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Effective methods to promote appropriate use of medicines

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Effective methods to promote appropriate use of medicines

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Editorial: Effective methods to promote appropriate use of medicines

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Editorial on the Research Topic
Effective methods to promote appropriate use of medicines

The importance of using medications appropriately cannot be overstated when it comes to effectively managing diseases and achieving positive health outcomes (Kim et al., 2018). Unfortunately, over the past two decades, there has been a global problem with the improper use of medications, particularly among older adults (Rochon et al., 2021). Research has shown that a substantial portion of older adults, ranging from 24% to 72%, are using potentially inappropriate medications (PIMs) (Tachi et al., 2019; Malakouti et al., 2021). This misuse is largely driven by two main factors: polypharmacy and the prescription of PIMs in individuals with multiple health conditions (Curtin et al., 2019). Improper medication use among older adults has serious consequences, including an increased risk of adverse drug events, unplanned hospitalizations, rising healthcare costs, and frequent visits to the emergency department (Curtin et al., 2019; Katsuno et al., 2021; Matsuyama et al., 2021). Additionally, self-medication and medication non-adherence further compromise patient health outcomes. Despite efforts to develop tailored interventions, the improvement in appropriate medication use has been slower than anticipated. One significant reason for this slow progress appears to be the absence of a thorough grasp of medication misuse and improper use, which is essential for crafting effective interventions (Costa et al., 2015).

It is worth highlighting that the benefits of using medication appropriately rely on accurate diagnosis, precise prescription, patient adherence to medication instructions, and regular monitoring by healthcare professionals. This Research Topic addresses the strategies to encourage proper medication use, considering a wide array of perspectives across various countries.

The initial step in understanding the challenges related to comprehending and effectively using medication information for making informed health decisions is to assess the user perception of this information. Alongside medication counseling, prescription drug label (PDL) instructions play a crucial role in guiding patients to adhere to their prescribed medications (Shiyanbola et al., 2016). When patients struggle to comprehend label instructions, it can lead to medication errors, reduced treatment effectiveness, and medication non-adherence. Schackmann et al. conducted a study to assess the comprehensibility of PDL instructions, comparing those presented on a personalized

medication overview to the standard instructions found on medication packaging. The results showed that those exposed to the overview had a higher percentage of correct answers, particularly regarding medications with complex instructions. This study suggests that a medication overview with additional information can enhance patients' understanding and adherence to medication instructions (Schackmann et al.). Another study examined the preferences of caregivers of children regarding accessible information on safe medication use for children, considering content, channels, and formats of healthcare information (Xu et al.). The findings indicated that caregivers primarily obtain information from medical institutions, healthcare professionals, and personal media. They favor text, pictures, and videos as content formats and prioritize the popularization of knowledge about safe medication for children (Xu et al.). Both studies address that to promote safe medication use, it is essential to disseminate accurate and comprehensible healthcare information about medications through diverse channels, accounting for user preferences.

Ensuring proper medication use also hinges on accurate prescribing to prevent serious adverse drug reactions (ADRs). Liu et al. conducted a retrospective analysis of inpatient prescribing practices for long-acting injectable (LAI) antipsychotics and their oral or short-acting injectable (SAI) equivalents in patients with psychological disorders. They discovered that LAIs were generally underutilized when compared to their oral or SAI counterparts from 2010 to 2016. The variations in antipsychotic prescribing patterns provide valuable insights for future research aimed at understanding the reasons behind disparities in medication utilization (Liu et al.). In another study, Shang et al. and their team performed a network meta-analysis involving 159 randomized controlled trials to evaluate the efficacy of pharmacological interventions for smoking cessation. Their findings suggested that varenicline was more effective than other monotherapies, and combination interventions outperformed monotherapy. Whether used as monotherapy or in combination, these interventions showed benefits for smoking cessation compared to a placebo (Shang et al.). Additionally, a separate network meta-analysis of 33 randomized controlled trials compared various pharmacological interventions for preventing opioid-induced hyperalgesia and its impact on postoperative pain. This analysis found that amantadine was the most effective in reducing postoperative pain intensity, while dexmedetomidine produced the best results in reducing the incidence of postoperative nausea and vomiting (Xie et al.). These findings, derived from longitudinal data and meta-analysis, provide valuable guidance for selecting medications to achieve better pharmacological effects while minimizing associated adverse effects.

Implementing drug monitoring as part of medication management aids in the identification of factors that may lead to ADRs and enables early intervention. A review of 26 articles investigated sex differences in ADRs associated with commonly used psychotropic, cardiovascular, and analgesic medications (Shan et al.). The findings pointed out over half of these studies revealed sex-specific patterns in ADR occurrence. Some severe ADRs exhibited variations related to sex, such as a higher prevalence of clozapine-induced neutropenia in women and a more pronounced incidence of liver function issues with simvastatin/atorvastatin in men. Consequently, accounting for sex differences in ADRs may be a critical consideration for clinical decision-making (Shan et al.). Cai et al. examined the current status of individualized pharmaceutical care in China, which includes therapeutic drug monitoring (TDM), pharmacogenetic (PGx) testing, and pharmacist-managed clinics. Their findings indicated that only a small percentage of hospitals conducted TDM and performed PGx testing. This study underlines the early stage of development and emphasizes the necessity for collaboration across various sectors to establish comprehensive individualized pharmaceutical care (Cai et al.). In the context of monitoring ADRs and addressing drug-related concerns, one study introduced a pharmacist-led olaparib follow-up program for patients with ovarian cancer, offering patient education and proactive monitoring (Wang et al.). The findings revealed common ADRs occurring early in treatment, allowing for medication adjustments. Additionally, pharmacists identified clinically significant drug-drug interactions, particularly in patients using multiple medications concurrently. This program effectively managed ADRs, optimized medication use, and improved patient care, providing valuable insights for follow-up services for patient care. In summary, increased awareness of risk factors associated with medication use and the implementation of drug monitoring and follow-up procedures enhance the early detection and mitigation of medication-related adverse events.

Medication non-adherence has consistently been identified as a fundamental challenge contributing to improper medication use. In a cross-sectional study conducted in China involving older adult stroke survivors, it was revealed that more than half of the participants displayed medication non-adherence (Cao et al.). This non-adherence was associated with lower educational levels, a higher number of prescribed medications per day, and specific concerns regarding medications. Conversely, higher health literacy and positive beliefs about medication were linked to improved adherence (Cao et al.). Another study in China focused on assessing adherence to infliximab treatment among patients with Crohn's disease and its correlation with medication beliefs (Li et al.). It found that lower concerns about medication beliefs were associated with better adherence. Factors such as gender, marital status, travel time to the infusion center, and accommodation accessibility also influenced adherence (Li et al.). These findings draw attention to developing interventions that target the factors contributing to medication non-adherence within high-risk populations. While medication non-adherence significantly impacts the effectiveness of chronic therapy and the sustainability of healthcare systems, Medication Adherence-Enhancing Interventions (MAEIs) are underutilized and rarely reimbursed. A study examined reimbursed MAEIs across 12 European countries and found that these interventions commonly focused on adherence through approaches such as education, medication regimen management, and adherence monitoring feedback, with limited utilization of technology-mediated interventions. Wider adoption and reimbursement of MAEIs are crucial to effectively combat medication non-adherence (Kardas et al.).

Pharmacists stand out as highly accessible and well-qualified healthcare practitioners, offering a spectrum of preventive measures, ranging from primary to tertiary, for managing diseases across various healthcare settings (Shiyanbola and Huang, 2020). An integral part of enhancing medication appropriateness is the strategic integration of pharmacists into patients' medication

management, fostering collaboration with other healthcare professionals (Huang et al., 2022). Within the realm of community pharmacy, Algarni et al. adopted a qualitative approach to delve into the viewpoints of Saudi community pharmacists regarding the misuse and abuse of over-the-counter (OTC) medications. Their investigation pinpointed commonly misused OTC products, often stemming from unprofessional guidance, a lack of patient awareness, and the influence of OTC advertising. Pharmacist competence comes to the fore in addressing misuse and abuse complexities by understanding customer behaviors and employing counseling skills to recommend appropriate OTCs and alleviate ailments. Alongside a comprehensive review of OTC regulations, Algarni et al. advocate for enhanced pharmacist training and patient education to curb OTC misuse and abuse (Algarni et al.). In the context of hospital practice, a study conducted in Pakistan shed light on the perceptions of healthcare professionals and patients concerning the involvement of pharmacists in tuberculosis management (Atif et al.). Physicians acknowledged pharmacists as highly qualified healthcare professionals, while patients mainly viewed them as dispensers. Both groups reached a consensus on the potential roles pharmacists could play, such as monitoring, counseling, medication selection, dosage adjustment, and polypharmacy assessment. Physicians, facing heavy workloads, expressed readiness to delegate specific duties to pharmacists, provided they received appropriate training. However, the broader adoption of expanded pharmacist roles faces challenges such as limited interest from regulatory authorities and policymakers and concerns about pharmacist competence (Atif et al.). Meanwhile, a study in Lebanon collaborated with a multidisciplinary team of healthcare professionals to develop a pharmacist-led medication review service with a focus on deprescribing in a care facility catering to low-income patients who received free medications (Alaa Eddine et al.). This intervention effectively identified problems related to medications and generated recommendations for physicians, with a notable 30% of these recommendations being accepted. Patients who received this intervention reported significantly higher satisfaction levels compared to those who received routine care (Alaa Eddine et al.). These studies collectively underscore the competence of pharmacists in delivering pharmaceutical care and collaborating with other healthcare team members to ensure the safe and effective use of medications.

The judicious application of digital technology can play a crucial role in ensuring the appropriate use of medications, especially in the context of a pandemic. An innovative study introduced a model for an internet hospital pharmacy service in China, driven by artificial intelligence (AI), with the aim of augmenting pharmacy services amid the COVID-19 pandemic (Bu et al.). This model seamlessly integrated AI for reviewing prescriptions, an offline self-pick-up system that utilized QR codes, and AI-powered medication consultations. The AI system exhibited a commendable success rate in reviewing prescriptions, and patients expressed a preference for the offline self-pick-up system. Notably, the study revealed the popularity of medication consultations outside regular working hours, with topics ranging from the dispensing process to disease diagnosis and patient education (Bu et al.). The utilization of technology throughout the patient care journey holds the potential to ensure the safe use of medications, enhance the efficiency of pharmacy workflow, and elevate the quality of pharmacy services, particularly in the midst of a pandemic.

In summary, promoting appropriate medication use is vital for effective disease management. This Research Topic has highlighted common challenges in the course of medication use, including medication misuse, labeling, prescribing, monitoring, and non-adherence. Pharmacists play a crucial role in proper medication use, while digital technology, exemplified by AI-driven pharmacy services, enhances healthcare during crises. These multifaceted strategies aim to ensure safe and effective medication use, making strides toward improving patient outcomes and reducing the global problem of medication misuse.

Author contributions

Y-MH: Conceptualization, Writing–original draft, Writing–review and editing. YK: Writing–review and editing. TT: Writing–review and editing, Conceptualization.

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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Reimbursed medication adherence enhancing interventions in 12 european countries: Current state of the art and future challenges

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Background: Medication non-adherence jeopardises the effectiveness of chronic therapies and negatively affects financial sustainability of healthcare systems. Available medication adherence-enhancing interventions (MAEIs) are utilised infrequently, and even more rarely reimbursed. The aim of this paper was to review reimbursed MAEIs across selected European countries.

Methods: Data on reimbursed MAEIs were collected from European countries at the ENABLE Cost Action expert meeting in September 2021. The identified MAEIs were analysed and clustered according to their characteristics, direct vs. indirect relation to adherence, and the targeted adherence phase.

Results: Out of 12 contributing countries, 10 reported reimbursed MAEIs, 28 in total, of which 20 were identified as MAEIs targeting adherence directly. Reimbursed MAEIs were most often performed by either doctors (*n* = 6), nurses (*n* = 6), or pharmacists (*n* = 3). The most common types of MAEIs were education (*n* = 6), medication regimen management (*n* = 5), and adherence monitoring feedback (*n* = 4). Only seven reimbursed MAEIs were technology-mediated, whereas 11 addressed two interlinked phases of medication adherence, *i.e.*, implementation and persistence.

Conclusion: Our review highlights the scarcity of reimbursed MAEIs across the selected European countries, and calls for their more frequent use and reimbursement.

KEYWORDS

medication adherence, non-adherence, persistence, interventions, Europe, reimbursement, drugs, healthcare systems

Introduction

Non-adherence to medications is one of the major issues faced by European healthcare systems. A recent scenario illustrating the problem is the common reluctance to accept anti-Covid-19 immunisation. Contrary to expectations, effective protection against potentially fatal infections, as well as all disadvantages of lockdowns and frozen economies, are not motivating millions of European citizens to accept freely available, effective vaccines (Robinson et al., 2021).

However, looking ahead, at least equally important are the consequences of non-adherence to chronic pharmacotherapy. Noteworthy, the need for such therapies has been rising in Europe due to the rapid aging of the European population, and the related increase in the number of those affected by multimorbidity (Quinaz Romana et al., 2020). Owing to pharmacologic therapies, the life expectancy of patients can be prolonged and their quality of life may be improved. Unfortunately, these benefits of evidence-based medicine are jeopardised by non-adherence. This is particularly apparent in its high prevalence, which reaches 50% among patients on chronic treatment, as underpinned by the dedicated World Health Organization (WHO) report (World Health Organization, 2003). Negatively affecting both individual and public health, it also leads to profound societal and economic consequences, such as increased morbidity, mortality, and healthcare utilisation (Walsh et al., 2019). Indeed, it has been estimated that medication non-adherence is associated with nearly 200,000 deaths as well as with up to 125 billion of potentially preventable direct (*e.g.*, hospitalizations, waste of medication) and indirect (*e.g.*, work productivity losses) costs annually in the European Union (European Commission, 2022). Finally yet importantly, it generates huge amounts of additional workload for healthcare professionals (HCPs) due to inaccurate diagnoses, ineffective treatments, need for additional consultations, or fear of medications as examples. In consequence, medication non-adherence seriously reduces financial sustainability of European healthcare systems.

The WHO model identified five clusters of factors affecting medication adherence, *i.e.*, patient, condition, therapy, healthcare system, and socio-economic factors (World Health Organization, 2003). Within each of these dimensions, multiple factors are identifiable (Kardas et al., 2013). After half a century of research in this area, several medication adherence-enhancing interventions (MAEIs) have been designed, addressing individual or multiple of these factors. A single MAEI does not solve the non-adherence problem, however, currently available interventions targeting chronic conditions may improve both adherence and clinical outcomes (Nieuwlaat et al., 2014).

Nevertheless, available MAEIs are not fully used. Stakeholders, including HCPs, still seem to be inadequately informed about the prevalence and consequences of non-adherence as well as the availability of effective solutions. Therefore, HCPs tend to overestimate the level of adherence of their patients, and thus, have low motivation to implement relevant interventions in practice (Kardas et al., 2015; Clyne et al., 2016; Kardas et al., 2021a). Without public investments and promotional activities, current application of preventive and corrective approaches is still mainly limited to clinical trials, thereby not reaching patients in real-life settings (van Boven et al., 2016).

Consequently, in the last decades, there has been little improvement in adherence management (Zullig et al., 2018). Therefore, wider implementation of MAEIs is urgently needed. It can lead to a multiple-win scenario: while contributing to the sustainability of European healthcare systems, it can also help individual patients and public payers, and at the same time increase the scope of innovation of the pharmaceutical industry, and boost overall economies. These effects have

recently been well-illustrated with a study addressing adherence management in five European countries, which proved that medication adherence can not only save patient lives but also save national healthcare system costs (Mennini et al., 2015).

