (50)
	NA*		3 (1)	0 (0)
"Anchor question": To what extent they believe they are following the recommendations from their doctor regarding their medication use	To a very large extent		259 (64)	29 (69)
	To a large extent		123 (31)	12 (29)
	To a limited extent		12 (3)	1 (2)
	To a very limited extent		4 (1)	0 (0)
	NA*		5 (1)	1 (2)
Utilizing pill organizer and/or pre-packed medicine	Yes		184 (46)	21 (50)
	No		214 (53)	21 (50)
	NA*		5 (1)	0 (0)

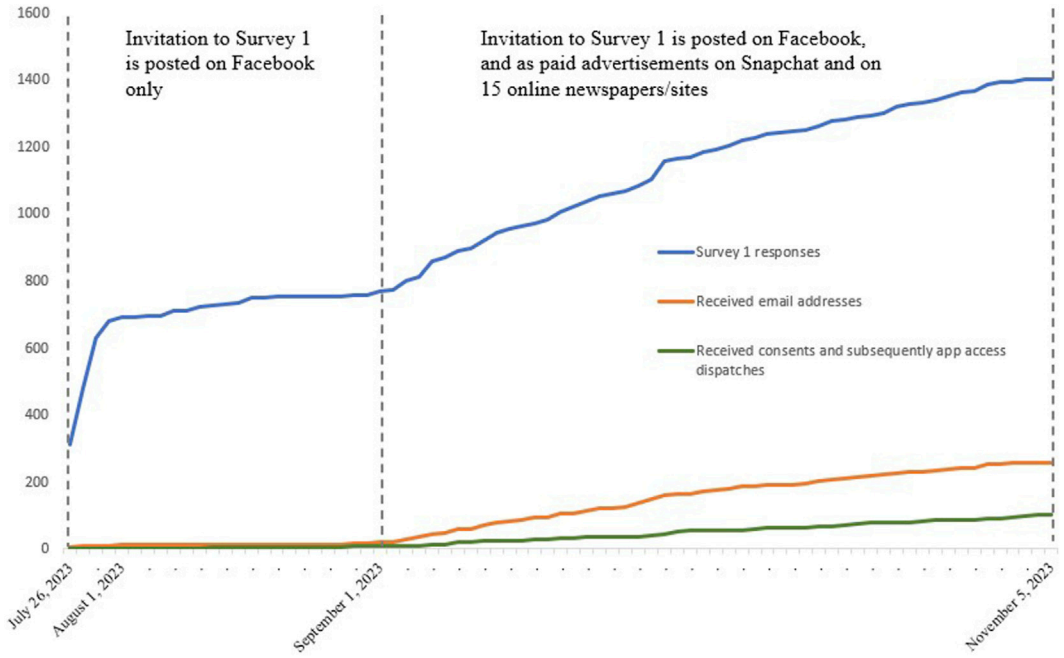

FIGURE 2
Timeline for Survey 1 recruitment and app access dispatches.

3.2 Adherence measurements

Among the app users, 60% (n = 25) had a decrease in non-adherence scores indicating enhanced adherence following access to the app. There was an observed decrease of approximately 39% in the total non-adherence score. A Wilcoxon Signed Rank Test revealed a statistically significant reduction in non-adherence scores, z = 3.57, n = 42, $p < 0.001$, with a medium effect size (r = 0.39). The median adherence score decreased from 8.5 pre-access to 5.2 post access, showing better adherence to medication after access to the app. Before access to the app 79% (n = 33) exhibited non-adherence scores from two points and above, indicating poor adherence. The highest score was 41 points, exhibited by one respondent. After access to the app 67% (n = 28) exhibited scores from two points and above. The highest score was then 25 points, exhibited by one respondent. Of the 40% who did not experience a decrease in non-adherence points following app access, 26% (n = 11) exhibited an increase, suggesting poorer adherence after accessing the app, while 14% showed no change in non-adherence scores before and after accessing the app.

3.3 Changes in the non-adherence score for the 37 causes of non-adherence

Table 2 displays the pre- and post-non-adherence scores for all the 37 causes of non-adherence sorted by highest total non-adherence score pre-access to app. Twenty-nine of the causes had a decrease in non-adherence scoring, meaning improved adherence. The largest changes were the decrease in 10 points for each of the causes "Taking medication is a reminder of being ill" and "Having difficulties taking medication due to specific instructions (e.g., with and without food, in upright position, etc.)". The *post hoc* comparison of the pre- and post-access scores for each cause individually revealed statistically significant differences in median score for the three causes "Taking medication is a reminder of being ill" ($p = 0.02$), "The medication has not had noticeable effect" ($p = 0.01$), and "Need to be able to drive a car" ($p = 0.04$). The causes "Forgot to take the medication" and "Having difficulties taking the medication to specific hours" were the most common causes for non-adherence both pre- and post-access to the app.

3.4 App use and evaluation

Among the 42 respondents 50% reported having utilized the app one to two times, 38% reported having used it three to five times, and 12% reported having used it more than five times. More than two-thirds (69%) of the respondents found the app useful, and 43% reported an increase in confidence in their usage of antidepressants after gaining access to the app (Table 3). The respondents were asked to rate the statement, "Think about the ways you gather information about the medications you use (excluding information from physicians and pharmacies) and compare these with the app". They were asked to provide a rating between one and ten, with one representing reliance solely on other sources, and ten indicating reliance solely on the app. The median score for this statement was found to be 7 (IQR 4), n = 42. A Wilcoxon Signed Rank Test did not give a significant result ($p = 0.14$), indicating that there was no significant preference for the app over other sources of information (scoring 5.5 and above). The app had no reminder function, so the respondents were also asked whether they were using any reminders on their mobile phone: 12% were using another reminder app, 48%

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TABLE 2 Pre- and post-access non-adherence scores and changes for the 37 causes of non-adherence. Arranged by highest total non-adherence score pre-access. *) Statistically significant changes.

Causes of non-adherence	Total non-adherence score pre-access to the app	Total non-adherence score post-access to the app	Difference in total non-adherence score pre-and post-access to the app
Forgot to take the medication	34	30	4
Having difficulties taking the medication to specific hours	32	24	8
Taking medication is a reminder of being ill	21	11	10 (p = 0.02)*
Cannot stand taking medication	19	16	3
Having difficulties taking medication due to specific instructions (e.g., with/without food, in upright position, etc.)	19	9	10
The medication was sold out/unavailable at the pharmacy	17	10	7
Feel stigmatized or ill by having to use the medication	14	11	3
Do not want others to know that I am taking medication	14	11	3
Feeling better	14	9	5
Financial reasons	14	7	7
Have no medication left	13	9	4
Fear of adverse drug reactions	13	5	8
Using many drugs simultaneously	13	4	9
Do not feel ill	11	6	5
The same type of medication has been used before without having good/satisfactory effect	11	5	6
Feel worse when taking the medication	11	2	9
The medication has not had noticeable effect	11	2	9 (p = 0.01)*
Reckon makes no differences whether using the medication or not	9	3	6
Incompatible with lifestyle	8	10	−2
Fear of becoming addicted to the medication	8	4	4
Feel clever when taking less than recommended by the physician	8	3	5
Need to be able to drive a car	8	3	5 (p = 0.04)*
Belief the medication is harmful/toxic, and/or cannot tolerate it	7	5	2
Am against medication as a matter of principle	5	4	1
Prefer alternative treatment	5	4	1
Difficulties accessing a pharmacy	4	2	2
Misunderstandings related to generic medication (medication with same content but from different manufacturers)	3	3	0

(Continued on following page)

TABLE 2 (*Continued*) Pre- and post-access non-adherence scores and changes for the 37 causes of non-adherence. Arranged by highest total non-adherence score pre-access. *) Statistically significant changes.

Causes of non-adherence	Total non-adherence score pre-access to the app	Total non-adherence score post-access to the app	Difference in total non-adherence score pre-and post-access to the app
Practical reasons (e.g., difficulty opening packaging or pressing tablets out of blister packs, or splitting/crushing the tablets)	3	2	1
Difficulties taking the medication due to disability or impaired vision	3	0	3
Little or no information from physician/pharmacy/other health personnel about how to use the medication	2	2	0
Being pregnant	2	1	1
Influenced by media/internet/friends/family/others	2	1	1
Did not understand the physician/pharmacist's instructions	0	1	−1
Breastfeeding	0	1	−1
Forgot how to take it	0	0	0
Ethical/religious reasons	0	0	0
Reluctance to visit a pharmacy due to the corona pandemic	0	0	0

TABLE 3 Respondents' utilization and evaluation of the app.

Questions		*n* = 42 (100%)
How frequently would you estimate you have utilized the app?	1–2 times	21 (50)
	3–5 times	16 (38)
	More than five times	5 (12)
How would you assess the usefulness of the app for your needs?	No usefulness	13 (31)
	Some usefulness	13 (31)
	Moderate usefulness	10 (24)
	Great usefulness	6 (14)
Has your confidence in using antidepressants increased after accessing the app?	No difference	24 (57)
	Somewhat safer	13 (31)
	Much safer	5 (12)

used the reminder function of the mobile phone, and 40% did not use any reminder on the mobile phone.

4 Discussion

There are many apps for mental health disorders like depression, but few of these seem to be supported by solid scientific evidence, regarding both evidence-based guidelines and statistically significant adherence improvements (Wasil et al., 2019; Ng et al., 2020; Eis et al., 2022). In addition, many apps attempt to cover too many topics, resulting in limited and insufficient information on each topic (Martinengo et al., 2022). In this study the app was tailored for SSRI/SNRI medication users based on our previous findings of main causes of non-adherence for this group. A statistically significant reduction of non-adherence score following access to the app was found, with a medium effect size - indicating improvement in adherence to medication after access to this app. The non-adherence scores decreased for 60% of the app users. Tailoring an app for specific medication users based on main causes of non-adherence presents a new approach in enhancing adherence to medication. This would be beneficial especially for patient groups that are facing numerous challenges with adherence and treatment, such as those using antidepressants.

4.1 Main findings and clinical implications

Improving adherence to antidepressants can enhance patients' quality of life and diminish resource use in the healthcare system (Ta et al., 2021). However, patients' reasons for non-adherence are complex (World Health Organization, 2003; Horne et al., 2019) and when developing interventions, it is important to address the main causes for whom the intervention is designed. This study has tailored an app for SSRI/SNRI medication users, after the main causes of non-adherence for this group were identified by using OMAS-37. Access to the app resulted in a statistically significant reduction in non-adherence scores, and a 12 percentage-point decrease in number of app users that scored equivalent with poor adherence. The most

common non-adherence cause, both before and after access to the app, was "Forgot to take the medication". This cause experienced a decrease of only 12%. This was anticipated, as although this issue was addressed in the app, a duration of 2 months is typically too short a duration to alter habits. There was no significant change in use of pill organizer pre- and post-access to the app. Non-adherence was improved in 29 of the 37 causes of non-adherence, where statistical significance was found for three of the causes, all three of which were directly addressed in the app. Although this was an explorative *post hoc* analysis, these results could be useful in future studies for generating hypotheses regarding the app-effect on individual causes. The main comments from the 12 respondents that had access to the app and did not use it, and the 10 respondents answering "Other" to the question "Why was the app of no or only little use to you?" - was that they already had knowledge of the information given in the app. The app users rated their reliance on the app compared to other sources of information (besides information given by physicians and pharmacies). The results showed a preference for the app, although not statistically significant. There were no significant demographic differences between the non-app users and the app users, suggesting that the app users are representative of SSRI/SNRI users. Given the vast number of individuals using SSRI/SNRI medication, it was expected that there would be variation in knowledge levels, and the app is tailored to those with a lower level of knowledge. Therefore, despite the fact that the app is designed for patients in the implementation phase of medication adherence–those actively using medication - it is plausible that not all users will discover new information within the app. The varied interest in accessing the app (58 out of 445) could likely be attributed as much to individual enthusiasm for testing new things as to challenges associated with the use of antidepressants. While only half of the app users felt more confident in their use of antidepressants after having accessed the app, two-thirds of the participants rated the app as useful to them. Given the number of overall antidepressant users, the potential availability of the app to a broader population could hold significant clinical implications, suggesting a substantial impact on a large number of patients. In Norway, between six and seven percent of females aged 20 to 25 used antidepressants in 2020, with a vast majority of them utilizing SSRIs (NIPH, 2024). Therefore, even if the app were to be exclusively used by young females, as many of the respondents in this study were, the app could have a significant impact.