Therefore, it is of particular interest to study the enabling mechanisms for the wide-scale implementation of effective MAEIs. One of the major ones is their reimbursement. However, current literature lacks information on this issue, which precludes cross-border benchmarking of effectiveness of various reimbursement models and taking lessons from good practices that have already been identified. This was one of the major stimuli to create a novel network of European researchers, launched in 2020 under the name of "European Network to Advance Best practices & technoLogy on medication adherencE" (ENABLE). The ENABLE is a COST Action, funded by the European Commission, which brings together researchers from 39 European countries and Israel. ENABLE aims to raise awareness of adherence enhancing solutions, foster and extend multidisciplinary knowledge on medication adherence at patient, treatment, and system levels; accelerate translation of this knowledge from producers to useful clinical application; and work collaboratively towards economically viable policy and implementation of adherence enhancing technology across different European healthcare systems (van Boven et al., 2021). ENABLE is composed of four cohesive Working Groups (WGs) among which WG3 aims to facilitate the implementation of MAEIs in European healthcare settings. To obtain this goal, ENABLE WG3 is going to review national healthcare systems as well as the reimbursement pathways for adherence-enhancing technologies across different European countries. This will further allow comparative analysis, and benchmarking of various reimbursement models. This is very important since currently only a few countries systematically monitor adherence, and international benchmarking is still not in place (Khan and Socha-Dietrich, 2018).

The need for such an activity is particularly pronounced now. Recent research undertaken by ENABLE showed that during the second wave of the COVID-19 pandemic, most of management of chronic conditions has been shifted towards remote care. However, none of the European countries was fully prepared to assure maintenance of chronic treatments, and the MAEIs are not routinely embedded into chronic conditions management cycles (Kardas et al., 2021b; Ágh et al., 2021).

This paper, developed as a result of the working meeting of ENABLE WG3, aims to review reimbursed MAEIs currently available and those planned to be implemented soon across selected European countries, and to critically assess them against the predefined criteria. We performed this study in order to fill this knowledge gap, and stimulate further introduction of verified MAEIs into European healthcare systems.

Methodology

Study design

A report from international expert round table, supplemented by consultation of national adherence experts across Europe.

Setting and data collection process

An ENABLE WG3 expert meeting was held in Lodz, Poland, between 16 and 17 September 2021. It was devoted to a discussion on pan-European challenges and opportunities for reimbursement of MAEIs. ENABLE partners (including academics with medical or pharmaceutical backgrounds, HCPs, health economists and other stakeholders) were invited to take part in the meeting and provide a review of current medication adherence reimbursement scenarios in their countries in 2021. Participants from 13 European countries (Croatia, Cyprus, the Czech Republic, Estonia, Hungary, Lithuania, the Netherlands, Norway, Poland, Portugal, Romania, Spain, Switzerland) attended the meeting either personally, or remotely, and gave presentations on MAEIs available in their countries, using a predefined template. In their presentations, the authors were instructed to adopt a national or regional perspective, rather than more local one, *i.e.*, disregard the interventions run by single institution, single-centre initiatives, clinical trials or research projects.

Public discussion during the meeting was followed by an iterative process of fine-tuning of individual countries' input, which took place remotely after the meeting in several rounds. It finally allowed collating a cohesive description of identified MAEIs, using the same operational definitions for their description and classification. The key elements of the standard framework, *i.e.*, the definition and classification of MAEIs, classification of adherence phases, and reimbursement status of MAEIs, are further described in the following sections.

Definition and classification of medication adherence enhancing interventions

MAEIs have been 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 individual patient level.

MAEIs were further divided into those directly or indirectly addressing medication adherence, of which the former were supposed to have medication adherence enhancement as either the primary focus, or at least one of the targets of a complex program.

TABLE 1 Medication adherence enhancing interventions' taxonomy adopted for this study.

Medication adherence enhancing interventions
1. Medication regimen management
2. Educational
3. Behavioural
4. Socio-psycho-affective
5. Reminders (physical and technical)
6. Technical equipment for monitoring the disease and providing feedback on outcomes
7. Adherence monitoring feedback based
8. Incentives and rewards
9. Complex (combination of two and more interventions as described above)
10. Other

A general consensus regarding the taxonomy of medication adherence enhancing interventions has not been reached yet. Therefore, in order to group the identified MAEIs into clusters, we have reviewed current literature and selected relevant publications (Demonceau et al., 2013; Kini and Ho, 2018; Torres-Robles et al., 2018; Wiecek et al., 2019; Cross et al., 2020). MAEI items extracted from these publications have been compared and modified to create a transparent and complete set of MAEI types to be used across this study, as illustrated in Table 1.

Classification of adherence phases

According to the ABC Taxonomy (Vrijens et al., 2012), three phases of medication adherence continuum can be distinguished:

- Initiation–which occurs when the patient takes the first dose of a prescribed medication–being typically a binary event.
- Implementation–the extent to which the patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose is taken–being a longitudinal description of patient behaviour over time, *i.e.*, their dosing history.
- Discontinuation–which occurs when the patient stops implementing the prescribed medication–being typically a binary event. Consequently, persistence is defined as the time elapsing from initiation, until eventual treatment discontinuation (*i.e.*, time to event).

Reimbursement of MAEIs

By "reimbursed MAEIs" we understood those 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 were not regarded as "reimbursed MAEIs." In other words, by "reimbursed interventions" we understood only those which were not paid by patients.

Results

Country updates on the MAEIs reimbursement status were provided by representatives from 12 European countries (i.e. Croatia, Cyprus, the Czech Republic, Estonia, Hungary, Lithuania, the Netherlands, Norway, Poland, Portugal, Spain, and Switzerland). In total, 32 reimbursed interventions were reported. These are numbered consecutively in the paragraphs below in braces, *e.g.*, {7}, and described in details, along with interventions planned to be implemented in the near future.

Croatia

There are no reimbursed MAEIs at any level of the healthcare system currently available in Croatia. Thus, implementation of this kind of interventions depends on the individual awareness of a particular HCP only. Reimbursed interventions indirectly targeting adherence are available at the primary care level, within the so-called Diagnostic Therapeutic Procedures (DTP) which are combinations of fee-for-service payments and performance bonuses for GPs. These are: {1} medication review for persons older than 65 years with three or more prescribed drugs aimed at increasing effectiveness and safety of the therapy (6.94 €) and {2} panels for chronic patients (*e.g.*, diabetes, chronic obstructive pulmonary disease or hypertension) (0.67 €). These panels facilitate the work of GPs through systematic recording, monitoring in predefined time intervals and IT support for treatment of chronic patients and consequent actions to improve disease management, *e.g.*, therapy modifications and/or patient education. The system alerts GPs in predefined time intervals of the need to monitor certain parameters for an individual patient with the aim of managing their chronic diseases. Monitoring of particular parameters (*e.g.*, glycated haemoglobin, HbA1c, lipid profile, spirometry etc.) is additionally reimbursed. However, due to the shortage of medical doctors, overwhelming tasks they provide and low awareness of the adherence problem, adherence focused interventions are rarely employed in daily practice.

Future plans for the introduction of new reimbursed MAEIs are proposed in the National Recovery and Resilience Plan for Croatia 2021–2026, released in July 2021 (Vlada Republike Hrvatske, 2021). One of the planned investments is "Introduction of a system for monitoring the outcomes of treatment of outpatient chronic patients in community pharmacies." As stated in the plan, using an appropriate

software the pharmacist would record all important medical and pharmacological data related to the patient's therapy (*e.g.*, adherence, side effects, achievement of targets, *etc.*). All data on the outcomes of treatment of an individual patient will be transferred to a central information system and will be available for analysis to prescribers and insurers. The proposed pharmacists' procedure will be structured into DTP and reimbursed by the Croatian Health Insurance Fund (CHIF). The estimated overall cost for initiation of the system is 574,056 €.

Cyprus, Republic of

Prior to the National Health Insurance System (NHS), which was launched in 2019 and completed in 2020, the existence of two different subsystems (public and private sector), hindered the implementation of a universally endorsed adherence monitoring system. After the implementation of NHS, a record system collecting information about patients' medication does exist. Electronic monitoring of adherence can be indirectly done by the system through the prescription issues and refill rates, limitation of repetitions of medical prescriptions (max. 6 months) and the number of packages dispensed (according to the defined daily doses, DDDs), and definition of a specific period during which the patient can take his/her medication. This monitoring includes structural assessment of the dispensation of several medicinal products prone to poor adherence, *e.g.*, {3} valsartan and {4} deferasirox. The monitoring is organized by the Health Insurance Organisation (which is the competent authority for managing NHS) at the national statistics level and it does not involve direct interaction with patients.

Introduction of new reimbursed MAEI is planned for the future. Firstly, the Health Insurance Organisation, in collaboration with the University of Cyprus, is drafting a new research program, whose objective will be observation of patient adherence in dementia and cardiovascular diseases, through Patient Reported Outcomes (PROs) and medical assessment. Moreover, there are plans to enrich current programs of assessment of dispensing of several medicinal products by adding parameters enabling indirect estimation of patient adherence, such as the rate of hospitalization, or ferritin levels for deferasirox therapy.

Czech Republic

Currently, several reimbursed MAEIs directly addressing adherence are available in the Czech Republic according to the list of reimbursed health interventions established by the Ministry of Health. The MAEIs comprise {5} an anti-asthmatic drug (Enerzair Breezhaler®) equipped with electronic sensor which sends reminders and registers the correct use of inhalations. Using this inhaler, the patients can voluntarily share their data with the attending physician in order to assess adherence. The drug is subject to prescription by a specialist (pneumologist, allergologist, immunologist), and the intervention has been reimbursed since May 2021, currently covering 100 patients only. Other reimbursed MAEIs directly targeting adherence include patient education provided by nurses, which should cover, among others, issues related to medication adherence: {6} in psychiatry (75 min, once a year), with elements of motivational interviewing; during the education procedure, the nurse uses teaching aids by which she demonstrates the importance of taking medication, or provides comprehensive written materials; {7} in diabetes mellitus, targeted education on the principles and practical skills to improve self-management of diabetes (50 min, six times a year). Similar MAEIs are provided by medical doctors: diabetologists provide targeted education on the principles and practical skills to improve self-management of diabetes, in the form of {8} a group session with max. six patients (30 min, once a year) or in the form of {9} an individual consultation (lasting for 40 min, four times a year). Medical doctors also provide {10} educational interviews with a patient/family, covering issues related to medication adherence (30 min, one time at new therapy initiation).

Two other reimbursed MAEIs available in the Czech Republic indirectly targeting adherence are: {11} education about inhalation technique, provided by nurses in chronic airways conditions (10 min, once a year, or in case of therapy change); and {12} complex assessment of the patient's risk of drug-related problems, determining of patient pharmacotherapy rationalization plan, and verification of the effectiveness of the patient's pharmacotherapy including education regarding the patient's prescribed pharmacotherapy, provided by clinical pharmacists in inpatients, (15–20 min, once or twice per hospitalization) as well as in outpatients (15 min upon a medical doctor's request).

Along with this, one non-reimbursed MAEI has been identified, *i.e.*, individual consultation in a community pharmacy about the patient's pharmacotherapy, including medication adherence. Since 2020, patients, medical doctors, and pharmacists have been provided with access to the shared medication list with all issued ePrescriptions recorded and this may contribute to evaluation and support of medication adherence among these stakeholders. There is also a plan to introduce a new reimbursed MAEI, *i.e.*, individual counselling with the patient in community pharmacies, which is supposed to target the evaluation of medication and actual or potential drug-related problems, including medication non-adherence, and lead to relevant modifications of the pharmacotherapeutic regimen.

Estonia

Several reimbursed MAEIs directly and indirectly targeting adherence are currently available in Estonia:

1. {13} Integrated drug-drug interaction database and clinical decision support system allowing GPs to assess the

compatibility of the prescribed medicines with all currently used ones. When non-compatibility is identified, the physician decides whether to intervene, *e.g.*, reduce the dose, *etc.* While potential interactions are identified early, it should prevent major drug-related problems and thus indirectly improve adherence. Pharmacists can use the same database to identify potential interactions between prescription and OTC medicines.

2. Specialised nurses - asthma nurses, diabetes nurses and mental health nurses - have independent (from physicians) appointments for outpatients: {14} The asthma nurse provides instructions on the use of medications and on disease control (25 min). If necessary, a second repeat visit is arranged to check the ability to use the medicine (up to 20 min). {15} A diabetes nurse teaches the patient how to use the glucometer and inject insulin. {16} At the appointment of the mental health nurse (regular visits up to 30 min), in addition to other topics, the administration of medicines under the supervision of the nurse is provided, drug information is shared, the treatment regimen is taught and the concentration of the medicine in the blood serum is monitored.

Along with these, two non-reimbursed MAEIs are currently available in Estonia:

1. Automated dose dispensing service - The service is provided by a private company for ambulatory and nursing home patients, however, in reality most of the clients are residents of nursing homes. Medicines that are needed for 2 months are dispensed in a plastic strip in daily units. The service includes an initial medication review by a pharmacist. The service (*i.e.*, packaging) is paid by patients.[1]
2. Pharmacy-based reminder service for patients to renew prescriptions - it is a phone-based prescription renewal service. The patient has to give the pharmacist access to their e-prescriptions and authority to communicate with the prescriber on their behalf. Once there is a need for prescription renewal, the pharmacist will contact the doctor. In case the prescription cannot be renewed or there is a need for consultation, the pharmacist will inform the patient by phone before they run out of medicines. For the patient, the service is free of charge. The service is linked to one of the online pharmacies, so that medicines are directly delivered to the patient.[2]

Moreover, there are some plans for the introduction of new MAEIs. Namely, Medication Review (MR) service at community pharmacies, directly targeting adherence, is prepared. This service has been already piloted in Estonia and the results have been presented to the authorities. A service standard is being developed according to which the MR service is provided to patients with chronic conditions and five or more medications. The need for the service is assessed and the service is recommended to the patient by a general practitioner or a pharmacist, however, the patient can also apply for the service independently. In order to achieve the objectives of the service, it must take place at least twice in a row at the beginning. The overall frequency of the service could be twice a year (Tuula et al., 2021).

Hungary

In the past few years, several MAEIs have been implemented in Hungary. In 2009, the National Health Insurance Fund (NEAK) established an indicator system for primary healthcare, which directly targets medication adherence (Kovács et al., 2019; NEAK, 2019). The system provides financial incentives for general practitioners (GPs) who reach the desired target values. Currently, 16 indicators are used to assess adult practices applied by GPs, and one of these directly evaluates medication adherence: {17} Indicator #7: the proportion of patients with myocardial infarction, coronary bypass, or percutaneous transluminal coronary angioplasty who filled prescriptions for beta-blockers at least 4 times in the previous 12 months. GPs are eligible for an extra payment if their patient achieves the goal value as set by the NEAK. However, this indicator system has only a negligible effect on the financing of primary care (3.8% in 2018) and thus it does not have a real motivational effect on everyday patient management (Rurik, 2019).

Another MAEI directly targeting adherence financed from public funds is the {18} "Three Generations for Health Program," which was introduced in 2018 by the Ministry of Human Resources for consortiums of general medical practices[3]. As part of the program, GPs could get financial support for improving medication adherence of chronic patients aged 40–65 years by means of education and regular monitoring (1–3 months) of medication adherence (*e.g.*, with a standardized questionnaire such as the Morisky scale). The program was pre-financed and its financial accounting has been based on a fee-for-service model. Since 2018 the program has had two 1-year calls; the second was closed in 2021 and no new call has been announced so far.

In Hungary, there are also other MAEIs which are financed by pharma companies or other organizations. Among them, the one that directly targets adherence is the {19} free e-health application

1 Automated Dose Dispensing. Available online: https://www.apotheka.ee/teenused/ravimite-personaalne-pakendamine/ (Accessed 17.02.2022).

2 Apotheka Reminder Service. Available online: https://www.apotheka.ee/teenused/apotheka-meeldetuletaja (Accessed 17.02.2022).

3 Three Generations for Health Program. Available online: https://okfo.gov.hu/3g-program (accessed on 03 Oct 2021).

called HABITA™, which was introduced in the middle of 2021. It is a Hungarian language digital blood pressure and medication diary application for hypertensive patients with reminders to take medications and to refill prescriptions. Another example is {20} the "Be Educated and Empowered Patient" (BEEP) program which was launched in 2016. BEEP is an education program for organ transplanted patients organized by the Hungarian Transplant Federation thanks to various funds from different pharmaceutical companies and state grants[4]. The program primarily aims to improve the health literacy level and health behaviour of newly transplanted patients and thus it has an indirect effect on medication adherence as well.