In addition, comparable app tailoring approaches may be implemented to assess their efficacy in improving medication adherence in other patient groups. Our findings are consistent with previous research that, although there is mixed evidence, regards mHealth interventions to be beneficial (Anglada-Martinez et al., 2015; Hamine et al., 2015).

4.2 Methodological considerations

It is reasonable to posit that the age discrepancy between the overall sample and the users of SSRI/SNRI medication may be attributed to the likelihood that Snapchat served as one of the platforms from which many app users likely were recruited. The paid advertisements on Snapchat and online newspapers/sites were much more effective in recruiting potential app users compared to postings on Facebook alone, as can be seen in Figure 1. In 2022, 86% of women and 82% of men aged between 18 and 29 years in Norway were using Snapchat, whereas it was less popular among those aged 50 years and older (Statista, 2023). A challenge was associated with the algorithms of specific social media platforms. We sought to avoid the algorithms from singling out individuals responding exclusively about antidepressant usage; instead, we extended the invitation to all medication users. Consequently, we anticipated that many respondents might not meet the inclusion criteria. As illustrated in Figure 1, out of the 1,367 respondents, only 445 met the inclusion criteria. Out of the 445 individuals meeting the inclusion criteria, only 255 expressed a willingness to participate in using the app. This reluctance could partly be due to the loss of anonymity upon participation. Among the 255 who provided their email addresses, only 40% responded with consent, a figure somewhat lower than anticipated. This lower response rate might be associated with less frequent usage of their private email accounts among young people, suggesting that utilizing social media for all of the correspondence could have been more effective (Janssen and Carradini, 2021). Among the 103 individuals who gave consent, 56% responded to Survey 2, a result in line with expectations for surveys of this nature.

The recruitment period was not long enough to recruit the number of participants (n = 62) necessary based on the power calculations. This was due to the given time frame. However, the final achieved sample of 42 was sufficient to show a significant reduction in non-adherence with medium effect size. Previous studies indicate that non-adherence increases over time of medication use (World Health Organization, 2003; Khan and Socha-Dietrich, 2018). The majority of participants (88%) had been using their medications for more than 2 years, and all had been using the SSRI/SNRI medication for at least the 2-month duration of the study. Despite this, a statistically significant increase in adherence was observed, which could further corroborate the effectiveness of the app. The hyperlink to Survey 2 was distributed 2 months after the participants gained access to the app. The trial period had to be long enough for changes to take place, but not so extensive that the participants would lose interest in the study. The app could primarily motivate change by providing information, advice, and guidance, and 2 months was considered long enough for motivational changes to take place.

The validated Mobile Application Rating Scale (MARS) (Terhorst et al., 2020) requires mobile mHealth knowledge and training. Consequently, the end-user version, uMARS, was chosen for the validation of the app by the resource group. Based on uMARS the App Quality Mean Score was 4.3 out of 5 from the resource group. The main reason for not scoring 5 was that the app did not have any interactivities or customizations, and thus scored very low in this section of uMARS. Interactivities or customizations can be created to a certain extent in Glide but were not developed in this project. Implementing these features in a web app could also interfere with the app users' anonymity. A significant advantage in app development lies in the simultaneous testing of functionality alongside quality assurance for content. Consequently, the feasibility was quality assured by the resource group concurrently with content assurance.

4.3 Limitations

This study was a single group study, and in a single pre-post intervention design one cannot easily control for extraneous variables or

determine causality. When conducting an intervention, the Hawthorne effect, which suggest that being examined in itself brings about behavioral changes, has to be taken into consideration. While this effect is commonly acknowledged, still little seems to be known about its mechanisms or magnitude (McCambridge et al., 2014). The effect size of accessing the app was medium, suggesting that this is likely not solely due to the Hawthorne effect. One potential bias is that while self-reporting is a frequently used method for assessing adherence due to its low cost, flexibility, discretion, and time efficiency, it tends to overestimate medication adherence. This overestimation can be attributed to social desirability bias, a phenomenon where individuals respond in a manner they believe will be viewed as socially acceptable or favorable, rather than providing responses that accurately reflect their true thoughts, feelings, or behaviors (Lehmann et al., 2014). Nevertheless, since this bias is presumed to be consistent in both pre- and post-surveys due to the parried test design, any changes in scores may not inherently reflect a bias. Recruitment via social media for patients using SSRI/SNRI could be less suitable for older patients. The median age for respondents in this study was 26 years IQR 17). In addition, literature indicates that women are more likely to seek health-related information online than men and are more inclined to respond to online inquiries (Smith, 2008; Bidmon and Terlutter, 2015; Wu et al., 2022). In this study 93% of the app users identified as women. Further studies are therefore required to determine whether the findings also apply for older adults and to men. Possible long-term effects on non-adherence could not be assessed, as the pre-post access part period of the study was restricted to 2 months.

4.4 Conclusion

This study describes the testing of a tailored app to enhance medication adherence for users of antidepressants, utilizing the OMAS-37 adherence assessment tool. Access to the app proved to enhance adherence to medication. This study is the first to use OMAS-37 as an adherence assessment tool for an intervention. Further studies are required to evaluate the applicability of the app to a broader range of antidepressants users, encompassing those in the initiation phase of medication adherence. Furthermore, to determine whether a comparable tailoring approach can be applied to other patient groups. The app is intended as an easily accessible supplement to the information and advice provided by prescribing physicians and dispensing pharmacists.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Norwegian Ethics Committee (REK). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

RL: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Writing–original draft. KH: Writing–review and editing. MS: Formal Analysis, Methodology, Writing–review and editing. CJ: Writing–review and editing. TK: Writing–review and editing. LH: Conceptualization, Formal Analysis, Investigation, Methodology, Supervision, Writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. The PhD-project of RL is funded through a scholarship from Ministry of Education and Research to OsloMet. The contributions from the other authors are funded as a part of their R&D-positions at Oslo Metropolitan University and Akershus University Hospital.

Acknowledgments

The authors extend their gratitude to the Resource group for their invaluable contribution to the quality assurance and testing of the app.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1379700/full#supplementary-material

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 22 May 2024
DOI 10.3389/fphar.2024.1362168

OPEN ACCESS

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RECEIVED 27 December 2023
ACCEPTED 16 April 2024
PUBLISHED 22 May 2024

CITATION
Barnestein-Fonseca P, Guerrero-Pertiñez G, Gúzman-Parra J, Valera-Moreno E and Mayoral-Cleries F (2024), Is it possible to diagnose therapeutic adherence in mild cognitive impairment and dementia patients in clinical practice?
Front. Pharmacol. 15:1362168.
doi: 10.3389/fphar.2024.1362168

Is it possible to diagnose therapeutic adherence in mild cognitive impairment and dementia patients in clinical practice?

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Background: Non-adherence is common and contributes to adverse health outcomes, reduced quality of life, and increased healthcare expenditure. The objective of this study was to assess the diagnostic validity to estimate the prevalence of non-adherence in patients with mild cognitive impairment (MCI) and dementia using two self-reported methods (SRMs) that are useful and easy in clinical practice, considering the pill count as a reference method (RM).

Methods: The cohort study was nested in a multicenter randomized controlled trial NCT03325699. A total of 387 patients from 8 health centers were selected using a non-probabilistic consecutive sampling method. Inclusion criteria were as follows: a score of 20–28 points on the Mini-Mental State Examination (MMSE); older than 55 years; taking prescribed medication; and are in charge of their own medication use. Participants were followed up for 18 months after the baseline visit, i.e., 6, 12, and 18 months. Variables related with treatment adherences were measured in all visits. The variables included age, sex, treatment, comorbidities, and the MMSE test. Adherences included pill counts and Morisky–Green test (MGT) and Batalla test (BT) as SRMs. Statistical analysis included descriptive analysis and 95% confidence intervals (CIs). The diagnostic validity included the following: 1) open comparison statistical association between SRMs and RMs and 2) hierarchy comparison: the RM as the best method to assess non-adherence, kappa value (k), sensitivity (S), specificity (Sp), and likelihood ratio (PPV/PPN).

Results: A total of 387 patients were recruited with an average age of 73.29 years (95% CI, 72.54–74.04), of which 59.5% were female. Comorbidities were 54.4% HTA, 35.9% osteoarticular pathology, and 24.5% DM. The MMSE mean score was 25.57 (95% CI, 25.34–25.8). The treatment adherence for the RM oscillates between 22.5% in the baseline and 26.3%, 14.8%, and 17.9% in the follow-up visits. For SRMs, the treatment adherence oscillates between 43.5% in the baseline and 32.4%, 21.9%, and 20.3% in the follow-up visits. The kappa value was statistically significant in all the comparison in all visits with a score between 0.16 and 035. Regarding the diagnostic validity, for the MGT, the sensibility oscillated between 0.4 and 0.58, and the specificity oscillated between

0.68 and 0.87; for the BT, the sensibility oscillated between 0.4 and 0.7, and the specificity oscillated between 0.66 and 0.9; and when both tests were used together, the sensibility oscillated between 0.22 and 0.4, and the specificity oscillated between 0.85 and 0.96.

Conclusion: SRMs classify non-adherent subjects correctly. They are very easy to use and yield quick results in clinical practice, so SRMs would be used for the non-adherence diagnosis in patients with MCI and mild dementia.

KEYWORDS

cognitive impairment, mild dementia, treatment adherence, adherence indirect test, self-reported methods

1 Introduction

The global demographic landscape is undergoing a profound shift, marked by an undeniable surge in cognitive conditions in the aging population across numerous countries. In Europe, this demographic transformation not only heralds major societal shifts but also carries substantial economic implications (WHO, 2007). As the prevalence of cognitive conditions increases within this aging cohort, the spotlight is cast on therapeutic adherence, a critical yet elusive aspect of managing chronic diseases in older adults. The implications of poor adherence reverberate across adverse health outcomes, diminished quality of life, and an alarming escalation in healthcare expenditure (Cutler et al., 2006)

Medication adherence, referring to the level of participation in terms of individuals taking medications as prescribed, is recognized as a public health problem, especially important in the treatment of chronic diseases. Older people are more likely to have concomitant chronic diseases, increasing the number of medications they take, which is a key risk factor for non-adherence. After half a century of adherence research and increased knowledge about the more than 200 factors known to influence adherence, adherence rates remain relatively unchanged (Vrijens et al., 2012; Conn and Ruppar, 2017; Ellis et al., 2023). Thus, although rates of adherence in clinical trials may be high (70%–90%), in clinical practices, they vary between 10% and 40% (WHO, 2015; Bhattarai et al., 2020). Medication adherence is essential for people to receive the full therapeutic benefits of prescribed medications, and its lack is associated with considerable morbidity and mortality. While patient behavior is important in medication non-adherence, medication adherence and its improvement are the result of complex systems that include not only individuals but also healthcare settings, healthcare policies, and healthcare professionals (Ellis et al., 2023). Effectively managing therapeutic adherence in individuals with mild cognitive impairment (MCI) and dementia is a complex task crucial for optimizing patient outcomes. In clinical practice, various methods are employed to assess adherence, each posing its unique set of challenges and opportunities.

Common methods employed to measure adherence, such as patient diaries, pill counts, and the analysis of computerized pharmacy records, bring both utility and limitations to the forefront (Osterberg and Blaschke, 2005). Pill count, while a straightforward approach, is constrained to oral medications and merely confirms the removal of the correct number of pills, offering no insights into ingestion, dosage, or frequency (Cutler et al., 2006). Simultaneously, the analysis of pharmacy records sheds light on refill patterns but remains blind to the actual ingestion or pattern of use. In the clinical setting, reliance on any single method of assessment proves potentially misleading. Therefore, the imperative emerges: it is crucial to determine the magnitude of non-adherence as the initial step toward developing targeted strategies to correct these behaviors.