In 2017, the National eHealth Infrastructure (EESZT)[5] was established in Hungary. EESZT is a cloud-based, communication interface that connects healthcare providers (from 2020 including also private service providers) and pharmacies. The system contains all medical data uploaded after 1 November 2017 and transfers the health data (including medical records, prescription and refill data) of all patients to a central database. The system could greatly contribute to monitoring medication adherence; however, currently there is no reimbursed national initiative for this, nor any firm plans of introducing new reimbursed MAEIs in Hungary in the near future.

Lithuania

In Lithuania, {21} GPs are able to hire another nurse whose employment is funded by the health insurance fund. These nurses monitor conditions of patients, including the use of medicines and, if necessary, provide them with advice, as well as refill prescriptions. However, only a few health care institutions have implemented such a practise so far.

Another intervention indirectly influencing adherence comes under the framework of the {22} Quality Guide of the Pharmacy Service which sets standards for the activities of community pharmacies, among the others a pharmacy care service aiming to teach patient how to use inhaled drugs. There is the rule book, how to teach patients to use inhaled drugs, approved by the Minister of Health[6]. The quality of service provision is monitored and evaluated through regular self-analysis. Pharmacists do not get any payment from health insurance for that service. The patients themselves have to pay out-of-pocket, therefore this service is not widely used.

The pharmaceutical policy document includes planned measures to implement IT systems to support monitoring medication adherence. However, the document neither provides clear indicators nor highlights dedicated activities.

Netherlands

In the Netherlands, a mandatory multiple private insurer system exists. Basic health insurance coverage is mandatory and health insurers need to accept all people and provide the basic service package. Items to be reimbursed out of the basic service package (drugs, primary care, secondary care, *etc.*) are selected by central assessment of the Dutch Healthcare Institute (Zorginstituut Nederland, ZIN) based on their efficacy, necessity, practicality and cost-effectiveness.

Two types of adherence enhancing interventions, *i.e.*, drug-device combinations, and complex (behavioural) interventions, have different routes to reimbursement in the Netherlands, according to the universal criteria.

Drug-device combinations are devices integrated with a drug and dispensed at the same time. An example of such a solution is the {23} smart inhaler (Enerzair® Breezhaler®) linked to mobile application which has been assessed by ZIN for maintenance treatment of asthma in adult patients, and found to be worth including in the Medication Reimbursement System (GVS) at List 1B, meaning free pricing by the manufacturer (not exceeding European averages). In principle, doctors prescribe it, however, patients receive automated reminders on their smartphones and do self-monitor themselves using the application. The results are available in the app and may be shared with the doctor during a consultation.

Complex behavioural MAEIs are reimbursed in other way: for this type of interventions a separate reimbursement code for healthcare providers/HCPs (pay per performance) can be applied for at the Dutch Healthcare authority (NZa) by stakeholders (*i.e.*, groups of healthcare professionals and/or individual insurers). An example of such a solution is an {24} adherence to asthma/COPD medication intervention that has a separate NZa coding ("NZa prestatie"). This intervention is provided by pharmacists. It entails identifying nonadherence, finding out reasons for nonadherence, providing adherence enhancing interventions and evaluating its outcomes. The price per performance of the "NZa prestatie" is negotiated between an individual HCP or chain of HCPs and a health insurance company. To get an "NZa prestatie" reimbursed, specific criteria need to be met, *e.g.*

1. A HCP (*e.g.*, a pharmacist) enhances adherence (*e.g.*, by motivational interviewing, counselling), makes changes regarding a medication and/or its dose based on available data.

4 Be Educated and Empowered Patient (BEEP) program. Available online: http://www.trapilap.hu/ (accessed on 03 Oct 2021).

5 National eHealth Infrastructure (EESZT). Available online: https://e-egeszsegugy.gov.hu/web/eeszt-information-portal/home (accessed on 03 Oct 2021).

6 Lietuvos Respublikos sveikatos apsaugos ministerija. ĮSAKYMAS DĖL FARMACINĖS RŪPYBOS PASLAUGOS ĮKVEPIAMUOSIUS VAISTINIUS PREPARATUS VARTOJANTIEMS PACIENTAMS TEIKIMO TVARKOS APRAŠO PATVIRTINIMO. TAR, 2016-06-20, Nr. 17250. Available online: https://e-seimas.lrs.lt/portal/legalAct/lt/TAD/2b4114c0372211e6a222b0cd86c2adfc?jfwid=https://e-seimas.lrs.lt/portal/legalAct/lt/TAD/2b4114c0372211e6a222b0cd86c2adfc?jfwid (accessed on 17.02.2022).[Not Available in CrossRef]

2. A HCP discusses medication intake issues with the patient and how the medication should be used.
3. A HCP highlights the importance of persistence and finds concordance with the patient.
4. A HCP provides the patient with structure (*i.e.*, integration of medication intake with daily routine such as brushing teeth or walking the dog) to help them use the medication properly
5. The adherence is tracked by assessment of prescription refill/dispensing patterns in the future to see changes.
6. Interventions are registered in the patient's record.

Norway

Currently, pharmacies in Norway provide several reimbursed MAEIs:

{25} Multidose drug dispensing (MDD), established in 2006, is a form of adherence aid that provides patients with machine-dispensed medicines in disposable plastic bags, usually for 14 days (Josendal et al., 2021). The MDD bags are labelled with the patient's name, drug names and the time the medicines should be taken. Tablets and capsules can be dispensed *via* MDD, while medicines such as mixtures, inhalators, topical formulations, *etc.*, are dispensed in their original packaging.

{26} Checking the inhaler technique - this service was officially launched in 2016 by the Minister of Health. Pharmacists check a patient's inhalation technique and provide guidance on how to use the device correctly.

{27} New Medicine Service (established in 2018) is intended for patients with cardiovascular diseases who start a new cardiovascular drug. The intervention consists of two 15-min counselling sessions (in a pharmacy or by phone). The first session takes place 1–2 weeks after the patient collects the medicine at the pharmacy, and the second session after the next 3–5 weeks. The focus of this MAEI is: *1*) building good habits, *2*) gaining knowledge and understanding of the prescribed treatment, and *3*) practical problems and difficulties related to adherence to treatment. The efficacy of this intervention was tested in a randomised controlled trial, and was found effective (Hovland et al., 2020).

Moreover, a new reimbursed MAEIs directly targeting medication adherence in diabetes is to be launched soon under the name of "Medicine start–diabetes."

Poland

No reimbursed MAEIs are currently available in Poland. One of the few mechanisms that might be regarded as a non-reimbursed MAEI indirectly addressing medication adherence is generic substitution. According to the legally binding regulations, instead of more expensive drug prescribed for a patient, pharmacists are formally obliged to propose a more affordable equivalent. This could certainly remove one of the major barriers towards adherence. Unfortunately, a recent analysis proved that this mechanism is used extremely infrequently: substitution of original drugs with their generic equivalents was observed in less than 5% (Kardas et al., 2021c). It is noteworthy that the pharmacists are not incentivised to provide this service.

Another non-reimbursed MAEI indirectly addressing adherence is freely available national IT solution dedicated for healthcare professionals: on-line platform www.gabinet.gov.pl. It allows for management of various daily patient-oriented tasks, e.g. prescribing of e-prescriptions. The new functionality, provided recently, allows checking whether an individual prescription has been filled in. This functionality is based on the comparison of e-prescription and dispensation data, which both are recorded within nationwide eHealth systems secured by a dedicated governmental institution, eHealth Center (Polish: Centum e-Zdrowia, CeZ). Commercial office IT systems for doctors tend to adopt this functionality, as well, and often allow for control of the amount of medications prescribed, preventing excessive prescribing and informing on gaps in drug possession due to insufficient prescribing.

There are some plans for a new reimbursed MAEI, indirectly targeting adherence, due to the recently passed Polish Act on the Profession of Pharmacists (Dziennik Ustaw, 2021) which introduces pharmaceutical care that has not existed in Poland before. Among innovations codified by the Act, there is a new service planned within pharmaceutical care which will cover identification, management and prevention of drug problems in general. It will also include drug reviews[7]. Originally targeted towards polypharmacy and drug-drug interactions, it might be expected to support patient adherence as well.

Portugal

Currently, there are no reimbursed interventions that directly target medication adherence available in Portugal. However, there are several interventions that target medication accessibility (thus indirectly helping medication adherence) that are reimbursed. One of these is {28} the "Operation Green Light," which was launched with the COVID-19 pandemic. It ensures transfer of medicines dispensing exclusive for ambulatory hospital pharmacies to community pharmacies, without any costs for the patients. This intervention was reimbursed by a special program from a social care

7 Ministerstwo Zdrowia. Raport opieka farmaceutyczna. Kompleksowa analiza procesu wdrożenia. Warszawa, 2020. Available online: https://www.gov.pl/web/zdrowie/opieka-farmaceutyczna--raport. (accesses on 17.02.2022)[Not Available in CrossRef]

association–Associação Dignitude - Programa Abem, and the recipients of the reimbursement were providers/medicine distributors.[8] However, pharmacists were not specifically paid for taking part in this intervention. This nationwide intervention is now undergoing evaluation to assess the possibility of its being maintained beyond the current pandemic context.

Moreover, it can be argued that the {29} co-payment system in place to facilitate the access to medicines at the community pharmacy is an indirect intervention regarding medication adherence.

Apart from maintaining this intervention in the future, there are no known plans to introduce any other intervention in the coming months. It is possible that pharmaceutical care consultations offered by community pharmacists' may be re-introduced in the coming years and may be reimbursed, however, for now it remains a scenario only.

Spain

At the national level, two major initiatives have been launched in Spain, having an indirect impact on adherence, *i.e.*, the Electronic Prescription program and the Electronic Health Record System (EHRS). In 2013, the interoperable electronic prescription service of the National Health System (RESNS) was launched, allowing dispensation of medication prescribed in another autonomous community from any pharmacy, by electronic means. The only requirement was to present an individual health card[9].

In recent years, several initiatives have been carried out in Spain to review the use and management of medicines where improving adherence to treatment is also particularly relevant. In 2016, the Plan for Treatment Adherence was launched as a collaborative work of scientific medical, pharmaceutical and nursing societies, patient representatives and other expert professionals, with the impulse of Big Pharma. The plan suggests facilitator activities (having adequate time-per-patient; reaching agreement with patients; individualising treatments) and establishes five main pathways to improve the level of patient adherence: raise awareness about the importance of adherence, establish a specific program with a system of information about it, simplify therapeutic regimens and increase patient self-management and empowerment[10].

The Plan has been partially followed in different Spanish regions that have developed several programs aimed at reviewing the use and management of medications. These are multidisciplinary intervention programs where joint efforts of doctors, nurses and pharmacists aim to improve medication adherence. For example, in Andalusia, they currently work on designing a {30} medication review in complex patients with multiple chronic conditions and 15 or more medications prescribed for 180 days or more. In order to meet this goal, functionality of EHRS is used. The ultimate aim of this activity is a Personalized Action Plan (PAP) based on a comprehensive assessment of the patient's health problems and current treatment, incorporating the pharmacological assessment. PAP involves the family doctor, the community nurse and the pharmacist in primary care.

One of the groups most involved in improving adherence in Spain are pharmacists. They are currently working on various strategies and new MAEIs. One of these strategies is the AdherenciaMED project, demonstrating the efficacy and effectiveness of the Therapeutic Adherence Service on health outcomes, at a clinical, economic and humanistic level (Gastelurrutia et al., 2020). Another approach adopted is the development of a Personalised Treatment Dosage Systems. However, no firm plans to introduce new MAEIs are known now.

Switzerland

Although health service research grants in Switzerland have been supporting innovative medication adherence programs, MAEIs have not been yet a priority for the Swiss public authorities. Yet, a few MAEIs have been reimbursed in Switzerland for a long time, *e.g.*, {31} the preparation of weekly pill-organizers either by pharmacists or nurses. This service targets polypharmacy patients on long-term conditions. For example, pharmacists are paid a fixed fee per week if the service is prescribed by the physician for patients taking at least three different long-term drugs (Hersberger and Messerli, 2016). Another intervention is {32} the Direct Observed Therapy (DOT) for any medication delivered in a community pharmacy and prescribed by a physician for patients encountering important adherence issues (*e.g.,* opioids, disulphiram, tuberculosis treatment, HIV treatment) (Hersberger and Messerli, 2016). Eventually, a new MAEI is being prepared based on the New Medicine Service implemented in the UK, where community pharmacists would be able to invoice two 10-min consultations for supporting a patient's initiation of any new long-term treatment.

8 Associação Dignitude. Emergência ABEM: COVID 19 [Internet]. 2020. Available online: https://abem.dignitude.org/emergencia-abem-covid-19/ (accessed on 06.10.2021.)

9 Ministerio de Sanidad, Consumo y Bienestar Social - Profesionales - Receta Electrónica. Available online: https://www.mscbs.gob.es/profesionales/recetaElectronicaSNS/home.htm (accessed on 25.10.2021.)

10 Farmaindustria. Plan de adherencia al tratamiento. Available online: https://www.farmaindustria.es/adherencia/ (accessed on 17.02.2022)[Not Available in CrossRef]

Synthesis of results: Identified MAEIs

After careful consideration, out of the aforementioned 32 reported interventions, four were not accepted as satisfying the operational definitions of reimbursed MAEIs, *i.e.*

- monitoring of the dispensation of products likely to cause poor adherence (valsartan {3} and deferasirox {4}, both coming from Cyprus) – as these monitoring is organised at the high level and does not affect individual patients in any way, it rather serves national statistics;
- patient education on how to use inhaled drugs in compliance with the standards set by the Quality Guide of the Pharmacy Service, reported from Lithuania {22}: due to the fact that the patients themselves need to pay for this service, and it is not subject to reimbursement; and
- co-payment system in place to facilitate the access to medicines at the community pharmacies–reported from Portugal {29}, yet most probably, available in each and every European country. Undoubtedly, reimbursement of prescription drugs is an important enabler of drug access, on the other hand, this system is not specifically aimed to improve adherence, nor targeting individual patients.

Thus, the final number of identified reimbursed MAEIs was 28. They are reported by 10 countries only (*see* Table 2). Out of that number, according to the adopted criteria, 20 interventions were identified as MAEIs directly targeting adherence, as listed in Table 3. The highest number of such interventions has been reported from the Czech Republic (6). MAEIs directly targeting adherence were performed most often by doctors (6), nurses (6), or pharmacists (3). The most common type of these interventions were the educational ones (6), followed by medication regimen management (5), adherence monitoring feedback based (4), and complex interventions (3). The least frequent interventions included the use of reminders (1) and technical equipment for monitoring the disease and providing feedback on outcomes (1). No reimbursed MAEI directly targeting adherence and representing the category of behavioural, socio-psycho-affective, or incentives and rewards has been reported. Only a minority of the reimbursed interventions (7 out of 20) were technology-mediated. Most of the interventions (11) addressed two interlinked phases of medication adherence continuum, *i.e.*, implementation and persistence, and 6 – all three phases, from the initiation to discontinuation (these belonging to either educational, or medication regimen management interventions only). Two MAEIs addressed only one adherence phase, and 1 could not be classified in terms of this dimension (for details, *see* Figure 1).

Characteristics of eight identified reimbursed MAEIs indirectly targeting adherence (Table 4) was similar to MAEIs directly addressing adherence: they were most often provided by doctors (three out of eight), represented the class of educational, or medication regimen management interventions (three in both cases). MAEIs indirectly targeting adherence were supported by technology even less frequently than those targeting adherence directly.

Discussion

Our review identified several reimbursed MAEIs available across the European countries discussed. Noteworthy, these interventions have diverse characteristics. There are interventions directly as well as indirectly targeting adherence. Moreover, they target different phases of the adherence continuum, most often the implementation and persistence. Finally, they are provided by various stakeholders (*i.e.*, doctors, nurses, pharmacists, patients). They employ various targets and methodologies, from educational ones, up to the use of technical equipment for monitoring the treatment and the disease.

On the other hand, only a minority (seven out of 20) of identified reimbursed MAEIs directly addressing adherence were technology-mediated, whereas most of them were based on interpersonal collaborative skills, *e.g.*, patient education, or directly observed therapy executed by HCPs. Several classes of MAEIs were not reported from the reviewed countries. Moreover, two reviewed countries (*i.e.*, Cyprus and Poland) did not report any reimbursed MAEIs or any plans for their upcoming introduction. It all, undoubtedly, points to the potential underuse of various available MAEIs, and particularly, the technology-mediated ones.

Along with these principal findings, we have identified an urgent need for setting uniform standards in terms of MAEI terminology and taxonomy. The operational definitions accepted by us in this review were inclusive by purpose. This, however, leads to certain freedom of interpretation, and thus, the differences between two types of MAEIs were not always clear, requiring one or more rounds of iterative discussions to obtain an internal consensus on their classification. For the same reasons of inclusiveness, we have adopted a "patient perspective" for the issue of MAEIs reimbursement, accepting all those which were free for patients as the reimbursed ones. Among such interventions, some are simply made available, by providing HCPs with relevant tools, standards, or guidelines in order to execute them. However, other MAEIs are subject to dedicated payment to those who execute them, perhaps much more completely fulfilling an intuitive definition of "reimbursed interventions." This definitely requires further studies which should collect more detailed economic data.

Currently, we clustered MAEIs based on their characteristics and/or the techniques employed. However, we found that the reimbursement of identified MAEIs comes from both private and public resources, which may be an important denominator of the interventions for further classification. Perhaps, MAEIs could be further grouped in relevant clusters according to the

TABLE 2 Statistics of reimbursed MAEIs identified across 12 European countries.

Country	Currently employed interventions, *N*		Interventions planned in the future, *N*	
	Directly addressing medication adherence	Indirectly addressing medication adherence	Directly addressing medication adherence	Indirectly addressing medication adherence
Croatia	0	2	0	1
Cyprus, Republic of	0	0	3	0
Czech Republic	6	2	0	1
Estonia	3	1	1	0
Hungary	3	1	0	0
Lithuania	1	0	0	0
Netherlands	2	0	0	0
Norway	2	1	1	0
Poland	0	0	0	1
Portugal	0	1	0	0
Spain	1	0	0	0
Switzerland	2	0	1	0
TOTAL	20	8	6	3

determinants of adherence being tackled by each individual intervention.

Wider implementation of effective MAEIs is of utmost importance as medication non-adherence places a significant cost burden on healthcare systems. According to the results of a recent systematic literature review, the annual cost of non-adherence per person ranged from $949 to $44,190 across 14 disease groups (Cutler et al., 2018). Therefore, even if healthcare systems need to assign special funds for reimbursement of MAEIs, it is reasonable to consider such expenditures. Improving adherence is shown to be an economically viable treatment option for patients with various chronic conditions. Many studies confirmed cost-effectiveness of various MAEIs. For example, a systematic review of interventions adopted in asthma management found that all of the assessed MAEIs were cost-effective considering the increased adherence rate, improved clinical effectiveness and the reduced costs of asthma care (Khaw et al., 2021). Similarly, the cost of a pharmacist-led medication adherence management service for chronic patients was estimated to be €27.33 ± 0.43 per patient for 6 months, which resulted in an incremental cost-utility ratio (ICUR) of €2,086.30/QALY, thus proving that the intervention was time-consuming, yet cost-effective (Valverde-Merino et al., 2021). In another study, despite increased drug costs, better medication adherence was assessed as cost-effective in chronic conditions. The average cost-benefit ratios from adherence for the four conditions examined varied from 1:3.8 for hyperlipidaemia to 1:13.5 for hypertension. Hence, one extra 1 USD spent on medications for adherent patients with typical chronic conditions (congestive heart failure, high blood pressure, diabetes and hyperlipidaemia) can generate between 3 and 13 USD in savings on emergency department visits and hospitalisations (Roebuck et al., 2011).

Several interventions have been shown to effectively improve long-term medication adherence. Therefore, another question is which one to adopt in a particular scenario. Perhaps, in order to optimize cost-effectiveness of these interventions, and thus improve the probability of positive reimbursement decisions, and their more frequent implementation, it is necessary to adopt targeted interventions, tailored to the needs of a specific patient. (van Boven et al., 2016). Thus, the choice of an individual MAEI is important. A recent meta-analysis found that the effect of MAEIs seems to be disease-specific: the most effective ones differed across various clinical conditions (*e.g.*, educational and technical MAEIs resulted in a major effect in terms of improving medication adherence in patients with HIV, circulatory system and metabolic diseases, whereas attitudinal MAEIs presented a more powerful effect on musculoskeletal and mental disorders) (Torres-Robles et al., 2018).

Similarly, there is evidence proving the beneficial role of novel MAEIs, based on eHealth, over medication adherence (Jeminiwa et al., 2019; Aardoom et al., 2020). However, not all technology-mediated MAEIs or eHealth interventions are of equal effectiveness (Mistry et al., 2015; Schulte et al., 2021). Thus, currently there is still some uncertainty regarding the timing, duration, intensity, and specific types of eHealth-enabled MAEIs that could be most effectively implemented by health care providers. The more widespread use of design science, implementation science or other co-creation methodologies which provide a high degree of interaction between all the

TABLE 3 Detailed characteristics of reimbursed MAEIs directly targeting adherence, identified across 12 European countries.

Nr[a]	Country	Intervention	Who performs?	Type	Technology mediated?
5	Czech Republic	Inhaled drug (Enerzair Breezhaler®) for asthma therapy equipped with sensor and dedicated app	Patients	Adherence monitoring	Yes
6		Patient education in psychiatry; with elements of motivational interview	Nurse	Education	No
7		Patient education in diabetes, covering issues related to medication adherence	Nurse	Education	No
8		Patient education (group sessions), covering issues related to medication adherence	Doctor (diabetologist)	Education	No
9		Patient education (individual consultation), covering issues related to medication adherence	Doctor (diabetologist)	Education	No
10		Educational interview with a patient/family member covering issues related to medication adherence, provided at therapy initiation	Doctor	Education	No
14	Estonia	Patient education in asthma, covering issues related to medication adherence	Nurse	Education	No
15		Patient education in diabetes, covering issues related to disease self-monitoring with glucometer and medication adherence	Nurse	Technical equipment for monitoring the disease and providing feedback on outcomes	No
16		Directly observed therapy of mental conditions, accompanied by drug concentration monitoring	Nurse	Medication regimen management	No
17	Hungary	Primary care performance indicator: the proportion of patients with myocardial infarction, coronary bypass, or percutaneous transluminal coronary angioplasty who filled prescriptions for beta-blockers at least four times in the previous 12 months	Doctor (GP)	Adherence monitoring	Yes
18		Patient education and regular monitoring of medication adherence by GPs in chronic patients aged 40–65 years under the "Three Generations for Health Program"	Doctor (GP)	Complex	No
19		Mobile application for hypertensives providing blood pressure and medication diary with reminders to take medications and to refill prescriptions - HABITA™ e-health application	Patient	Reminders	Yes
21	Lithuania	Monitoring patients' conditions including the use of medicines	Nurse (hired by GPs or Primary Health care institution)	Adherence monitoring	No
23	Netherlands	Inhaled drug (Enerzair Breezhaler®) equipped with sensor and app for asthma therapy	Patients	Adherence monitoring	Yes
24		Complex behavioural intervention targeting adherence to asthma/COPD medication	Pharmacists	Complex	No
25	Norway	Multidose drug dispensing providing patients with machine-dispensed medicines	Pharmacists (in collaboration with GPs and nurses)	Medication regimen management	Yes
27		New Medicine Service for patients with cardiovascular diseases	Pharmacists	Complex	No
30	Spain	Medication review in complex patients with multiple chronic conditions and 15 or more medications prescribed	Pharmacists, GPs and nurses in collaboration	Medication regimen management	Yes
31	Switzerland	Preparation of weekly pill organizers	Pharmacists or nurses	Medication regimen management	Yes
32		Direct Observed Therapy for any patient encountering important adherence issues	Pharmacists	Medication regimen management	No

[a]Numbers refer to consecutive numbers ascribed to interventions across the country related paragraphs, appearing in braces; GP, general practitioner.

relevant stakeholders and context, to design and implement eHealth-enabled MAEIs is a possible solution moving forward (De Geest et al., 2020; Gregório et al., 2021).

Unfortunately, despite all the evidence, clearly pointing at health, societal and economic benefits of improved medication adherence, healthcare systems do not take much

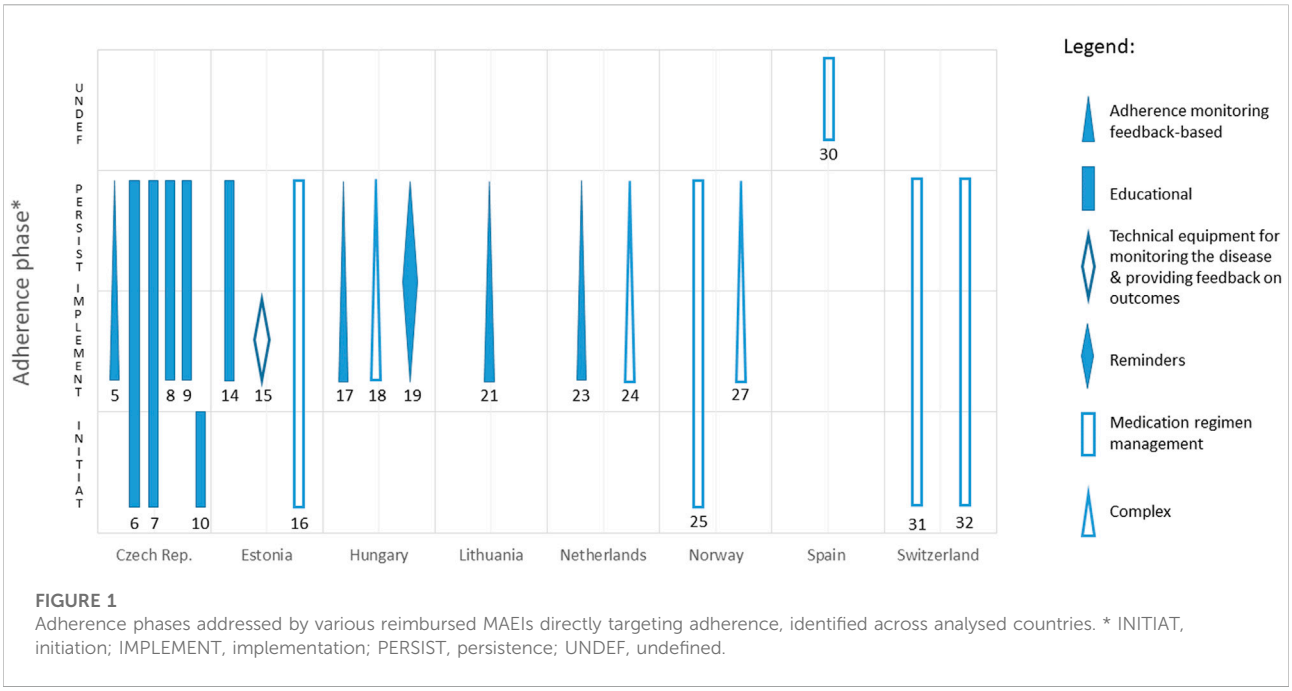

FIGURE 1
Adherence phases addressed by various reimbursed MAEIs directly targeting adherence, identified across analysed countries. * INITIAT, initiation; IMPLEMENT, implementation; PERSIST, persistence; UNDEF, undefined.

TABLE 4 Detailed characteristics of reimbursed MAEIs indirectly targeting adherence, identified across 12 European countries.

Nr[a]	Country	Intervention	Who performs?	Type	Technology mediated?
1	Croatia	Medication review for persons aged over 65 years with three or more prescribed drugs, aiming to increase effectiveness and safety of the therapy	GP	Complex	No
2		Panels for chronic patients (e.g. diabetes, COPD or hypertension) involving monitoring of chronic disease and relevant interventions to improve disease management, e.g. therapy modifications and/or patient education	GP	Complex	No
11	Czech Republic	Patient education about inhalation technique in chronic airways conditions	Nurse	Education	No
12		Assessment of patient risk of drug-related problems, determining his/her pharmacotherapy rationalization plan, provided to inpatients and outpatients	Clinical pharmacists	Medication regimen management	No
13	Estonia	Drug-drug interaction database and clinical decision support system, providing compatibility of the prescribed medicines with all existing medicines	GP	Medication regimen management	Yes
20	Hungary	"Be Educated and Empowered Patient" program aimed at improving health literacy and health behaviour in newly transplanted patients	Patient organisation	Education	No
26	Norway	Patient education in asthma, including checking inhaler use technique	Pharmacists	Education	No
28	Portugal	"Operation Green Light" allowing dispensation of medicines previously available exclusively in hospital pharmacies in community pharmacies	Pharmacists	Medication regimen management	No

[a]Numbers refer to consecutive numbers ascribed to interventions across the country related paragraphs, appearing in braces; COPD, chronic obstructive pulmonary disease; GP, general practitioner.

action to support medication adherence in patients with chronic conditions. In consequence, we are still far from a widespread use of MAEIs. The scenario was neither changed by the call to address medication non-adherence, clearly stated by the seminal WHO report in 2003 (World Health Organization, 2003), nor the policy recommendations for promoting medication adherence produced within the dedicated European research collaboration - the ABC project[11]. A survey administered in 2017 to the authorities of member countries of the Organization for Economic Co-

11 Final report of the ABC Project. Available online: http://abcproject.eu/img/ABC%20Final.pdf (accessed on 17.02.2022).

operation and Development (OECD) found that in most of them non-adherence is still not considered a priority on the national policy agenda. Interventions to enhance or support medication adherence are not well coordinated. They do not constitute part of a larger strategic policy programme either. Most countries dvelop guidelines, frameworks, and financial incentives for primary care physicians or interprofessional team to improve quality of care for patients with chronic diseases (Khan and Socha-Dietrich, 2018). However, no specific physician- and few interprofessional-delivered adherence interventions were reported by the participating countries.

In particular, reimbursement of MAEIs has not received much attention until now. Interestingly enough, this issue was neither tackled in the extensive Cochrane review on interventions for enhancing medication adherence (Nieuwlaat et al., 2014) nor in the WHO report on chronic diseases management in Europe (Nolte et al., 2014).

A limited success of many adherence-promoting programs may result from the lack of inclusion of and limited support for engaged stakeholders. Meanwhile, financial incentives play an important role in improving adherence (Khan and Socha-Dietrich, 2018). A study that examined physicians' preferences found that doctors' willingness to implement adherence-promoting programs in daily practice was determined by the time commitment to carry out the program (34.8% importance), reimbursement (33.3%), and validation status of the program (23.7%) (Müller et al., 2020). A better understanding of the impact of interprofessional collaborations to support medication adherence throughout the patient's therapeutic care journey is needed. It may indicate the added value of the reimbursed MAEIs which provide a win-win opportunity to both patients, and healthcare providers.

The results of our review undoubtedly point to the scarcity of reimbursed MAEIs across the studied European countries. Despite large availability of effective, and cost-effective interventions, the plans for implementation of new reimbursed MAEIs in these countries in the nearest future are not impressive either. Perhaps, the major lesson that one should learn from that scenario is that obviously, the time is high for a change. It does not only involve MAEIs which should be more widely implemented across Europe. There also exists an urgent need to create a well-balanced, evidence-based process of iterative improvement of medication adherence, as proposed in Figure 2. The patient plays an active part in the process as a member of the interprofessional team based on shared decision making. A careful approach to design, implementation and evaluation of reimbursement mechanisms is the key component of the process.