Direct patient interviews and caregiver reports emerge as commonly used methods to gauge adherence. These approaches provide valuable subjective insights into medication adherence, offering a firsthand account of the patient's experience. However, these methods may be limited by recall bias and the cognitive capacity of the patient, thus introducing potential inaccuracies in the assessment (Clifford et al., 2006). These questionnaires, adapted and validated for the Spanish population, are commonly used for chronic conditions such as hypertension and hyperlipidemia. The Morisky–Green test (MGT) measures the attitude toward treatment, while the Batalla test (BT) provides valuable information about the patients' understanding of their illness, adding another layer to the multifaceted landscape of adherence assessment (Batalla et al., 1984; Morisky et al., 1986). In addition to interviews and caregiver reports, observing the use of practical tools like pill organizers or blister packs can offer indirect evidence of adherence behavior. These visual cues provide clinicians with tangible information about the patient's ability to follow prescribed medication regimens and may offer insights into routine adherence patterns (Steiner and Prochazka, 1997).

Navigating the challenges of diagnosing therapeutic adherence in individuals with cognitive impairment demands a multifaceted approach. By acknowledging the limitations of subjective measures and exploring indirect indicators, clinicians can work toward a more comprehensive understanding of adherence behaviors in this unique patient population.

The objective of this study was to assess the diagnostic validity to estimate the prevalence of non-adherence in patients with MCI and dementia using two self-reported methods (SRMs) that could be useful and easy in clinical practice, considering the pill count as the reference method (RM).

2 Materials and methods

2.1 Study design

The cohort study was nested in an international multicenter randomized controlled trial SMART4MD: NCT03325699. The

SMART4MD trial was approved by the Malaga Provincial Ethical Committee (30/06/2016). The protocol of the study was broadly described in a previous article (Anderberg et al., 2019).

We used the CONSORT reporting guidelines (Schulz et al., 2010).

2.2 Setting, participants, recruitment, and follow-up

A total of 387 patients with MCI or mild dementia were chosen, using a non-random consecutive sampling method for the SMART4MD trial, from 8 primary care centers (PCCs) and memory unit in Málaga, Spain.

The inclusion criteria were as follows: a score of 20–28 points on the Mini-Mental State Examination (MMSE) whether or not a diagnosed neurodegenerative disease is present; a professional assessment of the patient's own experience of memory problems over a substantial period of time (more than 6 months); older than 55 years; taking prescribed medication; and are in charge of their own medication use. The exclusion criteria were as follows: a terminal illness with less than 3 years of expected survival; score above 11 on the Geriatric Depression Scale (GDS-15) (Yesavage et al., 1982a); or have another known significant cause of disease as an explanation for cognitive impairment such as abuse and other psychiatric diagnoses such as bipolar disorders, schizophrenia, and developmental disorders. These criteria were all ascertained from the patient's clinical record.

Participants were identified from a cohort of people with cognitive impairment that has been present for more than 6 months and who met all the study eligibility criteria. Participants were under primary care services and secondary care services, such as those who are being followed up in memory clinics, outpatient clinics, day hospitals or other components of specialist mental healthcare, geriatric medicine, and neurology services. Participants were also identified from patient databases such as those integrated in the center networks. The identification process consisted of screening using information gathered from medical notes, clinic records, and/or clinical consultations for initial eligibility based on inclusion criteria.

After a brief explanation of the study design and research goals, participants were invited to participate in the study, and an appointment with the researchers was scheduled. The participants were provided with all the information they need to make an informed decision via a participant information sheet. They were given a cooling-off period of at least 24 h between informally agreeing to participate in the study and being invited to formally consent in a meeting with the research team.

At the first visit, the researcher explained the study in detail and answered any questions the patient or caregiver may have. The patient's eligibility was confirmed, and their ability to consent was assessed. Once consent was officially given by signing an informed consent form by all parties, the subject was randomized into either the intervention or the control group for the SMART4MD trial, and a baseline visit was carried out, where all the variables were measured (this included the assessment of the treatment adherence, AT).

An 18-month follow-up was conducted after the initial visit: visit 0 (baseline), visit 1 (at 6 months), visit 2 (at 12 months), and visit 3 (at 18 months). In all visits, adherence by pill counts and self-reported adherence methods were measured.

2.3 Outcomes

2.3.1 Treatment adherence

Adherence to a medication regimen is generally defined as "the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a healthcare provider" (Lehane and McCarthy, 2009). Adherence was measured by the dose/pill count as a RM, alongside self-reported adherence methods to test the diagnostic validity.

Pill count is the number of pills or doses taken divided by the number of pills or doses prescribed, multiplied by 100 (expressed as a percentage) (Brian Haynes et al., 1980; Hansen et al., 2009). Sackett et al. (1975) suggested that good adherence is considered when the result of counting is between 80% (20% loss of doses/pills) and 110% (the patient consumes 10% more doses/pills) of doses/pills prescribed. This cutoff point was selected for consistency with other studies (Hansen et al., 2009).

Due to the polypharmacy presented in the sample, a maximum of two drugs for each participant were selected to measure the adherence. These drugs were selected following the prevalence of illness and comorbidity. In our case, medications for MCI or dementia were the most common, excluding dietary supplements, followed by hypertension and diabetes mellitus.

2.3.2 Self-reported adherence methods

Two SRMs were selected to evaluate treatment adherence: the MGT (Hansen et al., 2009) and the BT (Batalla et al., 1984). These questionnaires that assess adherence are normally used for chronic conditions and have been adapted and validated for the Spanish population for conditions such as hypertension and hyperlipidemia (Piñeiro et al., 1997; Pineiro et al., 1997).Furthermore, the MGT is used in the Andalusian Health Service as a screening test for adherence for some chronic conditions.

2.3.3 Morisky–Green test

We measured the attitude toward treatment using the MGT (Morisky et al., 1986):

(1) Do you ever forget to take your medication?
(2) Are you careless at times about taking your medication?
(3) When you feel better, do you sometimes stop taking your medication?
(4) Sometimes, if you feel worse when you take the medication, do you stop taking it?

We considered good adherence when all four questions were answered suitably.

2.3.4 Batalla test

The BT provides information about the patients' understanding of their illness (Batalla et al., 1984). The questions, adapted to the condition, used in this study were as follows:

TABLE 1 Sociodemographic and clinical profile.

Number of subjects	387
Gender % (n)	
Male	40.5% (156)
Female	59.5% (229)
Age (mean, 95% CI)	73.29 (95% CI, 72.54–74.04)
Education level % (n)	
Elementary school	71.7% (276)
Secondary school	18.4% (71)
Higher education	8.8% (34)
Civil status % (n)	
Unmarried	4.2% (16)
Married	64.2% (247)
Common law partner	1.3% (5)
Divorced	3.6% (14)
Widowed	26.5% (102)
Living arrangement % (n)	
Single	20.8% (80)
Spouse/common law	58.2% (224)
Children	15.3% (59)
Other	5.5% (21)
Smoking habit % (n)	
Non-smokers	57.3% (217)
Smokers	5.3% (20)
Ex-smokers	37.5% (142)
MMSE (mean, 95% CI)	25.57 (95% CI, 25.34–25.8)
GDS (mean, 95% CI)	3.29 (95% CI, 2.99–3.6)

CI, confidence interval; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale.

(1) Is MCI or dementia a lifelong disease?
(2) Can you control this disease with medication or cognitive exercises?
(3) Mention one or more organs that can get damaged by your condition.

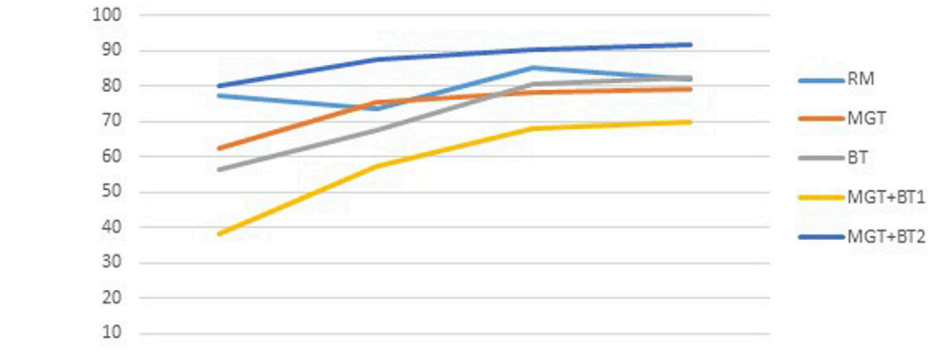
We considered good adherence when the patient answered these three questions suitably.

2.3.5 Co-variables

The co-variables included sociodemographic variables (age, sex, civil status, and educational level) and clinical variables (smoking habits, number of cigarettes, treatment, and comorbidity).

Cognitive function was measured by the MMSE (Folstein et al., 1975). It is also used to estimate the severity and progression of cognitive impairment and to follow the course of cognitive changes in an individual over time. To be included in the trial, individuals must score between 20 and 28 points on the scale. The use of an MMSE cutoff value of 28 is not common and has some risks but has been used in other studies (Doody et al., 2009). O'Bryant et al. (2008) showed that an MMSE cutoff score of 28 provided the best sensitivity and specificity for detecting mild dementia in a population with self-reported memory complaints. Medical history of persons with MCI includes family antecedents such as Alzheimer's disease, Parkinson's disease, other dementing illness, diagnosis of dementia, type of dementia, if they have undergone a magnetic resonance imaging scan, and if they are using any pharmacological treatment for their dementia.

The GDS-15 (Yesavage et al., 1982a) was used as an exclusion criterion to screen for depression. Participants scoring above 11 on the GDS will be excluded. The GDS is commonly used as a routine part of a comprehensive geriatric assessment. The grid sets a range of 0–4 as "normal," 5–8 as



	Visit 1	Visit 2	Visit 3	Visit 4
RM	77,5	73,4	85,2	82,1
MGT	62,3	75,6	78,1	79,1
BT	56,5	67,6	80,4	82,6
MGT+BT1	38,2	57,5	68,2	69,8
MGT+BT2	79,9	87,7	90,4	91,9

FIGURE 1
Evolution of the adherence treatment percentage after 18 months of monitoring % of patients. RM: pill count; MGT: Morisky–Green test; BT: Batalla test; MGT + BTl: adherent patients' diagnoses using at least two methods; MGT + BT2: adherent patients' diagnoses using the two methods.

"mildly depressed," 9–11 as "moderately depressed," and 12–15 as "severely depressed."

The health-related quality of life (QoL) was measured using the total score of the QoL-AD questionnaire (Logsdon et al., 2002; Thorgrimsen et al., 2003; Logsdon et al., 2002; Logsdon and Gibbons, 1999) and EuroQoL-5D. The QoL-AD questionnaire is a 13-item measure, which has been specifically designed to measure the QoL in individuals with dementia from the perspective of both the patient and the informal carer. It includes questions related to the interpersonal, environmental, functional, physical, and psychological status of the person with dementia, and thus, it is a global measure for QoL. QoL-AD will be assessed via an interview with the patient and via self-completion by informal carers. The EuroQoL-5D questionnaire is a self-completion questionnaire that consists of 5 questions plus a scale where the participant rates their health state on a scale of 0–100. EQ-5D has been shown to correlate well with QoL-AD, indicating that the two measures are compatible and can be used side by side (Thorgrimsen et al., 2003).

2.4 Statistical analysis

A descriptive analysis of all the study variables was conducted, calculating the mean, median, standard deviation, total frequency, and relative frequency of each category; 95% confidence intervals were calculated for the means and proportions.