Along with scarcity of interventions targeting adherence identified in the participating countries, we have also found major gaps in the current approach towards MAEIs,

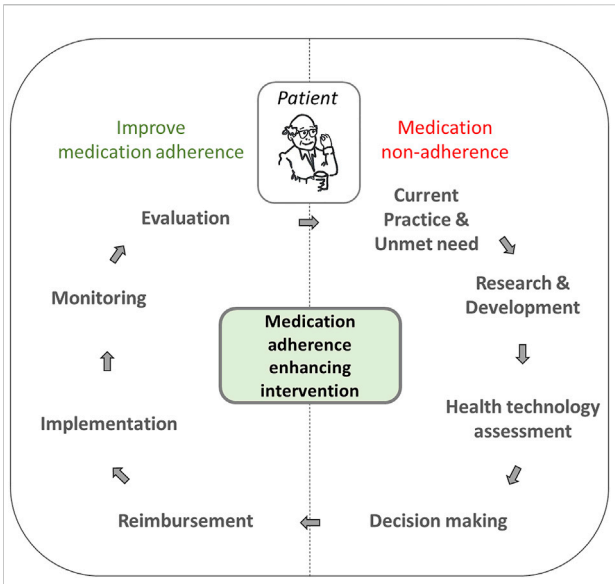

FIGURE 2
Scheme of iterative medication adherence-bettering process, involving reimbursement of medication adherence enhancing interventions.

which together creates an urgent need for adoption of a uniform approach to address the issue. Therefore, as a result of the ENABLE WG3 Lodz meeting, and this in-depth review, we have designed European level recommendations which call for:

1. A clear and uniform taxonomy for MAEIs.
2. Formulation of minimum standards for the clinical evaluation and health technology assessment of MAEIs.
3. Transferability of MAEIs from one healthcare system to another.
4. Recommendations on reimbursement pathways for the different types of MAEIs.
5. Standard evaluation procedures for the reimbursement and implementation of MAEIs embedded into national healthcare systems.

Medication adherence is accepted as a measure of care quality (Seabury et al., 2019). Taking this into consideration, international experts emphasized that adherence to treatment is a right of chronic patients. Thus they urged European healthcare systems to finance programs at optimising adherence and stimulating collaboration of other parties such as industry and national governments (van Boven et al., 2017). A practical use of such an approach has been proposed by a dedicated OECD report, which suggests a broadly-used medication adherence as a measure for performance-based reimbursement contracts. In its conclusion, the OECD report identifies four enablers of the improved medication adherence at the system level, these

being acknowledging, informing, incentivising, and steering/supporting. (Khan and Socha-Dietrich, 2018).

Our results should be considered in the light of certain limitations. First of all, it should be kept in mind that the method of collecting information on the availability of MAEIs, which was based on personal knowledge of the authors, may not entirely reflect all the interventions available in a particular country. Similarly, various professional backgrounds of the authors may add bias to the scope of the reporting. The authors made every effort (*e.g.*, by holding external consultations) in order to provide a full picture. Nevertheless, despite the iterative process of provision, and fine-tuning of the country feedback, certain MAEIs might have been underreported. For instance, some education programs comprising support for medication adherence and integrated in the standard clinical practice might have been considered as reimbursed MAIEs by some countries (*e.g.*, the Czech Republic), however, not by other (*e.g.*, Switzerland). It is also uncertain if any official list of reimbursed MAIEs is available in each country, which makes the situation even more difficult.

Moreover, lack of generally accepted taxonomy of MAEIs led to the use of the operational definitions, which not always were very precise, thus living the space for subjectivism in MAEI classification. In the future, this obstacle could be overcome by the use of a predefined taxonomy.

Finally, only infrequently the economic details of particular MAEIs were fully available, thus counteracting fair benchmarking of the identified interventions. In future studies, this dimension is worth special attention.

On the other hand, this study has a number of strengths. According to the authors' knowledge, the ENABLE WG3 working meeting which took place in Lodz, Poland, between 16 and 17 September 2021 was the first European expert meeting collecting information on the reimbursed MAEIs in a systematic way. Therefore, in future research, the findings of the meeting may serve as a source of inspiration for considering certain interventions to be MAEIs, and broadening the scope of reporting. Also, we believe that our operational definitions may stimulate further work on MAEIs taxonomy.

In conclusion, our review highlights the scarcity of reimbursed MAEIs across the selected European countries. However, we hope that our work, being the first review of its kind on reimbursed MAEIs, paves the way to further studies, which by advancing benchmarking of MAEIs, may stimulate their more common visibility, adoption, and reimbursement across European countries.

Data availabity statement

The original contributions presented in the study are included in the article further inquiries can be directed to the corresponding author/s

Author contributions

All authors contributed to conception and design of the study, and contributed to the manuscript drafting. PK coordinated drafting of the first version of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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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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Acceptance and needs of medication literacy education among children by their caregivers: A multicenter study in mainland China

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Background: This study aims to investigate the needs of child caregivers for popular science about safe medication for children, to deeply explore the characteristics of child caregivers' demand for safe medication and the shortcomings of current popular science work, and then to seek better coping strategies to ensure children's safe medication.

Methods: A questionnaire was designed based on Lasswell's "5W" communication model to investigate the needs of child caregivers in terms of content, channels, and forms of popular healthcare science on the safe usage of children's medication.

Results: The primary ways caregivers receive popular healthcare science education concerning safe medication usage knowledge are through medical institutions, notification by medical staff, and personal media. The caregivers of children have a high demand for the presentation of text, pictures, and videos in three forms of popular healthcare science content. Caregivers placed significant importance on the popularization of safe medication usage for children. The survey results showed that the top 3 ways for caregivers to think that the quality of popular healthcare science content was "very good" came from medical institutions, medical staff notifications, and personal media, effectively increasing popular healthcare information accuracy. The intelligibility and pertinence of content expression are urgently needed within the caregiver population.

Conclusion: Caregivers are very concerned about the popular science of safe medication for children, and are willing to learn about relevant content. Guided by the demand, we should actively disseminate accurate and easy-to-understand popular science about safe medication for children to caregivers through online or offline channels so as to promote safe medication for children.

KEYWORDS

caregivers, children, medication literacy education, popular science, health promotion, Lasswell's communication mode

1 Introduction

Health literacy has been recognized internationally as one of the important public health strategies in maintaining national health as well as achieving health equity (World Health Organization, 2016; Santos et al., 2017; Sentell et al., 2020). In 2018, the overall level of health literacy among Chinese residents was only 17.06%, which is still at an all time low (The Central People's Government of the People's Republic of China, 2018). Low levels of health literacy and inappropriate or inaccurate health communication may lead to medication errors within the public domain (Taylor and Harding, 2001). China's" Opinions of the State Council on Implementing Healthy China Initiative (2019–2030)" (State Council, 2019), contained one of the first major healthcare actions called the "Health Knowledge Popularization Action", which mentions rational drug use as the skillset and healthcare information that citizens should be most familiar with learning, retaining, and implementing. Medication education is not only an important way for the public to obtain information, but also is an indispensable strategic policy to improve the health literacy of the people as a whole (Aslam et al., 2020).

According to the "2015 Children's Medication Safety Report" released by Safe Kids Worldwide-China (Safe Kids Worldwide, 2015), drug poisoning was the leading cause of poisoning in children, and is still on the rise. A study in the United States (Schillie et al., 2009) showed that approximately 71, 224 children in the United States are admitted to the emergency department due to drug overdose each year. Therefore, these admissions account for 68.9% of the emergency department visits for children with poisoning, and the proportion of drug poisoning was twice that of non-drug poisoning. Among these cases of drug overdoses, 82.2% originated from self-medication administration without professional guidance, with medication errors and abuse accounting for 14.3% of the drug overdoses (Schillie et al., 2009). Medication education is one of the most important means of improving the health literacy of child caregivers in order for the caregivers to rationally administer drugs, thus, reducing the medication errors in children.

Due to the post-epidemic era, the public now has a heightened awareness of health, significantly improving an individual's awareness and physical health status (Sentell et al., 2020). Under these circumstances the popularization of health science literature is a public service; therefore, it should pay close attention to public satisfaction and demands for such information. The public is a key element and the target audience of health science literature, thus the needs of the public are the initial starting point when disseminating health related information (Ren and Zhao, 2014; Centers for Disease Control and Prevention, 2019). Health science literature's informatization is currently increasing; thus, the public's needs for health-based information are also changing. Furthermore, there are differences in the public's demand for drug science information among different groups and are affected by factors such as natural conditions, economic development, and personnel composition (Zhong et al., 2020).

The nature of the dissemination of medication knowledge is the dissemination of information, with the purpose of trying to influence the audience. The dissemination process of information includes: Who, Say What, In Which Channel, To Whom, With What Effect (Lasswell, 2013). Based on Lasswell's 5W communication model (Lasswell, 2013), this study has designed a questionnaire to investigate child caregivers' needs of popular science about safe medication for children. Furthermore, we have explored the characteristics of children's caregivers' demand for safe medication information as well as the shortcomings of the current popular science about safe medication. We then sought better countermeasures to enhance the dissemination of safe medication so as to improve the caregivers' medication literacy and reduce the incidence of children's medication errors. The results of the questionnaire survey are reported as follows.

2 Materials and methods

2.1 Study design

In this study from 1 April 2021 to 31 September 2021, the sample was selected using two-stage stratified sampling. In the first stage, we selected five children's hospitals from cities at prefecture level in Central China, North China, South China, Northwest China, and Northeast China. In the second stage, The sample size of the questionnaire was calculated by the proportional probability sampling method (PPS). According to the information standard of the information system of hospitalized children in the previous year in each hospital, 10% of the total number was selected. Caregivers of hospitalized children aged 0–6 years were randomly selected from each hospital. Face-to-face interviews were conducted by trained interviewers with the primary caregivers of children selected. Primary caregivers were defined as those who regularly cared for the children, such as parents or grandparents.

The inclusion criteria include: 1) The subjects are long-term and stable caregivers of the children; 2) The children in the family

are taking medicine or have a history of taking medicine; and 3) The doctor has confirmed that they have good communication and understanding skills. The exclusion criteria include: 1) Eliminate repeat questionnaires; 2) Questionnaires with inconsistent logic in the front and back options; 3) Filling time < 200 s.

2.1.1 Design of the questionnaire

Based on Lasswell's "5W" communication model (Lasswell, 2013), namely who (communication subject), say what (communication content), to whom (communication object), by which channel (communication channel), and what effect (communication effect), a questionnaire was designed to investigate the needs of a child's caregiver in terms of content, channels, and forms of popular health related literature.

2.1.2 Questionnaire evaluation criteria

Using the Likert 5-level scoring method we assigned points ranging from 1 to 5 and correspond to 1 "no need at all", 2 "not very necessary", 3 "general need", 4 "more need", and 5 "very necessary". Single-choice questions such as demographic and sociological information, including gender, permanent residence, highest education level, monthly household income, ethnicity and other basic information, are filled out on the form by the volunteer. Answers to the multiple-choice questions are guided in the presence of a pharmacist. When the selected answer conforms to the child's actual situation, the answers are considered valid.

2.1.3 Questionnaire quality control

The questionnaire quality control primarily includes investigation and data controls. 1) Prior to the investigation, we formulated an investigation implementation plan, and conducted a unified training for investigators and quality control personnel. If the respondents do not understand the question, they can ask the investigator; however, the investigator is not allowed to answer the relevant content of the question that involves the answers of the questionnaire as well as does not give leading questions or prompts. 2) During the data entry stage the double entry of questionnaire data is implemented, and a consistency check is carried out to ensure the entered data's accuracy.

2.2 Statistical analysis

The data was imported into the SPSS 25.0 software for analysis. The count data are expressed as frequencies and percentages. Univariate analysis compared the importance of safe medication and the demand for popular health information among caregivers with different demographic and sociological characteristics. The reliability and validity of the questionnaire were evaluated *via* the retest reliability and content validity index, respectively.

3 Results

3.1 Questionnaire distribution, reliability, and validity evaluation

A total of 1,002 questionnaires were distributed in this survey. According to the exclusion criteria, invalid questionnaires such as incomplete and irregular filling were screened out, and 963 valid questionnaires were recovered, with an effective rate of 96.1%.

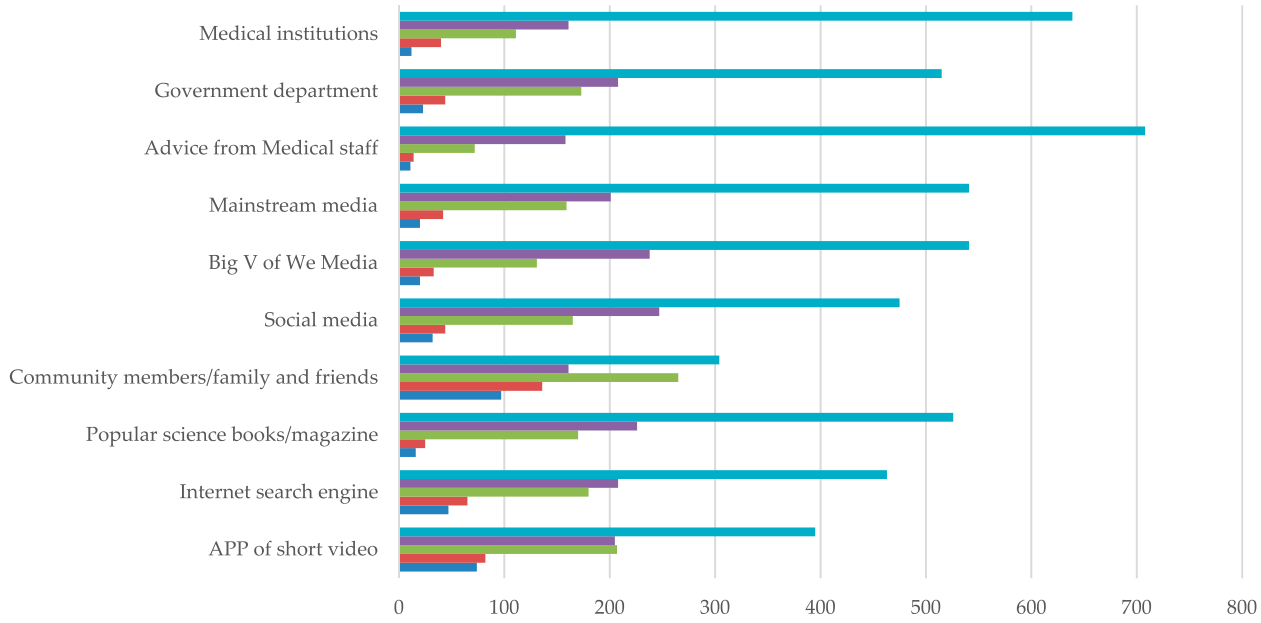
Five clinical pharmacists from different regions (2 chief pharmacists and 3 deputy chief pharmacists) evaluated and revised the questionnaire's semantics, expression habits, and professional nature. The content validity index of experts evaluation was found to be 0.928. After the questionnaire was formulated, 80 parents were pre-investigated. 1 week later, 43 parents were selected to repeat the same questionnaire, and the test-retest reliability was 0.767.

3.2 The main body of dissemination of popular health related information on safe medication use for children

The questionnaire survey results (Figure 1) show that the medical structure, medical staff, mainstream media, self-media big V, and popular science books/magazines were the main propagators of health related information on safe medication use for children. The results showed that the public had a higher demand and trust for health information popularizing medication use by medical institutions and personnel.

3.3 Demands of child caregivers for popular health related information concerning the safe medication usage among children

The survey results show that (Figure 2), the caregivers have an increased demand for information regarding the indications, contraindications, usage, dosage, precautions, and the diagnosis and treatment of adverse reactions of commonly used medication for children. Moreover, the demand for knowledge is used to identify counterfeit and sub-par drugs, equipping households with children's medicine boxes, as well as the storage methods of children's medication. This showed that the caregiver group had an excellent grasp of the basic information on preventing misuse;



	APP of short video	Internet search engine	Popular science books/magazine	Community members/family and friends	Social media	Big V of We Media	Mainstream media	Advice from Medical staff	Government department	Medical institutions
Very necessary	395	463	526	304	475	541	541	708	515	639
Quite necessary	205	208	226	161	247	238	201	158	208	161
General necessary	207	180	170	265	165	131	159	72	173	111
Not really needed	82	65	25	136	44	33	42	14	44	40
Not needed at all	74	47	16	97	32	20	20	11	23	12

FIGURE 1
The needs of caregivers based on the supply channels of popular health related information regarding children's safe medication usage knowledge.

however, the understanding of children's commonly used drugs and the diagnosis and treatment of adverse drug reactions was limited. Therefore, caregivers urgently needed targeted healthcare information popularization and education on medication and its usage.

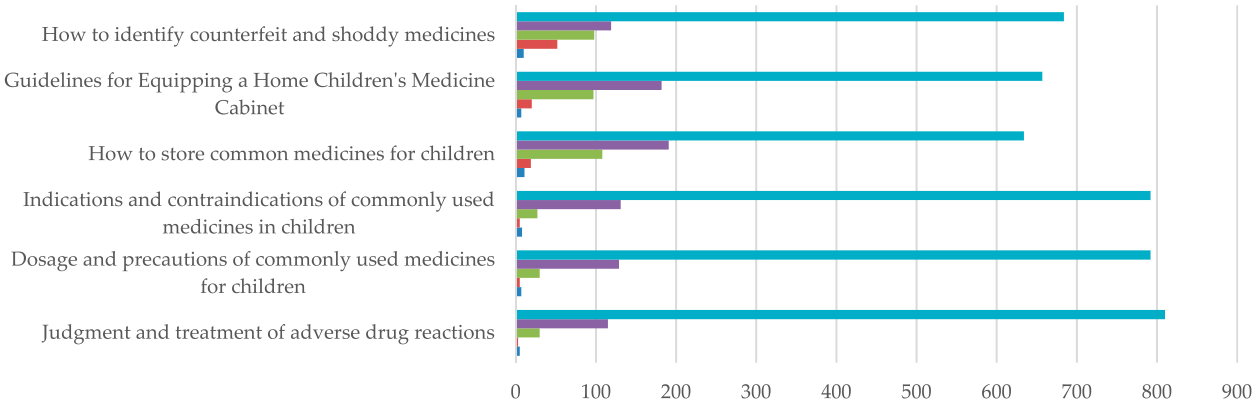
3.4 Recipients of popular health related information regarding safe medication usage among children

In this study, the children's caregivers were the recipients of popular health related information regarding the safe medication usage for children. Among the children caregivers surveyed, female respondents accounted for 82.5% of the total sample size, and male respondents accounted for 17.5%; in terms of age, the proportion of respondents aged 31 to 40 was 54.9%; in terms of permanent residence, the majority of respondents were urban residents, accounting for 89.9%; and in terms of education, 66.3% of respondents had a bachelor's degree or higher (Table 1).

3.5 Ways and media forms for child caregivers to accept popular health related information on children's safe medication usage

3.5.1 Approaches to receiving popular health care information on the safe medication usage for children

The results of the survey (Figure 3) show that the primary ways for caregivers to receive popular health care education



	Judgment and treatment of adverse drug reactions	Dosage and precautions of commonly used medicines for children	Indications and contraindications of commonly used medicines in children	How to store common medicines for children	Guidelines for Equipping a Home Children's Medicine Cabinet	How to identify counterfeit and shoddy medicines
Very necessary	810	792	792	634	657	684
Quite necessary	115	129	131	191	182	119
General necessary	30	30	27	108	97	98
Not really needed	3	5	5	19	20	52
Not needed at all	5	7	8	11	7	10

FIGURE 2
Caregivers' need for scientific content on safe medication usage for children.

regarding knowledge on children's safe medication usage were provided by medical institutions (publicity boards and pamphlets), medical staff notifications, and big V of We Media (Dr. Clove and Dr. Chunyu). Furthermore, unique groups such as medical institutions and personnel used their highly specialized knowledge and healthcare skillsets to conduct popular health care education topics and classes for the caregivers. In addition, social media also played an important role in disseminating health science information (Edington et al., 2016; Stellefson et al., 2020). Therefore, with the development of internet technology, the big V of We Media gained a significant audience base. In comparison, more traditional communication methods such as mainstream media (central or local TV stations and radio programs) and popular health care related science books and magazines are needed to further strengthen the knowledge and publicity concerning the safe usage of children's medication.

3.5.2 Accepting the media carrying form of popular science on safe medication for children

The survey results (Figure 4) show that the children's caregivers had an increased demand for three forms of popular health care content: text, picture and video.

3.6 The effect and satisfaction of children's caregivers receiving popular health care related science on safe medication for children

3.6.1 The degree of attention paid by children caregivers concerning the popularization of the safe usage of children's medication

The results of the survey showed that the children's caregivers paid more attention to the popularization of children's safe medication usage, with a large percentage of caregivers (99%) attributing great significance to this particular set of knowledge. This shows that the children's caregivers believed that it was an excellent questionnaire needed to understand the safe usage of children's medication through health care related science popularization which could, reduce medication errors and the risk of unreasonable medication administration. However, nearly half of the respondents (47.6%) indicated that they had never received popular health care education regarding the safe usage of children's medication. This indicates the educational gaps and deficiencies within the field of health care information popularization as well as the education on the safe usage of children's medication; thus, showing a mismatch between supply and demand.

TABLE 1 Sociodemographic characteristics of the children's caregivers (n = 963).

Variable	*n*	%
children's caregivers	963	—
Gender		
Male	169	17.5
Female	794	82.5
Age		
25 years and under	50	5.2
26 ~ 30 years old	209	21.7
31~ 40 years old	529	54.9
41 ~ 50 years old	127	13.2
51 years and over	48	5.0
Permanent residence		
Urban	866	89.9
Rural	97	10.1
Highest education		
Junior high school and below	54	5.6
High school	46	4.8
Technical secondary school	45	4.7
Junior college	180	18.6
Undergraduate	527	54.8
Postgraduate	111	11.5
Marital status		
Married	936	97.2
Divorced	20	2.1
Widowed	7	0.7
Average monthly income per person in family		
Below 2000 yuan	59	6.1
2000~4,000 yuan	186	19.3
4,000~6,000 yuan	267	27.8
6,000~8,000 yuan	169	17.5
More than 8,000 yuan	282	29.3
Current/pre-retirement industry		
Office staff and related personnel	404	42
Heads of state organs/party group organizations/enterprises/institutions	73	7.6
Soldier	1	0.1
Production personnel in agriculture/forestry/animal husbandry/fishery/water conservancy	13	1.3
Other employed/unemployed	270	28.0
Business/service personnel	82	8.5
Operators and relevant personnel of production/transportation equipment	18	1.8
Specialized technical staff (excluding medical staff)	101	10.5
Students	1	0.1

3.6.2 Evaluation of the quality of popular science content obtained by different dissemination channels

The results (Figure 5) also showed that among all the channels that can disseminate popular health care information on the safe usage of children's medication, the top three channels that considered the quality of popular health care content to be "very good" were medical institutions, medical staff notification, and the big V of We Media. This ranking was similar to the rankings mentioned above for the primary ways that the caregiver group receives popular healthcare education, thus, proving the outstanding contributions of medical institutions, medical personnel, and We Media influencers on the popularization of the information surrounding the safe usage of children's medication. The caregiver group affirmed the quality of the information transmitted through the above channels. Conversely, the quality of information obtained from the community resident, search engines, and the APP short video channels showed a bad or very bad situational outcome.

3.6.3 Suggestions for improving the overall quality of the existing popular healthcare information content

The results (Figure 6) show an urgent need for the caregiver group to effectively increase the accuracy of popular healthcare information as well as the intelligibility and pertinence of the content expression. Furthermore, some subjects pointed out that it was crucial to focus on the timeliness of the content of popular healthcare education. Drug and drug information is updated quickly over time, outdating some of the information found in hospital propaganda columns. In addition, in terms of content, it is necessary to strengthen and improve the construction of the healthcare information popularization system required for the safe usage of medications used to treat rare diseases in children.

4 Discussion

The respondents believed that they urgently needed popular healthcare education; however, they had very limited access to popular healthcare information on safe medication usage. The data shows that the popular healthcare work in this field of safe medication usage should be vigorously strengthened. The ways caregivers have received popular healthcare education have proven that the contributions made by medical institutions and medical staff in popularizing knowledge about the safe use of medication for children as well as the high recognition of the quality of the information disseminated are outstanding. Conversely, the quality of information obtained from community residents, search engines and APPs of short video channels has shown a poor or very bad situation; thus, it reflected a social phenomenon that proves dissemination of information from the network environment was mixed, and contained many untrue rumors (Berland et al., 2001; Kunst et al., 2002; Mheidly and Fares, 2020). It was suggested that relevant departments and platforms still needed to pay more attention to the quality of popular healthcare information.

The problems that exist within the quality of the current popular healthcare information have hindered the further

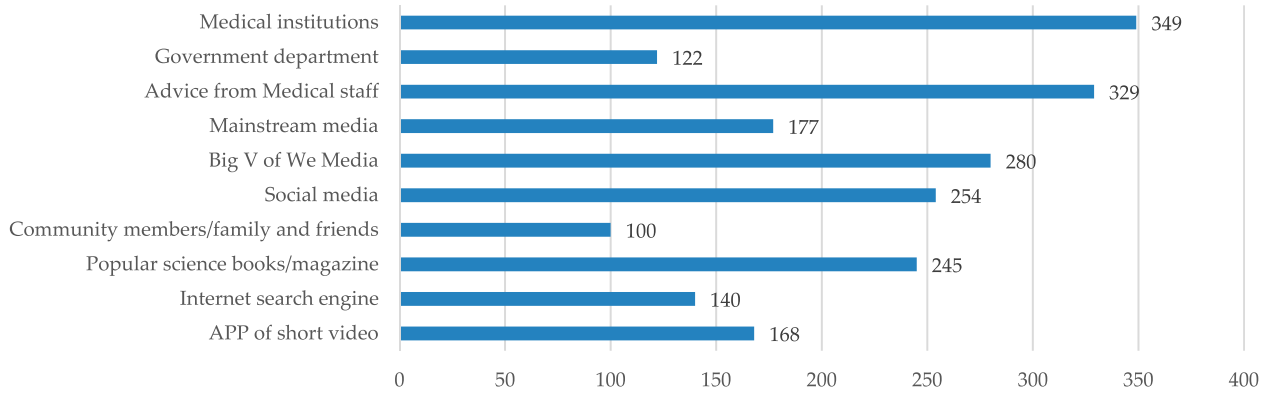
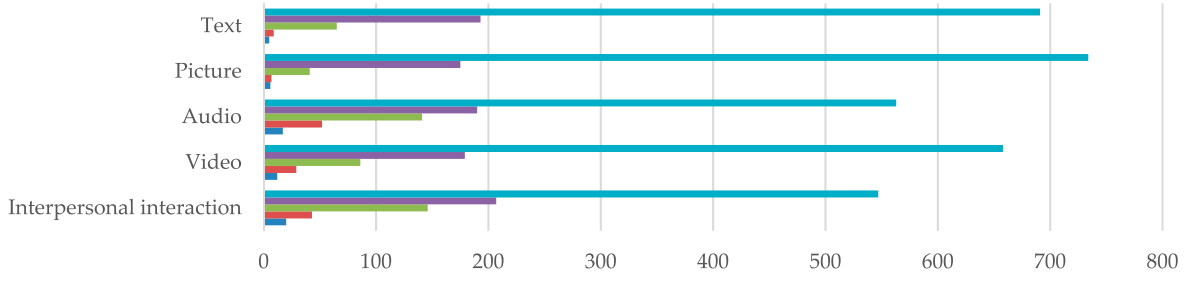


FIGURE 3
Access to healthcare science education regarding the safe usage of children's medication.

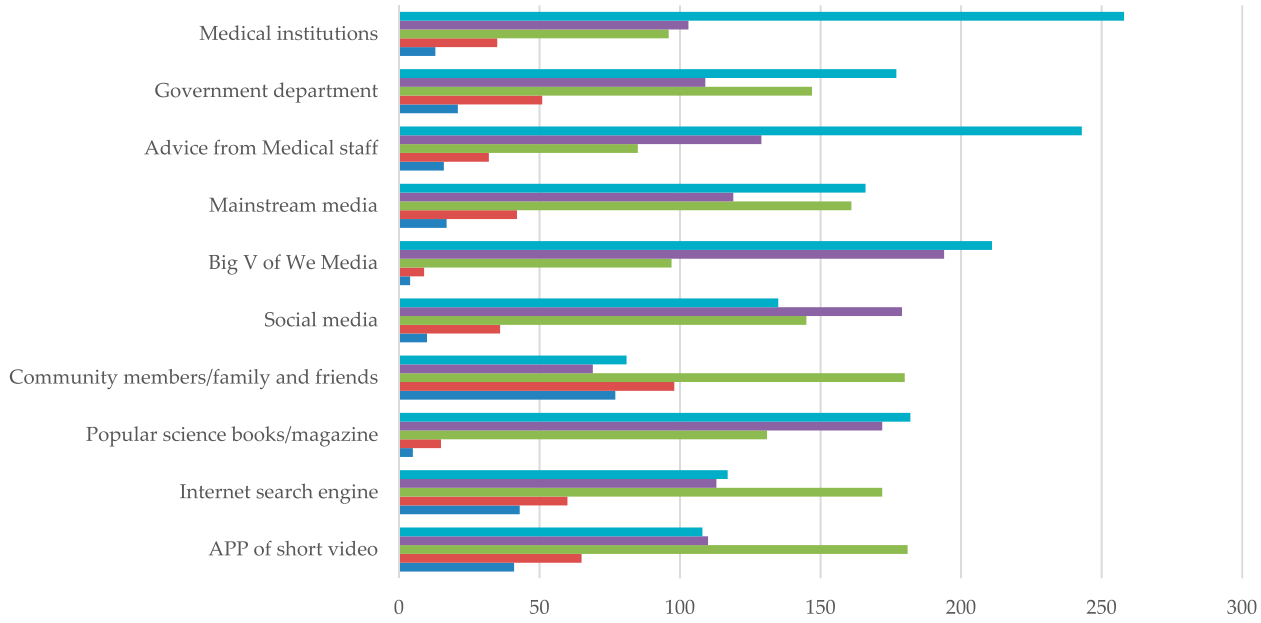


	Interpersonal interaction	Video	Audio	Picture	Text
Very necessary	547	658	563	734	691
Quite necessary	207	179	190	175	193
General necessary	146	86	141	41	65
Not really needed	43	29	52	7	9
Not needed at all	20	12	17	6	5

FIGURE 4
Demand from caregivers of a scientific form of healthcare knowledge concerning the safe usage of children's medications.

improvement of health literacy, including the information expression is not authentic and reliable as well as the information content is not updated in a timely manner. Currently, the contradiction between the public's urgent need for healthcare science popularization and the low degree of trust in content from some of the dissemination channels has been an urgent and significant problem that needs to be solved for the development of healthcare popularization works. Comparing the existing communication channels shown in Figure 2, it has been revealed that the mainstream media has not currently exerted significant, influential power. Therefore, it is imperative to make full use of mainstream media resources (Robinson et al., 2014) in order to disseminate large amounts of information regarding healthcare content with high fidelity and to the desired audience in a timely and rapid manner. The primary age group of people who are the children's caregivers is the elderly. Unfortunately, this age group has a fixed way of thinking and uses traditionally passed down remedies that may or may not have any medical evidence of working. It is the belief of the younger generation to be disseminators of peer-reviewed evidence-based medical advice and knowledge to this group of caregivers in order to better provide care to the children and circumvent any adverse medication related reactions.

With the development of economy, society, and network technologies, China's popular healthcare related work has shown an informatization trend; thus, the needs of the caregivers as well as



	APP of short video	Internet search engine	Popular science books/magazine	Community members/family and friends	Social media	Big V of We Media	Mainstream media	Advice from Medical staff	Government department	Medical institutions
Very good	108	117	182	81	135	211	166	243	177	258
Relatively good	110	113	172	69	179	194	119	129	109	103
General	181	172	131	180	145	97	161	85	147	96
Not very good	65	60	15	98	36	9	42	32	51	35
Very bad	41	43	5	77	10	4	17	16	21	13

FIGURE 5
Overall quality of knowledge regarding the safe usage of children's medication obtained from various sources.

the popular healthcare information have become more diversified. Designing and carrying out popular healthcare related work in accordance with the "demand-oriented" principle could effectively improve the efficiency and satisfaction of popular healthcare works (Zhang and Ran, 2019; (von Rüden et al., 2021). Therefore, based on the results of this survey, the country and the government should place significant importance on the safe usage of children's medication, and organically combine the formulation of laws and policies suitable for the country's national conditions and effectively implement the existing guidelines to further promote the "Popularization Action of Children's Safe Medication" at the macro level. For medical institutions and practitioners related to popular healthcare information, the accuracy and pertinence of popular medical information should be strictly controlled with professional and obscure healthcare knowledge being converted into layman's easy-to-understand language and presented so that the caregivers can easily grasp and readily use. Moreover, in the process of carrying out the relevant publicity and education of popular healthcare information, special attention should be paid to disseminating different and personalized methods of education for different educational levels, income levels and population distribution regions (Ruben, 2016; Lin and Huang, 2018). Electronic media such as media platforms and search engines should rely on the strong development of network technologies as well as scientific management in order to improve the authoritative, professional, and comprehensive medical knowledge database. This would improve the network environment, and meet the needs of caregivers regarding the knowledge needed for the safe usage of children's medication (Morahan-Martin, 2004).