We considered the dose/pill count to be the RM for assessing adherence. We performed two types of analytical strategies (Bautista Cabello Lopez and Pozo Rodríguez, 1997) to evaluate their validity to diagnose adherence: 1) open comparison to explore the existence of a statistical association between each self-reported questionnaire and the RM using the chi-squared test and 2) hierarchy comparison in which we assumed that the RM is the best method to assess non-therapeutic adherence. We then calculated the kappa value, k (as a measure of agreement between the reference method and each self-reported test), the basic diagnostic descriptors (sensitivity and specificity), and their combination (likelihood ratio: PPV and PPN) for each of the SRMs. To achieve this, we elaborated 2 × 2 tables and calculated the following indicators of diagnostic validity for each test: sensitivity = true positive/(true positive + false negative); specificity = true negative/(true negative + false positive); positive likelihood ratio = sensitivity/(1-specificity); and negative likelihood ratio = (1-sensitivity)/specificity.

A 5% significance level ($\alpha = 0.05$) and the SPSS statistical package, version 25.0, were used to run the analysis described.

3 Results

3.1 Baseline characteristics

The sample consisted of 387 patients with MCI or mild dementia, of which 59.5% were female, with a mean age of 73.29 years (95% CI, 72.54–74.04), with a low educational level (71.1% with elementary school-level education). At the time of the study, 37.5% were ex-smokers, and 57.3% had never smoked (Table 1). HTA (54.4%), osteoarticular pathology (35.9%), and DM (24.5%) were the more prevalent comorbidities.

Cognitive status: The MMSE mean score was 25.57 (95% CI, 25.34–25.8), and the GDS mean score was 3.29 (95% CI, 2.99–3.6). Among the participants, 29.2% had family antecedents of dementia, and 61% were in their parents. Of these, 30.9% had Alzheimer's disease, 38.3% did not know the kind of dementia, 5.7% had vascular dementia, 2.3% had dementia with Lewy bodies, and 1.1% had frontotemporal dementia.

Drug therapy: Among the participants, 39.5% had medication for dementia, and the rest had prescription at least for another

TABLE 2 Open comparison of adherence prevalence between the self-reported methods and the reference method using the chi-squared test.

	Baseline	6 months	12 months	18 months
Pill count	77.5% (77.08–77.9)	73.4% (72.9–73.9)	85.2% (84.85–85.55)	82.1% (81.7–82.48)
Morisky–Green test (MGT)	62.3% (61.8–62.78) $p \leq 0.001$	75.6% (75.17–76.07) $p = 0.006$	78.1% (77.69–78.51) $p \leq 0.001$	79.7% (79.3–80.1) $p \leq 0.001$
Batalla test	56.5% (56–57) $p \leq 0.001$	67.6% (67.13–68) $p \leq 0.001$	80.4% (80–80.8) $p = 0.002$	82.6% (82.2–82.9) $p \leq 0.001$
MGT + BT	79.9% (79.5–80.3) $p \leq 0.001$	87.8% (87.47–88.13) $p = 0.039$	90.4% (90.1–90.7) $p = 0.001$	91.9% (91.6–92.1) $p = 0.001$

chronic condition, i.e., 40.2% for HTA and 20.3% for DM. These drugs were considered to measure the adherence in the baseline and in the follow-up visits. Regarding medication for dementia, 47.5% of the participants with a prescription had acetylcholinesterase inhibitors, 25.4% had antidepressants, 12.4% had memantine hydrochloride, 4% had antipsychotics, and 12.4% used another treatment for cognitive impairment or dementia.

Quality of life: The total QoL-AD score was 33.96 (95% CI, 33.32–34.6). For EuroQoL-5D, the subjects reported no problem with mobility (69.4%), self-care (91.9%), and daily activities (80.5%). Furthermore, 46.5% reported no pain or discomfort, and 43.4% had moderate pain or discomfort. Regarding anxiety/depression, 64.7% reported no symptoms, 30% felt moderately anxious or depressed, and 4.4% were extremely anxious or depressed.

3.2 Follow-up

V2: A total of 283 patients (73.3%) of the 386 included in the study attended the first follow-up visit 6 months after inclusion. A total of 103 patients did not attend this visit, i.e., 22.34%. A total of 23 patients were dropped out for this visit because they were unable to attend the visit (19) or were unreachable (4). A total of 80 participants (20.72%) were dropped out for the study because they did not want to continue in the study, were excluded because they did not meet the inclusion criteria, or were deceased.

V3: A total of 250 patients (64.8%) of the 386 included in the study attended the second follow-up visit 1 year after inclusion. A total of 136 patients did not attend this visit, i.e., 35.2%. A total of 28 patients were dropped out for this visit because they were not able to attend the visit (25) or were unreachable (3). The dropout rate for the study increased by 28 participants, resulting in a dropout rate of 27.9% (108), because the participants did not want to continue in the study, were excluded because they did not meet the inclusion criteria, or were deceased.

V4: A total of 223 patients (57.8%) of the 386 included in the study attended the second follow-up visit 1 year after inclusion. A total of 163 patients did not attend this visit, i.e., 42.2%. A total of 42 patients were dropped out for this visit because they were not able to attend the visit (38) or were unreachable (4). The dropout rate for the study increased by 17 participants, resulting in a dropout rate of 32.3% (125), because the participants did not want to continue in the study, were excluded because they did not meet the inclusion criteria, or were deceased.

3.3 Treatment adherence and diagnosis validity of the self-reported test

Figure 1 shows the evolution of the treatment adherence during the study measured by the different reported methods: pill count as RMs, MGT, BT, and the combination or both (MGT + BT1 and MGT + BT2).

In the baseline, non-adherence prevalence using the RM was 22.5%. The non-adherence prevalence for the self-reported adherence methods was 37.7% for the MGT and 43.5% for the BT. The MGT detected 39 of the 67 patients classified as non-adherent using the RM, while the BT found 42. Considering both tests together and when the subject is classified as non-adherent for both tests (MGT + BT2) in the baseline, 24 non-adherent patients were detected. Finally, when we consider both tests together and when the subject is classified as non-adherent for at least one of the tests (MGT + BT1), 54 non-adherent patients were detected.

The chi-squared test showed a significant association between the RM and the SRMs (Table 2). The measure of agreement by kappa (k) between the MGT and the RM was 0.215 ($p \leq 0.001$), for the BT, k = 0.25 ($p \leq 0.001$), and when we considered both tests together, k = 0.262 ($p \leq 0.001$) for MGT + BT2 and k = 0.214 ($p \leq 0.001$) for MGT + BT1.

In visit 1, 6 months after inclusion, the non-adherence prevalence using the RM was 26.2%. The non-adherence prevalence for the self-reported adherence methods was 24.2% for the MGT and 32.4% for the BT. The MGT detected 24 of the 61 patients classified as non-adherent using the RM, while the BT found 33. Considering both tests together and when the subject is classified as non-adherent for both tests (MGT + BT2), 12 non-adherent patients were detected. Finally, when we consider both tests together and when the subject is classified as non-adherent for at least one of the tests (MGT + BT1), 40 non-adherent patients were detected.

The chi-squared test showed a significant association between the RM and the SRMs (Table 2). The measure of agreement by kappa (k) between the MGT and the RM was 0.2 ($p \leq 0.001$), for the BT, k = 0.344 ($p \leq 0.001$), and when we considered both tests together, k = 0.153 ($p = 0.012$) for MGT + BT2 and k = 0.337 ($p \leq 0.001$) for MGT + BT1.

In visit 2, 12 months after inclusion, the non-adherence prevalence using the RM was 14.8%. The non-adherence prevalence for the self-reported adherence methods was 21.9% for the MGT and 19.6% for the BT. The MGT detected 17 of the 31 patients classified as non-adherent using the RM, while the BT found 12. Considering both tests together and when the subject is

TABLE 3 Diagnostic validity of self-reported methods to detect non-adherent patients with the prescribed treatment.

	Baseline	6 months	12 months	18 months
Non-adherence (reference method)	22.5	26.2	14.8	17.9
Morisky–Green test				
Non-adherence	37.7	24.2	21.9	20.3
Sensitivity	58.2% (46.4–70)	39.3% (27–51.6)	54.8% (37.3–72.3)	54.5% (37.5–71.5)
Specificity	68.4% (62.4–74.4)	80.7% (74.7–86.6)	83.7% (78.2–89.1)	87.2% (81.8–92.6)
Positive predictive value	35%	42%	37%	48%
Negative predictive value	85%	78%	91%	89%
Positive likelihood ratio	1.84	1.96	3.55	4.15
Negative likelihood ratio	0.6	0.76	0.53	0.53
Batalla test				
Non-adherence	43.5	32.4	19.6	17.4
Sensitivity	70% (81.5–58.4)	61.1% (48.1–74.1)	40% (22.4–57.5)	50% (32.6–67.3)
Specificity	64.25% (56–72.5)	77.3% (70.8–83.7)	84.4% (79–90)	90% (85–95)
Positive predictive value	35%	47%	31.5%	53%
Negative predictive value	88%	85%	88%	89%
Positive likelihood ratio	1.95	2.77	2.5	5
Negative likelihood ratio	0.46	0.5	0.71	0.55
MGT + BT1 (non-adherent at least by one of the two methods)				
Non-adherence	30.2	31.8	42.5	61.8
Sensitivity	90% (82.4–97.5)	74% (62.3–85.7)	66.6% (50–83.5)	78.1% (63.8–92.4)
Specificity	46.1% (39.5–52.7)	68.1% (61–75.2)	74.2% (67.6–80.8)	80.7% (74.1–87.2)
Positive predictive value	31%	43%	66%	48%
Negative predictive value	94%	88%	92%	94%
Positive likelihood ratio	1.66	2.31	2.54	3.9
Negative likelihood ratio	0.22	0.38	0.46	0.275
MGT + BT2 (non-adherent by the two methods)				
Non-adherence	20.1	12.3	9.6	8.1
Sensitivity	40% (27.6–52.4)	22.2% (11.1–33.3)	26.6% (0.11–0.42)	25% (10–40)
Specificity	85.5% (80–90)	90.7% (86.3–95.2)	93.4% (89.6–97.1)	95.7% (92.3–99)
Positive predictive value	42%	44%	42%	57%
Negative predictive value	84%	77%	87%	84%
Positive likelihood ratio	2.66	2.2	3.71	6.25
Negative likelihood ratio	0.7	0.45	0.79	0.78

classified as non-adherent for both tests (MGT + BT2), eight non-adherent patients were detected. Finally, when we consider both tests together and when the subject is classified as non-adherent for at least one of the tests (MGT + BT1), 20 non-adherent patients were detected.

The chi-squared test showed a significant association between the RM and the SRMs (Table 2). The measure of agreement by kappa (k) between the MGT and the RM was 0.321 ($p \leq 0.001$), for the BT, k = 0.22 ($p \leq 0.001$), and when we considered both tests together, k = 0.236 ($p = 0.001$) for MGT + BT2 and k = 0.282 ($p \leq 0.001$) for MGT + BT1.

In visit 3, 18 months after inclusion, the non-adherence prevalence using the RM was 17.9%. The non-adherence prevalence for the self-reported adherence methods was 20.3%

for the MGT and 17.4% for the BT. The MGT detected 18 of the 33 patients classified as non-adherent using the RM, while the BT found 16. Considering both tests together and when the subject is classified as non-adherent for both tests (MGT + BT2), eight non-adherent patients were detected. Finally, when we consider both tests together and when the subject is classified as non-adherent for at least one of the tests (MGT + BT1), 25 non-adherent patients were detected.

The chi-squared test showed a significant association between the RM and the SRMs (Table 2). The measure of agreement by kappa (k) between the MGT and the RM was 0.399 ($p \leq 0.001$), for the BT, k = 0.41 ($p \leq 0.001$), and when we considered both tests together, k = 0.265 ($p \leq 0.001$) for MGT + BT2 and k = 0.474 ($p \leq 0.001$) for MGT + BT1.

The diagnostic validity of the SRM is shown in Table 3.

4 Discussion

The analysis found that the diagnostic validity of self-reported questionnaires to measure non-adherence administered independently in patients with MCI or early stages of dementia is low, especially when non-adherence is infrequent. Using the two questionnaires studied together and considering a patient non-adherent if deemed so by at least one of the two questionnaires is an acceptable way to estimate non-adherence. Additionally, it imposes minimal burden on clinicians and/or researchers, as well as on patients, since they are brief tests that can be administered at the same time. The BT yielded slightly better results than the MGT, and therefore, we recommend its use if administering both is not feasible.