Popular science about safe medication is a word with Chinese characteristics. It is generally called medication consultation and medication education in other countries. Few studies have explored the needs of child caregivers for safe medication education in other countries. A study has been conducted in the United States to explore how children with chronic diseases and their parents want to

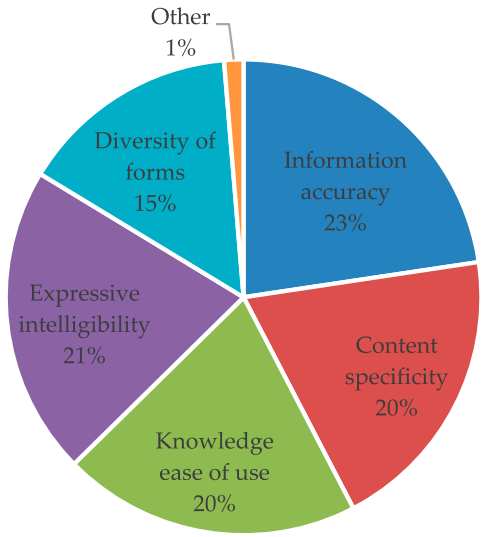


FIGURE 6
Specific aspects of improving the overall quality of science content.

learn about medicines and their perceptions on medication counseling provided by community pharmacists (Abraham et al., 2017). This is similar to our study in that the public's demand for medication knowledge has been investigated. And the difference is that our research object is limited to child caregivers, while the above study includes children and caregivers. This inspires us, and we can also include children as subjects in the follow-up research to discuss children's needs for popular science about safe medication.

There are a few limitations of this study including the proportion of males and females, age level, highest educational level, occupational status, and structure of the survey samples were significantly biased, which affected the data analysis results to a certain extent.

5 Conclusion

With the enhancement of health awareness, child caregivers pay more and more attention to the knowledge of children's safe medication, and expect to learn as much as possible about relevant popular science works. Then, in response to the needs of caregivers, we should think about how to transmit effective and high-quality popular science works on safe medication for children.

From the results, we can see that, the use of big data and other information tools helps to realize the accuracy of popular healthcare content, and accelerate the construction process of popular healthcare science channels; therefore, improving the trust of information channels, the expression forms of popular healthcare science related information as well as the effectiveness of healthcare science popularization. Additionally, the content of safe medication for children that caregivers are most interested in should be focused on, analyzed, and tracked. Furthermore, through the use of content mining and user management technologies, we can integrate popular healthcare information and user data, observe the potential relationship between content characteristics and user behavior, and use big data analysis to understand child caregivers' different needs for popular science about safe medication for children (Wang et al., 2017; Zhang and Ran, 2019). Professionals such as doctors and pharmacists need to ensure that the popular science of safe medication for children are scientific and easy-to-understand, and actively popularize the knowledge about children's safe medication online (new media) or offline (face-to-face education) to improve the awareness of safe medication among caregivers for reducing medication errors of children at home (Hart et al., 2017).

Data availability statement

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

Author contributions

Conceptualization, XW; methodology, LX; formal analysis, YW; investigation, YL and XX; writing-original draft preparation, XX and ZW; writing-review and editing, XW and LH. All authors have read and agreed to the published version of the manuscript.

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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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Pharmacological interventions on smoking cessation: A systematic review and network meta-analysis

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Objective: A network meta-analysis based on randomized controlled trials was conducted to investigate the effects of pharmacological interventions on smoking cessation.

Methods: English databases were searched to obtain randomized controlled trials reporting the effect of pharmacological interventions on smoking cessation. The risk of bias for the included trials was assessed using Cochrane Handbook tool. Stata 15.1 software was used to perform network meta-analysis, and GRADE approach was used to assess the evidence credibility on the effects of different interventions on smoking cessation.

Results: A total of 159 studies involving 60,285 smokers were included in the network meta-analysis. The analysis involved 15 interventions and which yielded 105 pairs of comparisons. Network meta-analysis showed that varenicline was more helpful for smoking cessation than other monotherapies, such as nicotine replacement therapy [Odds Ratio (OR) = 1.42, 95% confidence interval (CI) (1.16, 1.73)] and bupropion [OR = 1.52, 95% CI (1.22, 1.89)]. Furthermore, combined interventions were superior to monotherapy in achieving smoking cessation, such as varenicline plus bupropion over bupropion [OR = 2.00, 95% CI (1.11, 3.61)], varenicline plus nicotine replacement therapy over nicotine replacement therapy [OR = 1.84, 95% CI (1.07, 3.18)], and nicotine replacement therapy plus mecamylamine over naltrexone [OR = 6.29, 95% CI (1.59, 24.90)]. Finally, the surface under the cumulative ranking curve value indicated that nicotine replacement therapy plus mecamylamine had the greatest probability of becoming the best intervention.

Conclusion: Most pharmacological interventions demonstrated a benefit in smoking cessation compared with placebo, whether monotherapy or combination therapy. Moreover, confirmed evidence suggested that some combination treatments, such as varenicline plus bupropion and nicotine

replacement therapy plus mecamylamine have a higher probability of being the best smoking cessation in

KEYWORDS

pharmacotherapy, smoking cessation, Systematic review, network meta-analysis, tobacco

Introduction

The tobacco epidemic remains a medical, social, economic, and public health problem. As of 2019, there were about 847 million male smokers and 157 million female smokers worldwide, according to the World Health Organization's 2021 report (Burki, 2021). Tobacco use remains a major contributor to the global burden of disease, responsible for an estimated 12% of deaths among 30-year-olds worldwide, killing 8 million people globally each year, including 1.2 million non-smokers exposed to second-hand smoke (GBD 2017 Risk Factor Collaborators, 2017; Bernabe-Ortiz and Carrillo-Larco, 2021). Deaths from tobacco use are mainly caused by some smoking-related diseases, including malignant tumors (such as lung cancer), cardiovascular diseases (such as heart disease), respiratory diseases (such as chronic obstructive pulmonary disease), tuberculosis, stroke, diabetes, and gastrointestinal diseases (Zheng et al., 2018; WHO, 2020). Moreover, the economic burden of smoking cannot be ignored. A systematic review was performed to assess the economic burden of smoking, and the results showed that smoking-related diseases were responsible for 1.5%–6.8% of the national health system expenditures and 0.22%–0.88% of GDP of a country (Rezaei et al., 2016). Correspondingly, in an effort to reduce smoking, the World Health Organization is supporting 100 million smokers to quit smoking for good through its "Commit to Quit" campaign, launched on World No Tobacco Day. Therefore, providing some support for smokers to quit smoking is one of the effective ways to achieve this goal.

In general, among the numerous smoking cessation interventions, pharmacological treatments are relatively mature and widespread in clinical practice. It is important to note that pharmacological therapy is a systematic intervention that includes many types of drugs, such as nicotine replacement therapy, Bupropion, and Varenicline (West, 2003; Hartmann-Boyce et al., 2018; Jordan and Xi, 2018). For these specific drugs, the smoking cessation effects have been investigated more often in randomized controlled trials, but the limitation is that the evidence is relatively isolated. Therefore, systematic reviews based on randomized controlled trials provide higher evidence for smoking cessation, especially in combination with quantitative analysis using network meta-analysis. By reviewing published studies, the results showed that in 2009, Strassmann et al. (2009) conducted a network meta-analysis of smoking cessation in chronic obstructive pulmonary disease populations, which involved nicotine replacement therapy, but comparisons between pharmacological interventions were not reported. In 2013, a network meta-analysis was published in the Cochrane Library, which comprehensively investigated the smoking cessation effects of numerous pharmacological interventions (Cahill et al., 2013). However, the randomized controlled trials included in this analysis were derived from published systematic reviews, and the scope of the search was limited to the Cochrane Database of Systematic Reviews.

Gradually, the abstinence effects of pharmacological treatments in specific populations of smokers were found in several reviews. For example, in 2004, a study by Wagena et al. (2004) first reported the effectiveness of Nicotine, Bupropion, and a combination intervention for smoking cessation in a COPD population. Similarly, several similar studies have successively reported the effects of pharmacological interventions (Jiménez-Ruiz and Fagerström, 2013; Tønnesen, 2013; Tashkin, 2015). Moreover, numerous studies have found greater benefits (e.g., lower mortality) of pharmacological interventions (nicotine and bupropion) for smoking cessation in cardiovascular disease populations, with studies finding higher rates of cessation with active treatment (Ludvig et al., 2005; Eisenberg et al., 2010; Grandi et al., 2013). Several studies have also reported the smoking cessation effect of Varenicline in patients with alcohol dependence, alcohol use disorder and alcoholism (Erwin and Slaton, 2014; Oon-Arom et al., 2019; Guo et al., 2021). Additionally, studies by Yousefi et al. (2011), Tsoi et al. (2013) found that Bupropion and Varenicline helped improve withdrawal in smokers with schizophrenia. The study by Claire et al. (2020) was based on 11 studies investigating the effect of Nicotine on smoking cessation during pregnancy. In 2021, a study by Yan and Goldman (2021) reported that Bupropion was more effective than other drugs in improving short-term adolescent withdrawal. As far as the current network meta-analysis results are concerned, in 2016, a network meta-analysis conducted by Roberts et al. (2016) reported the efficacy of pharmacotherapy for smoking cessation in adults with serious mental illness. Then in 2017, another similar study was published, while its target population was patients with cardiovascular disease (Suissa et al., 2017). In 2020, Siskind et al. (2020) also conducted a network meta-analysis reporting on pharmacological interventions for smoking cessation among people with schizophrenia spectrum disorders. However, these network meta-analyses involving smoking cessation effects in different populations are relatively limited in the number of trials included and the types of pharmacological treatments reported. Inversely, the analysis by Mishra et al. investigated the effect of

pharmacological interventions for smoking cessation in healthy adults, it is worth noting that the data in this network meta-analysis came from 97 randomized controlled trials (Mishra et al., 2021). Undoubtedly, this study may miss data on non-healthy populations (e.g., diseased populations), which could affect the comprehensiveness and applicability of the findings.

Overall, there are currently fewer network meta-analyses of pharmacological interventions for smoking cessation than traditional meta-analyses (which are based more on direct comparisons). Moreover, in the published reviews, most network meta-analyses are only for specific populations or compare only a few limited drugs, which are relatively incapable of providing comprehensive and high-level evidence. Therefore, a comprehensive evidence review of the effect of pharmacological interventions on smoking cessation is of great practical importance. In this network meta-analysis, the purpose is to include all randomized controlled trials of pharmacotherapy for smoking cessation, comprehensively compare the differences in abstinence effects of different pharmacological interventions and seek the best intervention, in order to provide reference for clinical smoking cessation practice.

Materials and methods

Guidance and search strategy

This study was strictly conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA-NMA) reporting guideline Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Interventions (Hutton et al., 2015).

PubMed, The Cochrane Library, Web of Science, and Embase databases were searched from the date of their inception to 25 June 2022. Meanwhile, a supplementary search was conducted to obtain relevant trials by forward citation tracing and backward citation tracing of the included studies. The main search strategies were (medicine OR drug OR pharmaco*) AND (smok* OR cigarette OR tobacco OR nicotine) AND (cessation OR quit* OR abstinence OR stop* OR withdraw) AND (random* OR randomized controlled trial OR blind OR double). See Supplementary Table S1 for a more detailed presentation of the search strategy.

Inclusion and exclusion criteria

Studies with the following criteria were included: 1) randomized controlled trials evaluating the efficacy of pharmacological interventions on smoking cessation; 2) the study population was smokers who continued to smoke while receiving treatment, where the threshold of daily smoking was identified in each trial, which was generally ≥ 1 cigarette per day; 3) the interventions included different pharmacological treatments, there was no limit to the number of arms, with at least one arm receiving one type of drug intervention, either monotherapy or combination, and 4) the main outcome measures were continuous abstinence rate or point abstinence rate, these outcomes were generally confirmed with biochemical validation based on self-reported smoking status; 5) as for duplicate publication (i.e., duplicate publication can be broadly defined as the publication of two or more articles of seemly identical material that share most of the same authors) (Lundberg, 1993), we selected the study with the largest sample size or with the longest follow-up or with the most comprehensive outcomes according to the definition of duplicate publication which were not fraudulent (e.g., a manuscript extends an original database by 50% or more) (Büchler and Farthmann, 2001).

Studies were excluded if 1) non-pharmacological interventions (e.g., behavioral interventions and some physical therapies) were used as comparators or combinations, or 2) they were fraudulent duplicate publications, had incomplete data (e.g., only continuous smoking cessation data are available), were only protocols.

Literature selection and data extraction

Relevant literature was imported into EndNote X9 software, and duplicate articles were eliminated. Two independent reviewers screened the titles and read through the abstracts of the extracted articles for preliminary inclusion consideration. After extracting the irrelevant articles, the authors read through the full texts of the remaining studies. Trials and other irrelevant studies were further removed and reasons for exclusion were noted to identify studies that ultimately met the criteria. Each study was strictly evaluated against inclusion criteria, and any discrepancies were settled by consensus.

A pre-set standardized form was used by two reviewers who independently extracted the main information. The main data was as follows: 1) basic information, including first author, country, and year of publication. 2) The characteristics of participants, including sample size, age, gender, cigarettes per day, physical condition (with or without other diseases). 3) Intervention details, including the name of treatment, dosage of pharmacotherapy, treatment duration, process, and follow-up period. 4) Outcome indicators, including continuous abstinence rate (defined as continuous abstinence during the intervention or from the end of the intervention to the follow-up time point) or 7-day point prevalence abstinence (defined as no smoking within 7 days before the follow-up time point), validation method of abstinence (self-report or biochemical validation), the number of abstinences at different follow-up periods. For follow-up, we usually selected follow-up data for about 6 months (e.g.,

24 weeks), and if the time point is not reported in a trial, data from other time points (e.g., 12 or 48 weeks) was considered.

Risk of bias

The risk of bias in the included studies was assessed by two independent reviewers using Cochrane Collaboration's bias risk assessment tool (Sterne et al., 2019), and disagreements were resolved by consensus. Seven domains were considered in the evaluation process, including sequence generation, allocation concealment, blinding of the participants and personnel, blinding of outcome assessments, incomplete outcome data, selective outcome reporting, and other potential sources of bias. Studies were judged to have a low-risk bias if all items were low risk. When one item had unclear risk bias, the study was rated as having an unclear risk of bias. When one item was high risk, the study was rated as having a high risk of bias (Hendarto et al., 2019; Luo et al., 2020; Li et al., 2022).

Data analysis

Stata 15.1 software (network package and network graphs package) was used to conduct network meta-analysis (Lin et al., 2017; Xu et al., 2018). The network package performed the network meta-analysis based on the frequentist framework using random-effects models. The approach was to test the research hypothesis, as this was simpler than the problem of establishing prior probability (Hutton et al., 2014). This approach is not complex and has few limitations for ordinary researchers using network meta-analysis (Shim et al., 2017). A network diagram with nodes and lines was constructed to represent all interventions, where the size of nodes represents the number of populations, and the thickness of lines between nodes represents the number of studies. In the analysis, the number of quitters per arm and the total sample size were obtained, so the OR with 95% CI was used to estimate the effect size. The results of network meta-analysis were summarized based on all possible pairwise comparisons, including mixed comparisons (direct effects merged indirect effects) and indirect comparisons.