MCI has been associated with problems to adhere to the multiple medication regimens frequently followed by older adults (Kröger et al., 2017). Medication adherence is fundamental to adequately treat conditions that could negatively impact cognitive impairment and dementia, such as diabetes and hypertension. Likewise, non-adherence to medication has been associated with a worse prognosis of cognitive deficit (Gard, 2010). Therefore, having a reliable, valid, and simple method to evaluate adherence in this population is essential to evaluate and develop interventions and achieve improvements that result in a better prognosis and quality of life in this population.

When we considered both tests, both tests classify the patient as non-adherent, observing a considerable increase in the specificity with a reduction in sensitivity. These values match those of other trials for chronic diseases, in which the specificity overcomes sensitivity (Pineiro et al., 1997; Pineiro et al., 1997). In our case, this means that we would classify correctly adherent subjects (true negative) because sensitivity is low, and specificity is high. In clinical practice, this is very useful because when both tests are used with a patient, and they are classified as adherent, it indicates that they are well diagnosed. If we consider the likelihood ratio to detect non-adherent patients, we see that both tests identify a patient as non-adherent with the scheduled inhaled treatment, and it is nearly 6-fold more likely to be a true positive value.

It has been observed that participants' adherence throughout the study increases, which may be explained by the Hawthorne effect (Sedgwick and Greenwood, 2015), wherein the continuous assessment of adherence throughout the study may modify the negative pattern of medication intake and increase the likelihood of following pharmacological guidelines correctly. On the other hand, being aware of a future evaluation also increases motivation and improves performance. Furthermore, the improvement in adherence over visits may also be attributed to selective experimental mortality (Jurs and Glass, 1971), i.e., fewer trial dropouts among those adhering to the treatment.

Despite initial concerns about the reliability of questionnaires for estimating pharmacological treatment adherence in patients with cognitive impairment or dementia (Arlt et al., 2012), given memory problems (Luck et al., 2007) and difficulties in monitoring behavior (Volicer, 2018), the results are comparable or even better than those found in similar studies with samples of patients without cognitive impairment (Barnestein-Fonseca et al., 2011). Another noteworthy point is that the BT, although inferring non-adherence in a less direct manner, seems to have obtained better results, which could be attributed to social desirability (Stirratt et al., 2015), affecting the questionnaire validity when directly inquiring about adherence. The use of two forms of measuring adherence, one more direct and the other more indirect, might explain why using both and considering non-adherence with only one of the methods can be an acceptable way to estimate non-adherence due to the high specificity of these tests. In general, it has been frequently observed that adherence estimates from self-reported questionnaires often do not align with other methods (Garber et al., 2004).

4.1 Limitations

The obtained results have several limitations. First, pill counting involves biases and is not a perfect method. The most well-known bias is that it tends to overestimate adherence, possibly explaining the differences in the percentages of non-adherent individuals obtained through the two methods, with more non-adherent individuals when questionnaires are used. Additionally, the study is based on a clinical trial, representing a specific population with high levels of adherence, especially among those who complete follow-ups, thus limiting external validity. Furthermore, the study population comes from only one of the three centers participating in the clinical trial, thus limiting the generalizability of the results.

5 Conclusion

The studied self-reported tests used collectively can provide valuable information regarding adherence in older individuals with MCI, as extensively demonstrated in this and other medical conditions (Stirratt et al., 2015). However, they exhibit low sensitivity, which must be considered when used, and is related to the challenge of accurately measuring treatment adherence. On the other hand, the specificity is high, and in daily clinical practice, this is very useful because when both tests are used with a patient and he or she is classified as adherent, then this is the case.

Although the methods used to measure adherence are not perfect, it is better to use them in a homogeneous and structured manner rather than not to take them into account. The dose/pill count could be chosen in clinical practice, even though we know that it overestimates adherence. An alternative to the pill count is an SRM, but the diagnostic validity of the two tests performed

independently is low. Nevertheless, when they are considered together, they have a higher potential to detect patients with non-adherence to therapeutic regimens and at a low cost and in a reliable way in daily clinical practice.

In the context of aging societies and the promotion of dementia-friendly societies, this work contributes by shedding light on the importance of medication adherence in managing cognitive decline in MCI and early-stage dementia patients, thereby potentially improving their quality of life and overall wellbeing.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Comité Provincial de Málaga, SAS, Málaga Spain. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

PB-F: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, writing–original draft, and writing–review and editing. GG-P: conceptualization, investigation, writing–original draft, and writing–review and editing. JG-P: conceptualization, investigation, writing–original draft, writing–review and editing, and supervision. EV-M: investigation and writing–review and editing. FM-C: funding acquisition, resources, supervision, and writing–review and editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This research project was funded by a grant from the European Commission, Horizon 2020 (project 643399).

Acknowledgments

The authors thank the practitioners and patients for their participation in this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 04 October 2024
DOI 10.3389/fphar.2024.1390629

OPEN ACCESS

EDITED BY
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RECEIVED 23 February 2024
ACCEPTED 24 June 2024
PUBLISHED 04 October 2024

CITATION
Ágh T, Garuolienė K, Granas AG, Gregório J, Aksoy N, Khanyk N, Ortner Hadžiabdić M, Kardas P and European Network to Advance Best Practices and Technology on Medication Adherence (ENABLE) Collaborators (2024), Identifying and presenting key country-specific indicators related to medication adherence: a comprehensive study across European countries.
Front. Pharmacol. 15:1390629.
doi: 10.3389/fphar.2024.1390629

Identifying and presenting key country-specific indicators related to medication adherence: a comprehensive study across European countries

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This study tackles the critical challenge of medication non-adherence in healthcare by pinpointing indicators related to medication adherence (IRMAs) across 39 European countries and Israel. Utilizing a structured expert survey methodology within the European Network to Advance Best Practices and Technology on Medication Adherence (ENABLE; COST Action CA19132), our research identified key country-specific IRMAs and collected data on these indicators to understand the multifaceted nature of medication adherence. The research was conducted in two phases: firstly, defining key IRMAs through a two-round expert survey, and secondly, gathering country-specific data on these IRMAs through literature reviews and additional expert surveys. The study revealed a diverse range of 26 top-ranked IRMAs, including six related to country characteristics, four to social/economic factors, three each to therapy-related and patient-related factors, one to condition-related factors, and nine to healthcare system-related factors. The availability of country-specific data on these IRMAs varied among the countries, highlighting the need for more comprehensive data collection and research. The findings from this study not only underscore the complexity of predicting medication adherence but also lay the groundwork for developing targeted, country-specific interventions to improve adherence. Moreover, this research offers valuable insights for policymakers, highlighting the importance of understanding the multifaceted nature of medication

adherence and offering a valuable resource in formulating targeted health policies to enhance health outcomes and reduce the economic burden associated with medication non-adherence.

KEYWORDS

medication adherence, persistence, health policy, indicator, Europe

Introduction

Adherence, as defined by the ABC taxonomy of the International Society for Medication Adherence (ESPACOMP), pertains to patients adhering to their prescribed medication regimen (Vrijens et al., 2012). This encompasses three phases: initiation, implementation, and discontinuation. Initiation marks the patient consuming the initial dose of the prescribed medication. Discontinuation marks the deliberate cessation of the medication by the patient. Implementation measures the degree to which a patient's actual intake of medication aligns with the prescribed dosing schedule, spanning from the initiation to the last administered dose. Research highlights that medication adherence rates for chronic disorders, such as hypertension, diabetes mellitus, or cardiovascular diseases, often fall below optimal levels. Approximately 50% of patients fail to adhere to their prescribed medication regimens (WHO, 2003; Foley et al., 2021).

Medication non-adherence is associated with higher morbidity and mortality rates, leading to deteriorating health outcomes, progression of diseases, worsening symptoms, and reduced therapy effectiveness (Mongkhon et al., 2018; Inotai et al., 2021). Consequently, healthcare costs escalate as non-adherent patients may require more expensive treatments, longer hospital stays, increased emergency room visits, or face more severe complications from untreated diseases (Mikyas et al., 2014; Cutler et al., 2018). Moreover, patients may experience a decline in their overall quality of life (Ágh et al., 2011; Márquez-Contreras et al., 2017). Medication non-adherence poses significant implications for individual patients, healthcare professionals and healthcare system. The financial impact of non-adherence is substantial, with 80–125 billion EUR lost annually in Europe due to increased use of healthcare resources and the emergence of preventable health problems (European Commission, 2011).

Medication non-adherence stands out as a significant issue in modern medicine, representing a critical challenge to the sustainability of existing healthcare systems (Stewart et al., 2023). The persistence of this problem undermines the potential advantages of medical interventions and places strain on the overall viability and efficiency of contemporary healthcare systems. Addressing this concern becomes paramount for the effective functioning of healthcare structures. Achieving progress and resilience in clinical practices necessitates a comprehensive understanding and strategic response to medication non-adherence, establishing these elements as imperative pillars in fortifying the foundations of healthcare systems.

Medication adherence is a complex issue (Kardas et al., 2013; Gast and Mathes, 2019), which–according to the World Health Organization (WHO) model (WHO, 2003)–is influenced by multiple factors including socio-economic, healthcare team and system-related, condition-related, therapy-related, and patient-related considerations. Given the intricate factors influencing this problem, it is essential to prioritize comprehensive strategies that effectively address these challenges to improve medication adherence and, thereby, health outcomes. Understanding non-adherence statistics and identifying potential indicators at the country level are critical for tailoring health policies that are sensitive to socio-economic differences, cater to the unique needs of populations, and to gain a better understanding of the causes of non-adherence. Through such targeted approaches, significant enhancement of health outcomes and reduction of the economic burden associated with non-adherence could be achieved.

In the context of addressing these challenges, the European Network to Advance Best Practices and Technology on Medication Adherence (ENABLE), a COST Action supported by the European Commission, is as a pivotal initiative. ENABLE aims to foster best practices and technological advancements in medication adherence, emphasizing the importance of interdisciplinary understanding, the application of innovative technologies in clinical settings, and the development of economically viable policies for the adoption of adherence-enhancing technologies in healthcare systems (van Boven et al., 2021). Aligned with these efforts, our study focuses on identifying key country-specific indicators associated with medication adherence [referred to as country-specific indicators related to medication adherence (IRMAs)] and presenting country-specific data on these key IRMAs for European countries and Israel. By doing so, we aim to contribute to a more nuanced understanding of medication adherence, facilitating targeted interventions that address the specific needs and challenges within these countries.

Material and methods

Study design

This mixed-methods study was designed around two main phases: (i) identification of IRMAs through a two-round online expert survey, and (ii) collection of country-specific data on IRMAs through a targeted literature review and data validation by an online expert survey.

The initial phase of the study involved a two-round expert survey approach to define the key IRMAs specific to each country (i.e., all 39 European countries and Israel; Figure 1). In the Expert Survey #1, participants were requested to itemize significant indicators spanning multiple domains, such as country characteristics, as well as the WHO model-related dimensions, i.e., socio-economic, therapy-related, patient-related, condition-related, and healthcare system-related factors (WHO, 2003). Subsequently, during the Expert Survey #2, participants ranked the relevance of identified indicators on a 5-point Likert scale, with 1 representing "not relevant at all" and 5 indicating

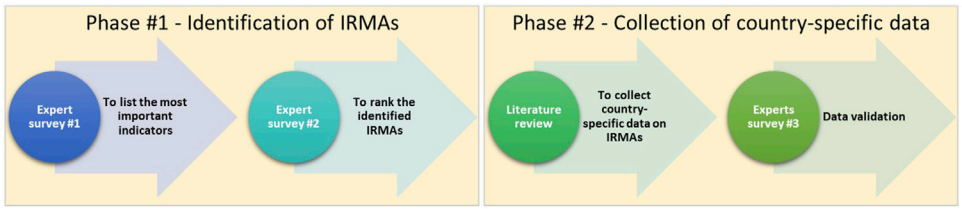

FIGURE 1
Study flow diagram IRMA, indicator related to medication adherence.

"extremely relevant." Indicators with a mean score of ≥3.5 were classified as key IRMAs. The outcomes of this round facilitated the formulation of a definitive list of country-specific IRMAs, assuming that the intervals between response categories are equidistant. Concurrently, both terminology refinement and the development of comprehensive definitions for each indicator were undertaken through an iterative process by the research team. This process began with preliminary definitions crafted based on existing literature and the collective expertise within our team. These definitions served as the initial framework and were continually refined and modified throughout the study, especially after the data collection phase. The refinement was significantly influenced by the definitions present in the data sources we utilized, ensuring our terminology aligned with prevailing standards. Importantly, this process of refining and validating the definitions was carried out internally, without the involvement of external experts.

The second phase of the study focused on collecting country-specific data related to the finalized list of IRMAs (Figure 1). This phase was initiated with a comprehensive targeted literature review. The review employed a search strategy using Medline (via PubMed) for peer-reviewed articles, supplemented by searches in grey literature sources such as Eurostat and Google. The search strategy was designed to capture relevant studies and reports using a combination of specific keywords associated with the list of included IRMAs and the focus countries, which encompass all European countries and Israel. To enhance the integrity of the acquired data, expert survey #3 was implemented, reaching out to ENABLE country representatives (i.e., all European countries and Israel). The goal was to validate and, if necessary, update the data based on the insights received.

Data collection

Surveys utilized in this research were administered via SurveyMonkey.com (www.surveymonkey.com). Participation was voluntary. Invitations for the first two surveys were sent to ENABLE members (i.e., medication adherence experts from various clinical fields: physicians, pharmacists, psychologists, and nurses), while the third targeted only country representatives of the ENABLE team from all European countries and Israel. Online surveying system settings were set to block multiple entries from the same IP address. No incentives were provided for participation. At the beginning of each survey before providing informed consent, participants were informed about the objectives, data usage and storage, and expected duration. The average completion times for the first, second and third surveys were estimated to be 20, 15, and 45 min, respectively. Each survey was administered in a single session. Expert Survey #1 was conducted from 14th to 31st October 2022, Expert Survey #2 from 14th to 30th November 2022, and Expert Survey #3 from 5th January to 31st May 2023.

This study was conducted under the ENABLE COST Action research program, received favorable approval from the Research Ethics Committee of the Province of Malaga on 29 April 2021. The study collected individual opinions and publicly available information from ENABLE members. Names were collected solely from participants who consented to be acknowledged in the manuscript. All study data were collected and analysed anonymously, and ethical standards were strictly followed to ensure participant privacy and data protection.

Data analysis

The collected country-specific data on IRMAs were summarized in a descriptive manner, providing detailed insights into each country's unique context. This approach involved profiling each indicator separately, highlighting the availability of data and specific national circumstances and trends. Although this information effectively illustrates variations across countries within each indicator, direct comparisons between countries were not conducted. This maintains the study's focus on descriptive analysis rather than on comparative metrics.

Results

Out of 34 ENABLE members invited for the Expert Survey #1, 17 participants actively contributed, collectively providing 205 indicators, which are detailed in Supplementary Table S1. In the Expert Survey #2, 21 participants (representing a response rate of 62%) ranked these 205 indicators. From these, 25 indicators reached a relevance score above 3.5 (Supplementary Table S2). Additionally, the 'country population' indicator was included by the research team, recognizing its essential role in facilitating future comparative analyses across countries. The mean scores for the ranked indicators varied between 2.76 and 4.52, with a median of 3.89. The final set of included indicators encompassed various domains: six indicators pertained to country characteristics, four to social/economic factors, three to therapy-related aspects, three to patient-related factors, one

TABLE 1 Final list and definition of top-ranked country-specific indicators related to medication adherence.

Domain	Indicator	Definition
Country characteristics	IRMA #1–Method of payment	Refers to the process by which patient is reimbursed for healthcare expenses
	IRMA #2–Medication adherence assessed and reported on the national level	Is medication adherence assessed and reported on the national level? (yes/no)
	IRMA #3–Healthcare provider	Refers to the system by which patient can access healthcare services (e.g., public, private)
	IRMA #4–Model of healthcare system financing	Refers to the system of healthcare financing (e.g., taxes, voluntary health insurance, co-payment)
	IRMA #5–Proportion of population aged 65 and over	Proportion of population aged 65 and over
	IRMA #6–Country population	Population size (based on projection for a given year)
Social/economic factors	IRMA #7–Patient co-payment	The amount of money that a patient is required to pay out-of-pocket for medications
	IRMA #8–Percentage of prescriptions dispensed at no cost to patients	Percentage of prescriptions dispensed at no cost to patients at population level
	IRMA #9–Population coverage	Proportion of population that has access to healthcare services (public, private)
	IRMA #10–Availability of doctors' services for citizens at no payment	Availability of healthcare services without requiring any out-of-pocket payment
Therapy related factors	IRMA #11–Average number of medicines per patient	Average number of medicines per patient
	IRMA #12–Proportion of adults aged 75 years and older who are taking >5 medications concurrently	Proportion of adults aged 75 years and older who are taking >5 medications concurrently
	IRMA #13–Self-reported use of prescribed medicines	Proportion of population using prescribed medication
Patient related factors	IRMA #14–Persons reporting a chronic disease	Proportion of population reporting asthma, COPD, hypertension, diabetes mellitus, chronic depression
	IRMA #15–Self-perceived health	Proportion of population with very good level of self-perceived health
	IRMA #16–Current depressive symptoms	Proportion of population reporting current depressive symptoms
Condition related factors	IRMA #17–General health literacy	Proportion of population with inadequate/problematic/sufficient/excellent general health literacy
Healthcare system related factors	IRMA #18–Percentage of patients receiving adherence interventions	Proportion of patients received interventions designed to improve medication adherence
	IRMA #19–Nationwide availability of e-prescription (Yes/No)	Is e-prescription system nationwide available for patients? (yes/no)
	IRMA #20–Waiting time for prescriptions/medical appointments	Average waiting time for prescriptions and medical appointments
	IRMA #21–Number of practicing physicians	Number of practicing physicians per 100,000 inhabitants
	IRMA #22–Proportion of healthcare expenditure on pharmaceuticals	Proportion of healthcare expenditure on pharmaceuticals
	IRMA #23–Number of practicing pharmacists	Number of practicing pharmacists per 100,000 inhabitants
	IRMA #24–Total healthcare expenditure	Total healthcare expenditure expressed in percentage of GDP
	IRMA #25–Public pharmaceutical expenditure as % of total pharmaceutical expenditure	Public pharmaceutical expenditure expressed in percentage of total pharmaceutical expenditure
	IRMA #26–Self-reported consultations of a medical professional	Distribution of the population according to the number of consultations of a medical doctor in the past 4 weeks

COPD, chronic obstructive pulmonary disease; GDP, gross domestic product; IRMA, indicators related to medication adherence.

to condition-related aspects, and nine to healthcare system-related factors (Table 1).

Data on the identified key IRMAs were collected for a total of 39 European countries and Israel. The gathered country-specific data were subjected to a validation process by the ENABLE country representatives to ensure its accuracy and reliability. Although efforts were made to validate the data from all participating countries, only 75% successfully completed this process. Unfortunately, we did not receive responses from ENABLE's representatives in Austria, Belgium, Denmark, Ireland, Israel,

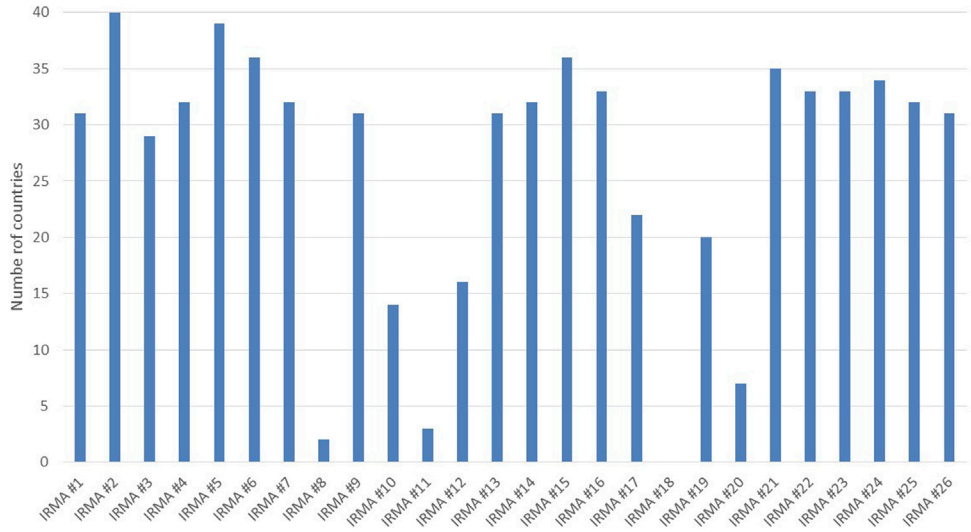

FIGURE 2
Data availability on indicators related to medication adherence for the studied countries.

Luxembourg, Moldova, the Netherlands, Sweden, and the United Kingdom by the study's deadline. Detailed country-specific data on key IRMAs can be found in Supplementary Table S3, where countries are listed alphabetically. To maintain transparency and credibility, all data sources are cited alongside the information presented in this table. The availability of data on IRMAs varied among the countries studied, as illustrated in Figure 2.

Country characteristics

The availability of data for the six indicators under this subgroup was relatively high compared to the other categories (Figure 2). For IRMA #2, which assesses and reports on medication adherence at the national level, information was available for all countries. However, only two countries reported having an established system in place: Croatia, which uses a self-report questionnaire in pharmacies, and Italy, where the method of adherence measurement was not specified during the data validation process. Additionally, the proportion of the population aged 65 and over (IRMA #5) was reported for all countries except one (Israel), ranging from 9.5% in Türkiye to 23.5% in Italy.

Social/economic factors

Regarding patient co-payment (IRMA #7), data was available for 32 countries. For IRMA #8, which tracks the percentage of prescriptions dispensed at no cost to patients, valid data came exclusively from Serbia (14.8%) and Slovenia (51.9%). For population coverage (IRMA #9), information was accessible from 31 countries, while data on the availability of doctors' services for citizens without payment (IRMA #10) was reported by 14 countries. The coverage of the population with access to healthcare services was above 90% in all countries with valid data, except for Bulgaria at 85% and Ukraine at 83%.

Therapy-related aspects

The average number of medications per patient (IRMA #11), data was only accessible from a few countries: Germany reported an average of 4.1 medications per patient, Poland 3.7, and Slovenia 8.9. Considering the proportion of adults aged 75 years or older are taking more than five medications concurrently (IRMA #12), there was a notable variation among the 16 countries with available data. This proportion ranged from a low of 10% in Türkiye to a high of 87% in Luxembourg. Additionally, the self-reported use of prescribed medicines (IRMA #13) had data available for 78% of the countries (n = 31). The reported use of medicines varied widely, from 23% in Romania to 71% in Norway, illustrating the diversity in medication usage patterns among countries. Country-specific data for IMRA #12 (Proportion of adults aged 75 years and older who are taking more than five medications) and IRMA #13 (Self-reported use of prescribed medicines) are presented in Figure 3.

Patient-related factors

The availability of country-specific data for patient-related IRMAs was at or above 80%. Data on persons reporting a chronic disease (IRMA #14), such as asthma, chronic obstructive pulmonary disease (COPD), hypertension, diabetes, and depression are illustrated in Figure 4. The proportion of the population with a very good level of self-perceived health (IRMA #15 Self-perceived health) varied significantly, ranging from 6.5% in Türkiye to 46.9% in Greece. The proportion of the population reporting current depressive symptoms (IRMA #16) showed less variability, ranging from 2% (Albania) to 10.8% (France).

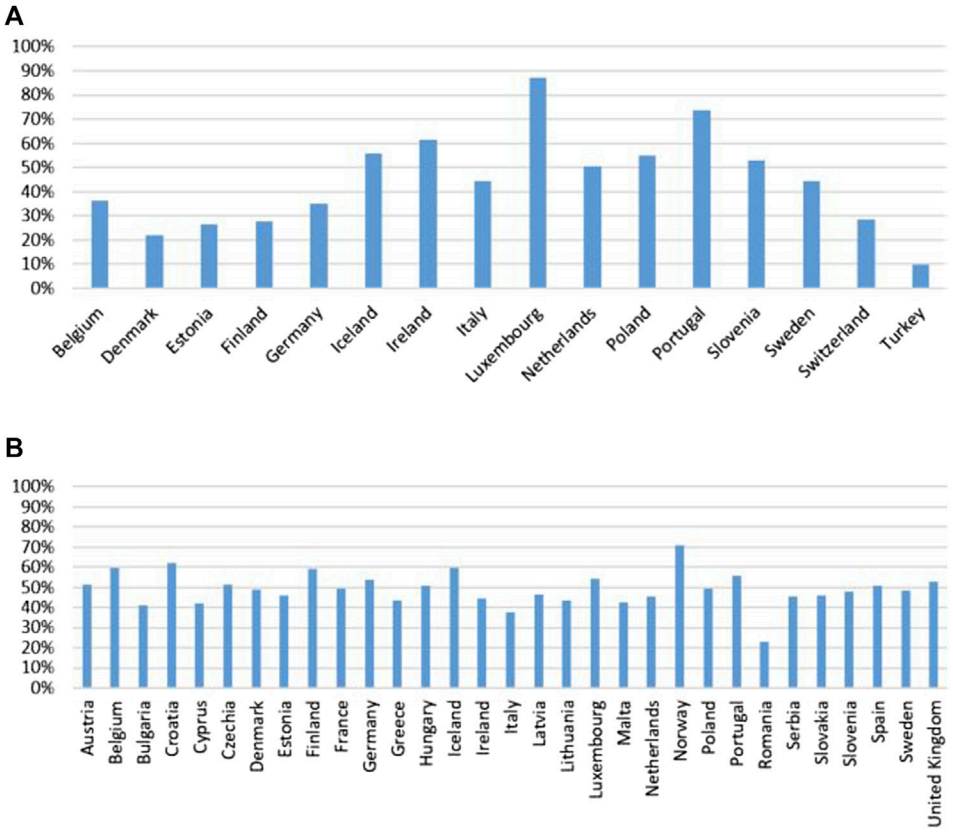

FIGURE 3
Proportion of adults aged 75 years and older who are taking more than five medications **(A)** and self-reported use of prescribed medicines in the countries with available data **(B)**.

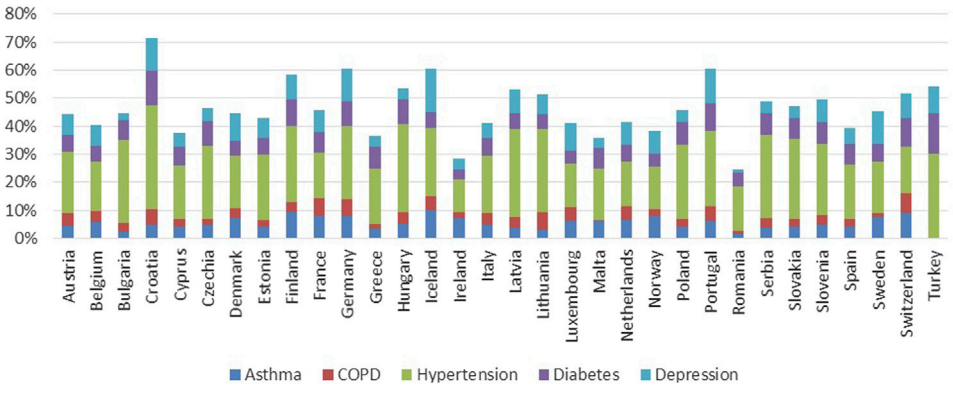

FIGURE 4
Proportion of population reporting asthma, COPD, hypertension, diabetes mellitus, chronic depression in the countries with available data.

Condition-related aspects

Data on the proportion of the population with varying levels of general health literacy (IRMA # 17)–categorized as inadequate, problematic, sufficient, and excellent—was reported by 55% of the countries studied (n = 22), is presented in Figure 5.

Healthcare system-related factors

No country provided data for IRMA #18, which concerns the percentage of patients receiving adherence interventions. Regarding IRMA #19, which focuses on the nationwide availability of e-prescription systems, only 50% of the countries provided data, and all reported having some form of

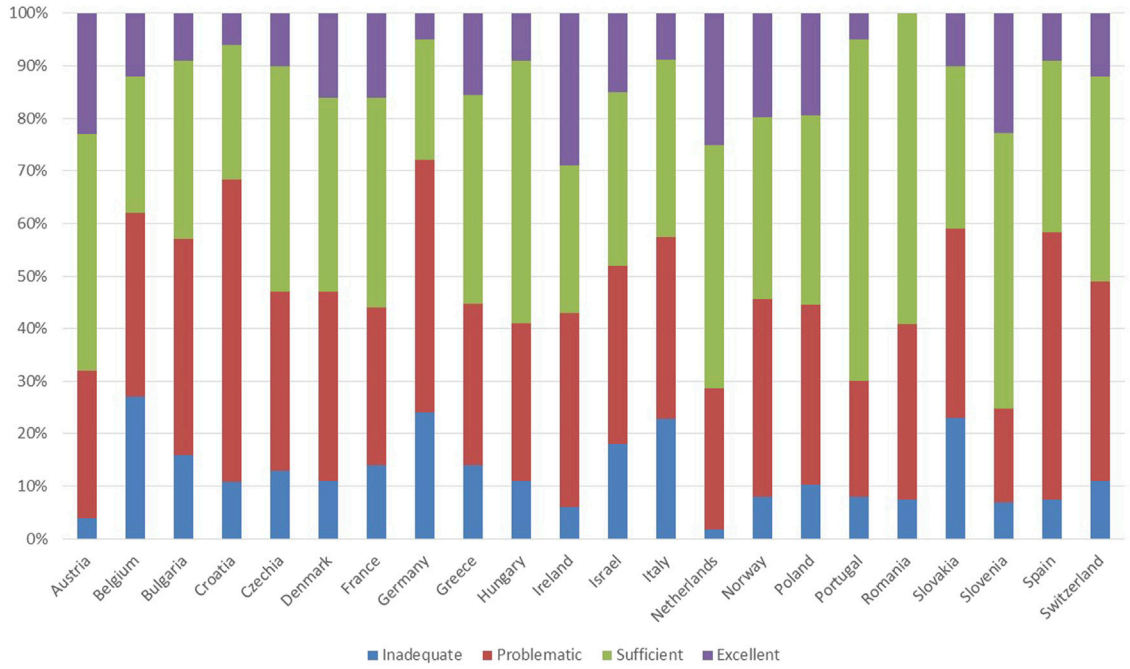

FIGURE 5
Proportion of the population with varying levels of general health literacy in the countries with available data.

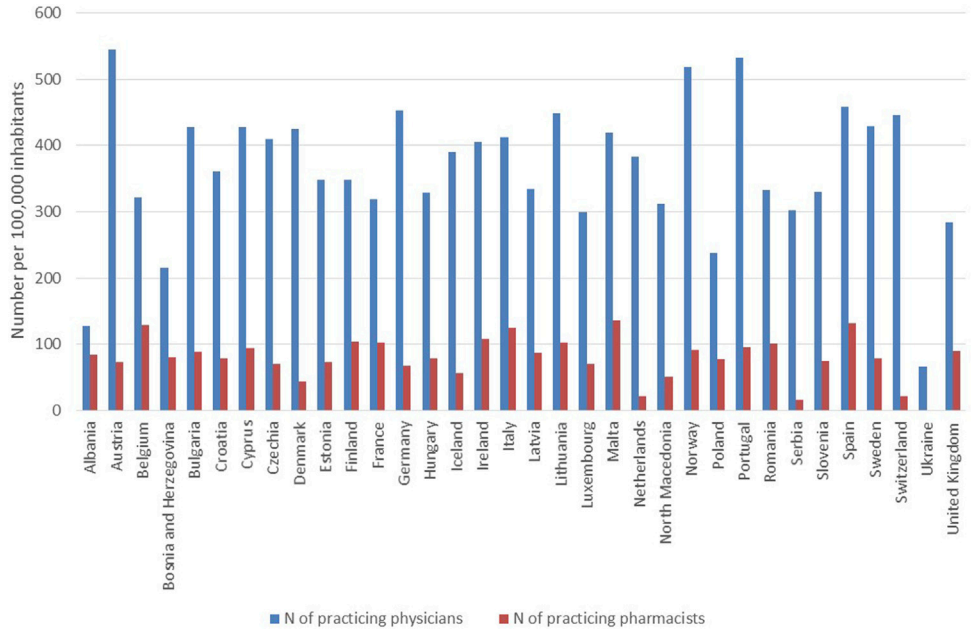

FIGURE 6
Number of practicing physicians and pharmacists per 100,000 inhabitants in the countries with available data.

e-prescription system in place. Additionally, information on the average waiting time for prescriptions and medical appointments (IRMA #20) was available from just seven countries: Bulgaria, Estonia, Finland, Germany, Italy, Norway, and Poland (data varied across countries, for details see Supplementary Table S3).

For the other IRMAs in this subcategory the country-specific data availability was around or above 80%. Country-specific data on the number of practicing physicians (IRMA #21) and pharmacists (IRMA #23) per 100,000 inhabitants are presented in Figure 6. Total healthcare expenditure as a percentage of GDP *per capita* (IRMA #24), the proportion of

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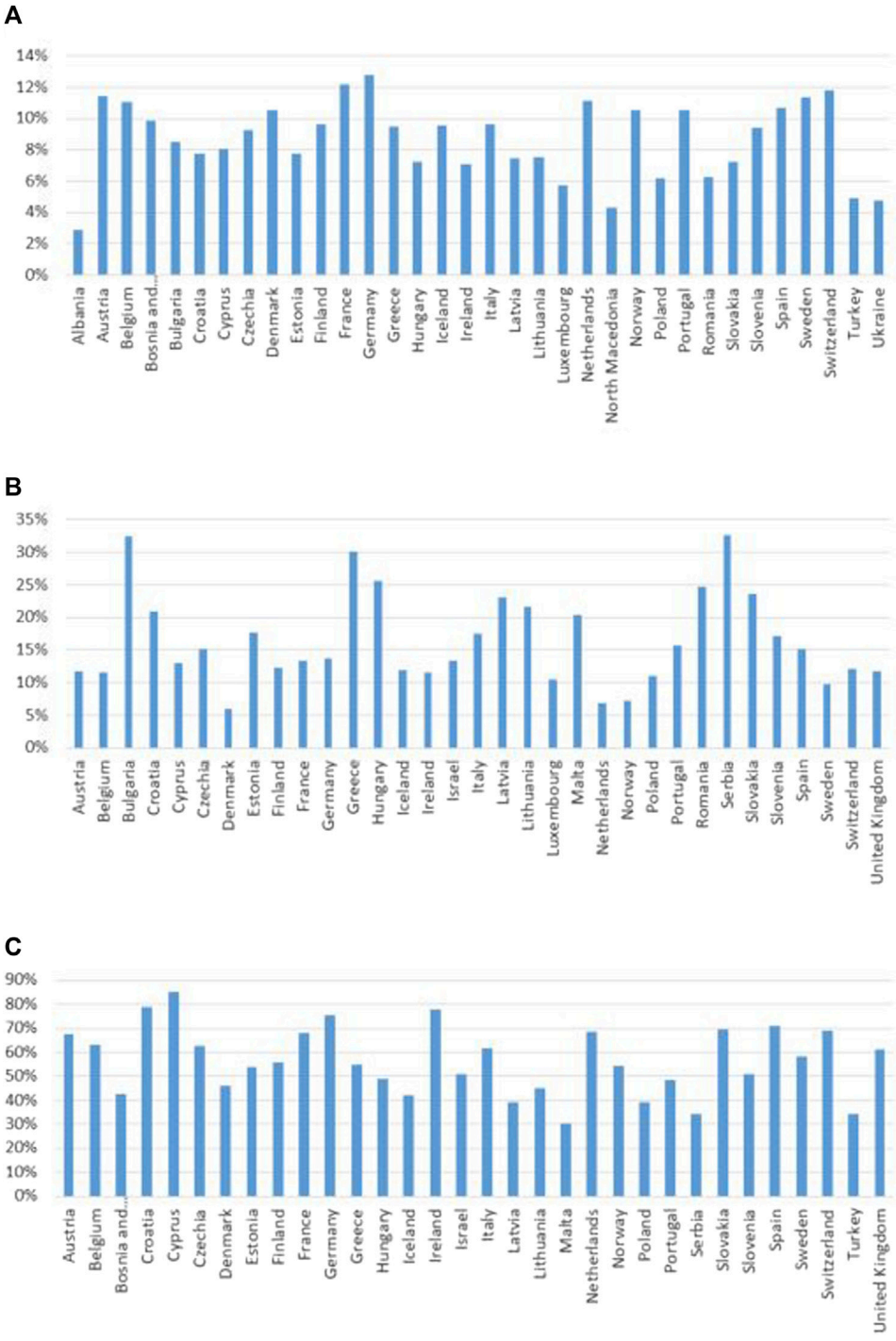

FIGURE 7
Total healthcare expenditure as a percentage of GDP *per capita* **(A)**, the proportion of healthcare expenditure on pharmaceuticals **(B)**, and public pharmaceutical expenditure as a percentage of total pharmaceutical expenditure in the countries with available data **(C)** GDP, gross domestic product.

healthcare expenditure on pharmaceuticals (IRMA #23), and public pharmaceutical expenditure as a percentage of total pharmaceutical expenditure (IRMA #25) are illustrated in Figure 7. Lastly, results on the distribution of the population according to the number of consultations with a medical doctor in the past 4 weeks are depicted in Figure 8.

Discussion

The identification and collection of data on key IRMAs through a structured expert survey methodology have provided valuable insights into the multifaceted nature of medication adherence. Findings of our study underscore the complexity of indicators

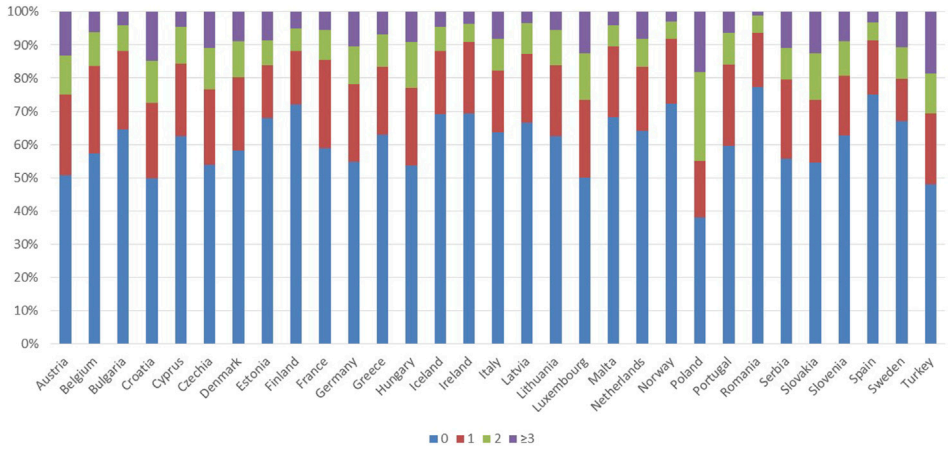

FIGURE 8
Distribution of the population according to the number of consultations with a medical doctor in the past 4 weeks in the countries with available data.

that might predict medication adherence across European countries and Israel, highlighting the pivotal role of country-specific IRMAs.

The methodology employed in identifying and ranking key IRMAs through expert surveys within the ENABLE network has successfully highlighted the priority areas as perceived by professionals engaged in this field. The emphasis on healthcare system-related factors, with nine indicators, underscores the systemic challenges inherent in medication adherence. Additionally, the inclusion of indicators across social/economic, therapy-related, patient-related, and condition-related domains recognizes the multifaceted nature of medication adherence. The consensus on certain indicators (e.g., IRMA #1 Method of payment, IRMA #5 Proportion of population aged 65, and over, and IRMA #7 Patient co-payment), reflected by the standard deviation scores (Supplementary Table S2), points to a shared understanding of core indicators of medication adherence within a country. Nevertheless, the variation in relevance scores and the comprehensive range of domains represented by the final indicators highlight the complexity of medication adherence challenges (Mathes et al., 2014; Yeam et al., 2018). These results suggest that effective adherence-enhancing interventions must extend beyond addressing patient and therapy-related factors to include broader socio-economic and healthcare system-related determinants.

The vast variability in the availability of data on key IRMAs across the studied countries highlights the need for further research and more comprehensive primary data collection. Data for certain IRMAs, such as IRMA #8 (Percentage of prescriptions dispensed at no cost to patients), IRMA #11 (Average number of medicines per patient), IRMA #18 (Percentage of patients receiving adherence interventions), and IRMA #20 (Waiting time for prescriptions/medical appointments), were either not available or very limited in a number of countries. Nonetheless, according to expert opinions, these factors may significantly influence the level of medication adherence at the country level and thus warrant closer attention.

Our study revealed that the majority of European countries do not assess medication adherence on a national scale (Indicator: IRMA #2–Medication adherence assessed and reported at the national level). However, the prevalent use of electronic medical record datasets and e-prescription systems across Europe could facilitate the production of these data (Brennan et al., 2015; Ágh et al., 2021). Moreover, the initiative to integrate big data within European nations (European Health Data Space—EHDS) would further enable cross-country comparisons (European Commission, 2024). The EHDS initiative could be instrumental in understanding and improving medication adherence trends both within individual countries and across Europe as a whole. Such data integration could lead to more informed healthcare policies and better patient outcomes.

The absence of country-level medication adherence rates for chronic therapies did not allow for an investigation into the correlation between the identified key IRAMs and medication adherence rates. This is not surprising, as a recent OECD report demonstrates a majority of the European countries are neither monitoring adherence nor taking regular actions to improve it (Khan R and Socha-Dietrich, 2018). Despite this limitation, the country-level data collected in this study emphasize the variability of these indicators across countries, pointing out the importance of contextual factors such as healthcare infrastructure, patient education, and access to medications. Strategies to improve medication adherence should be tailored to address the specific barriers and opportunities within each country's unique healthcare ecosystem (Riley et al., 2021). In this context, it is crucial to recognize that adherence-enhancing interventions effective in one country are not guaranteed to work in another. Transferability analysis can help to identify key factors of variability and formulate implementation strategies for the application of interventions across different jurisdictions, ensuring that strategies are both effective and adaptable to local contexts.

The potential effect on country-level adherence could be multifaceted. Countries with a higher incidence of polypharmacy among their elderly populations might face challenges with adherence due to the complexities of managing multiple medications simultaneously, as depicted in Figure 3 (Sinha et al., 2021; Franchi et al., 2022). These complexities can lead to increased risks of adverse drug reactions, poor adherence and decreased effectiveness of treatment regimens (de Vries et al., 2014;

Zazzara et al., 2021). Conversely, high rates of prescription usage across a population could indicate robust healthcare systems, suggesting potentially higher adherence rates due to better access to medications and more streamlined healthcare processes. However, a strong prescription culture does not inherently assure superior health outcomes without effective medication management and patient education. The varied percentages of populations using prescribed medications, ranging from 23% in Romania to 71% in Norway, suggest differing healthcare service utilizations that could also impact adherence levels. Furthermore, the proportion of the population reporting chronic conditions such as asthma, COPD, hypertension, diabetes mellitus, and chronic depression varies significantly across countries (Figure 4), which could influence both the extent of polypharmacy and the complexity of medication regimes. Additionally, the distribution of health literacy levels, from inadequate to excellent, varies widely between countries (Figure 5) (Sørensen et al., 2015). Higher levels of health literacy are typically associated with a better understanding and management of one's health conditions, which facilitates medication adherence (Arad et al., 2021; Hyvert et al., 2023). In contrast, lower levels of health literacy can lead to misunderstandings about medication usage, resulting in lower adherence and poorer health outcomes (Miller, 2016).

Healthcare system-related factors might also be critical in influencing medication adherence. A higher *per capita* number of practicing physicians and pharmacists can facilitate more consistent and personalized patient care, especially among populations with a high prevalence of chronic conditions (Schneider et al., 2020). Better access to healthcare providers enhances the monitoring and adjustment of medications, potentially improving adherence rates (Figure 6) (Kini and Ho, 2018). Healthcare spending (Figure 7) may also effect in medication adherence. Investments in healthcare, particularly those earmarked for pharmaceuticals, can improve access to healthcare services and medications. Adequate funding may allow for the implementation of comprehensive medication management programs and patient education, which can improve adherence by ensuring that patients understand their treatment plans and the importance of following them (Viswanathan et al., 2012). The frequency of medical consultations (Figure 8) further underscores the importance of healthcare access. Regular contact with healthcare providers is a key factor in adherence, as it enables ongoing health education, timely identification of side effects, and medication non-adherence, as well as implementation of adequate interventions. Countries where populations have fewer medical consultations may need to enhance healthcare accessibility and encourage regular provider-patient interactions to support adherence.

Our study's findings have significant implications for policymakers, healthcare providers, and researchers. By identifying key country-specific IRMAs, our study provides a foundation for the formulation of targeted health policies and medication adherence enhancing interventions. These adherence interventions should aim to address the unique challenges and leverage the specific strengths of each country's healthcare system and patient population. Medication adherence is a measure of quality and effectiveness of the entire healthcare system (Khan R and Socha-Dietrich, 2018). Therefore, despite its crucial role in strengthening the sustainability of the national healthcare systems, it may also serve as a valid indicator of their effectiveness, allowing for fast and objective benchmarking. This is of utmost importance for unfavorable conditions as those set by recent COVID-19 pandemic, and current economic crisis (Ágh et al., 2021; Ágh et al., 2023). Moreover, our study highlights the need to further refine and validate the identified IRMAs, thereby enhancing the effectiveness of medication adherence interventions.

Our results must be considered in light of certain limitations. The potential for bias in participants' responses is notable, as the majority of respondents had an academic background and may not have had comprehensive access to or familiarity with various data sources, affecting the adequacy of data validation. Moreover, the data validation process was carried out by only one representative per country, potentially diminishing its robustness. These factors suggest that the study's conclusions must be interpreted with caution, as the integrity of data and subsequent analyses may not fully capture the complex and varied landscape of medication adherence across different countries. Additionally, while the expertise of the selected professional panel provided valuable insights into medication adherence, the exclusion of patient representatives from the panel may limit the diversity of perspectives considered. Future studies could benefit from incorporating patient viewpoints to enhance the comprehensiveness and applicability of the findings.

In conclusion, the iterative approach employed in this study successfully facilitated the identification of key country-specific IRMAs, providing a valuable resource for policymakers and stakeholders to deepen their understanding of medication adherence across European countries and Israel. The cohesive list of indicators not only promotes fair benchmarking among countries but also serves as a foundation for future studies aiming to assess the predictive value of these indicators in determining medication adherence rates within a given country. Our findings highlight the importance of targeted, country-specific interventions and the potential of technological advancements in improving medication adherence. Further research is needed to rank these indicators accordingly and better comprehend their impact.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

TÁ: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing–original draft, Writing–review and editing. KG: Conceptualization, Methodology, Writing–review and editing. AG: Conceptualization, Methodology, Writing–review and editing. JG: Conceptualization, Methodology, Writing–review and editing. NA: Conceptualization, Methodology, Writing–review and editing.

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Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This research is based upon work from COST Action CA19132 "ENABLE," funded by COST (European Cooperation in Science and Technology). The funder had no role in the study design, data collection, analysis and interpretation, or preparation of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1390629/full#supplementary-material

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