The node-splitting test was used to assess local inconsistency between direct and indirect comparisons. Differences between direct and indirect coefficients (*via* the *p*-value) were used to estimate the inconsistency: if $p < 0.05$, local inconsistency existed. If inconsistency was observed, non-transitivity was suspected to exist, and potential modifiers influencing treatment effect were examined (Spineli, 2019). The smoking cessation effect of different interventions was estimated based on the surface under the cumulative ranking curve. The surface under the cumulative ranking curve value ranges from 0% to 100%, where a surface under the cumulative ranking curve value of 100% indicates that the treatment was the most effective, and the smaller the value, the poorer the treatment effect.

Certainty assessment

The quality of evidence associated with all paired comparisons was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation system (Guyatt G. et al., 2011). Five downgrade factors (i.e., the risk of bias, inconsistency, imprecision, indirectness and publication bias), were considered to rate the level of evidence. Each factor was judged as "not serious" (not degraded), "serious" (degraded by one level), or "very serious" (degraded by two levels); finally, a high, moderate, low, or very low level of evidence quality was identified (Schünemann et al., 2020).

Results

Literature screening process and results

As shown in Figure 1, the initial electronic search identified 8,909 potentially relevant studies. After removal of 4311 duplicate, 4,598 records were screened based on reading of titles and abstracts, which led to the exclusion of 4,189 records. Of the remaining 409 publications that were eligible for full-text review, 250 studies were excluded based on inclusion and exclusion criteria. Finally, a total of 159 randomized controlled trials, including 35 trials with backward citation tracing, were included in the network meta-analysis. A reference list of included trials is provided in the Supplementary Material.

Description of included studies

For all included 159 trials, a total of 60,285 smokers were involved. In terms of the physical characteristics of the participants, 104 of the trials reported on the normal population, and the rest reported smokers with alcohol dependence (20 trials), mental disease (10 trials), cardiovascular diseases (seven trials), chronic obstructive pulmonary disease (five trials), pregnancy (three trials), posttraumatic stress disorder (two trials), substance use disorder (two trials), cancer (two trials), AIDS (one trial), asthma (one trial), tuberculosis (one trial), and medical disease (one trial). Moreover, a total of 15 interventions were reported, including 11 monotherapies (Bupropion, Clonidine, Cytisine, Fluoxetine, Nicotine replacement therapy, Naltrexone, Nortriptyline, Selegiline, Topiramate, Varenicline, Placebo) and four combination interventions (Bupropion + Nicotine

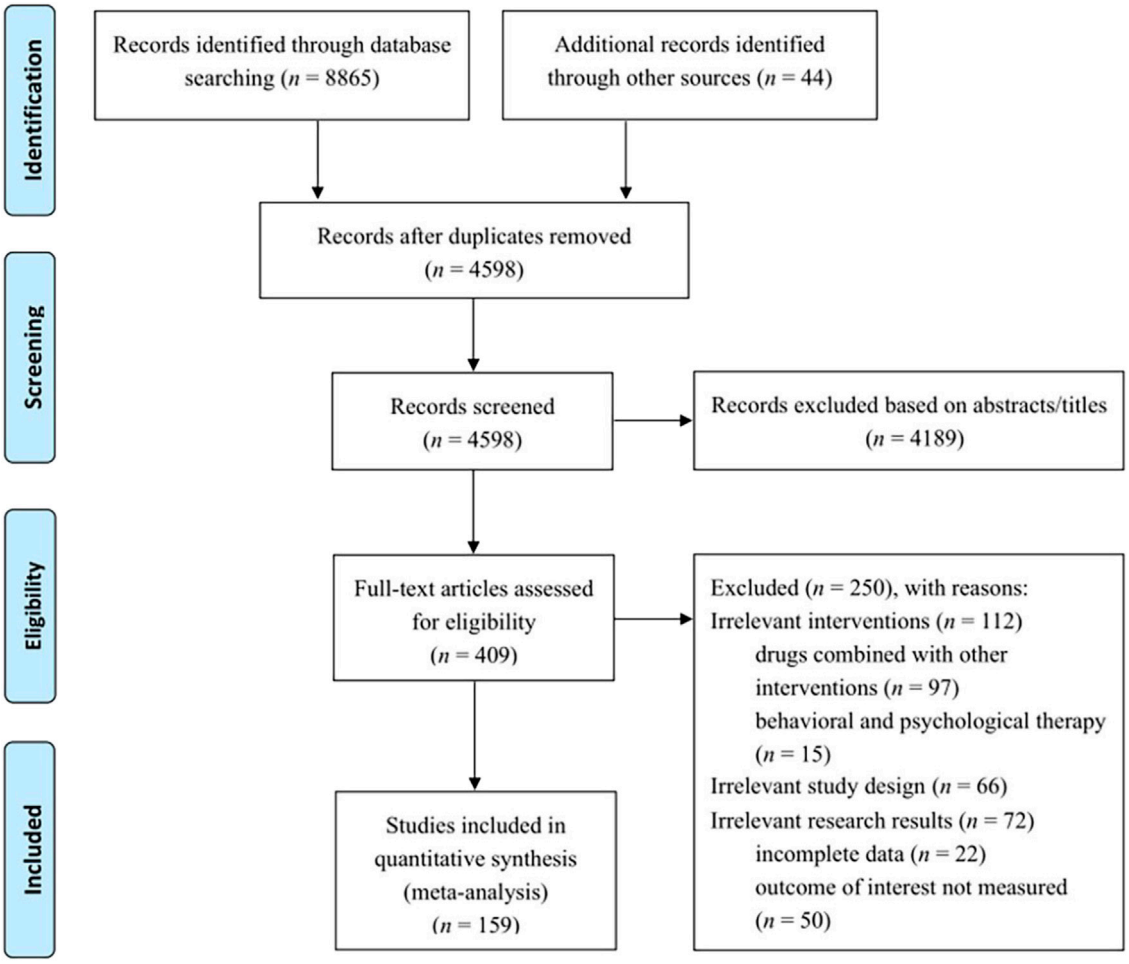

FIGURE 1
Literature screening flow chart.

replacement therapy, Mecamylamine + Nicotine replacement therapy, Varenicline + Bupropion, Varenicline + Nicotine replacement therapy). Meanwhile, the most of trials reported the consumption of tobacco, and the reported results showed that the average number of cigarettes smoked per day exceeded 10. The treatment duration for most trials lasted for 12 weeks (90 trials), some were 8 weeks (17 trials), 7 weeks (nine trials), 24 weeks (seven trials), 4 weeks (four trials), or 10 weeks (four trials), and the reported follow-up were centered at 24 (39 trials), 26 (10 trials), 48 (28 trials), or 53 weeks (34 trials). The outcome measure was continuous abstinence rate (137 trials) or 7-day point abstinence rate (106 trials), and the abstinence outcomes were generally confirmed with biochemical validation based on expired carbon monoxide level (140 trials), salivary cotinine concentration (12 trials), urine cotinine concentration (12 trials), serum cotinine concentration (two trials), plasma cotinine concentration (four trials), or self-reported zero smoking (two trials). See Supplementary Table S2 for more details.

Risk of bias

A total of 16 studies were rated as high risk of bias for the incorrect randomization, non-assigned concealment, non-blinded assessment, or incomplete data. 11 studies were rated as low risk of bias, and the remaining 132 studies were rated as unclear risk of bias because of insufficient information and unclear reporting. See Supplementary Table S3 for more details.

Network diagram

A network diagram was for overall abstinence rate performed based on 15 interventions, forming a total of 105 pairs of comparisons (including 28 pairs of direct comparisons and 77 pairs of indirect comparisons). In all pairwise comparisons, Varenicline vs. Placebo had the highest frequency (49 trials), followed by Nicotine replacement therapy vs. Placebo (39 trials)

and Bupropion vs. Placebo (34 trials). Accordingly, population in Placebo group had the largest sample size (21,818 participants), followed by Varenicline (11,414 participants), Nicotine replacement therapy (10,671 participants), and Bupropion (7,324 participants) (Figure 2A). Furthermore, a subgroup network diagram based on continuous abstinence rate and 7-point continuous abstinence rate was performed separately. For continuous abstinence rate, the same interventions as the overall outcome were involved, the difference was that 123 studies were included (Figure 2B). For 7-point continuous abstinence rate, only 90 trials involving 11 interventions were included in the network diagram (Figure 2C).

Inconsistency test

A global inconsistency test was performed and no difference was found (p = 0.825). Furthermore, to better explore local inconsistencies, a node-splitting test was conducted. A total of 28 pairwise comparisons involving loop were analyzed, the results showed that the significant inconsistency was found in Nicotine replacement therapy vs. Naltrexone (p = 0.017) and Naltrexone vs. Placebo (p = 0.011) (Table 1).

Network meta-analysis

As shown in Table 2A, the estimated effect of network meta-analysis of overall abstinence rate for each intervention on smoking cessation was generated. The network meta-analysis showed that compared with placebo, nine interventions yielded the benefits of quitting smoking, such as Varenicline [OR = 2.58, 95% CI (2.22, 3.01)] and Nicotine replacement therapy [OR = 1.83, 95% CI (1.56, 2.14)]. Meanwhile, Varenicline has greater withdrawal benefits than Naltrexone [OR = 2.61, 95% CI (1.64, 4.16)] and Clonidine [OR = 2.25, 95% CI (1.15, 4.39)]. Then, Varenicline combined with Nicotine replacement therapy is superior to monotherapy such as Bupropion [OR = 1.98, 95% CI (1.13, 3.48)], Nicotine replacement therapy [OR = 1.84, 95% CI (1.07, 3.18)], Naltrexone [OR = 3.40, 95% CI (1.69, 6.84)], and Clonidine [OR = 2.94, 95% CI (1.26, 6.83)] in smoking cessation. In addition, Varenicline + Bupropion intervention was also superior to Naltrexone [OR = 3.45, 95% CI (1.68, 7.07)], Nicotine replacement therapy [OR = 1.87, 95% CI (1.04, 3.35)], Clonidine [OR = 2.97, 95% CI (1.25, 7.05)] and Bupropion [OR = 2.00, 95% CI (1.11, 3.61)]. Compared with Naltrexone, the abstinence superiority was found in Bupropion [OR = 1.72, 95% CI (1.07, 2.76)], Nicotine replacement therapy [OR = 1.84, 95% CI (1.16, 2.93)], Cytisine [OR = 2.08, 95% CI (1.04, 4.16)], and Bupropion + Nicotine replacement therapy [OR = 1.97, 95% CI (1.15, 3.39)]. Moreover, Nicotine replacement therapy + Mecamylamine was superior to Naltrexone [OR = 6.29, 95% CI (1.59, 24.90)], Fluoxetine [OR = 5.05, 95% CI (1.06, 24.12)] and Clonidine [OR = 5.43, 95% CI (1.27, 23.26)]. It is worth noting that Varenicline was superior to Nicotine replacement therapy [OR = 1.42, 95% CI (1.16, 1.73)] and Bupropion [OR = 1.50, 95% CI (1.22, 1.89)].

A subgroup network meta-analysis based on different outcomes and populations was conducted. For subcategory outcomes, continuous abstinence rate and 7-point continuous abstinence rate were analyzed separately. In the continuous abstinence rate, a total of 15 interventions were involved, the network meta-analysis results showed that Varenicline + Nicotine replacement therapy, Varenicline + Bupropion, and Nicotine replacement therapy + Mecamylamine all were superior to Placebo, Naltrexone, Fluoxetine, and Clonidine (See Table 2B). In the 7-point continuous abstinence rate, a total of 11 interventions were involved, the network meta-analysis results showed that Varenicline + Nicotine replacement therapy, Varenicline + Bupropion, and Bupropion + Nicotine replacement therapy all were superior to Placebo and Naltrexone. Moreover, Varenicline monotherapy was superior to Nicotine replacement therapy [OR = 1.58, 95% CI (1.19, 2.09)] and Bupropion [OR = 1.37, 95% CI (1.02, 1.83)] (See Table 2C). For the subcategory populations, more specific types of smokers, such as alcohol dependence, chronic obstructive pulmonary disease, and mental disorders were analyzed independently. In these specific populations, the main reported interventions included Varenicline, Bupropion, Nicotine replacement therapy, and Placebo. In general, both Varenicline and Bupropion were superior to Placebo in most populations, but in smokers with asthma and cancer, neither Varenicline vs. Placebo nor Bupropion vs. Placebo showed significant statistical differences. Interestingly, Bupropion combined with Nicotine replacement therapy was found to be superior to Placebo [OR = 16.14, 95% CI (2.91, 89.58)] and Bupropion [OR = 6.86, 95% CI (1.23, 38.29)] in a population with mental illness. See Table 3 for more details.

Probability ranking

The surface under the cumulative ranking curve for all interventions is showed in Figure 3. For overall abstinence rate, the value predicted the possibility of different interventions as the best treatment and the result showed that Mecamylamine + Nicotine replacement therapy had the greatest probability (93.8%) of becoming the best intervention. For other interventions, the smoking cessation effect were ranked as follows, Varenicline + Bupropion (87.0%), Varenicline + Nicotine replacement therapy (86.9%), Varenicline (76.9%), Cytisine (59.1%), Bupropion + Nicotine replacement therapy (57.1%), Nortriptyline (52.5%), Nicotine replacement therapy (51.2%), Bupropion (44.1%), Topiramate (35.2%), Selegiline (28.3%), Fluoxetine (28.1%), Clonidine (22.9%), Naltrexone (13.7%), and Placebo (13.3%). In the continuous abstinence

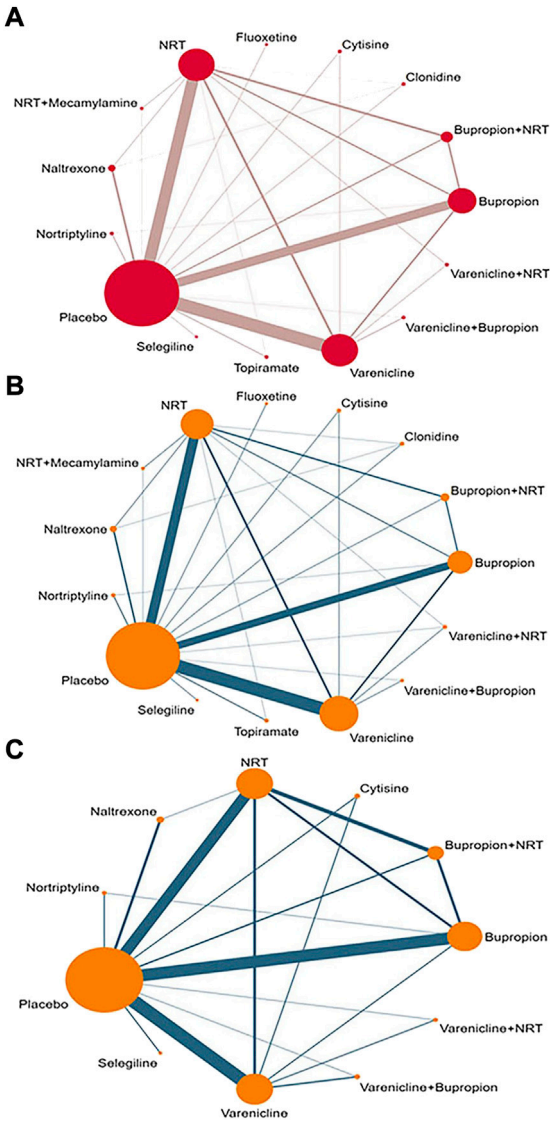

FIGURE 2
The network diagram for all interventions. **(A)** Overall abstinence rate; **(B)** Continuous abstinence rate; **(C)** 7-point continuous abstinence rate; NRT: Nicotine replacement therapy.

rate, the first four interventions were in the same order as overall abstinence rate, the difference was that Naltrexone was in fifth place (57.9%). In 7-point continuous abstinence rate, Varenicline + Nicotine replacement therapy had the greatest probability (82.1%) of becoming the best intervention, followed by Varenicline + Bupropion (80.0%).

Certainty of evidence

The evidence quality for all 105 comparisons was evaluated by the GRADE system. In the comparison of 28 pairs of mixed effects (the combination of direct and indirect effects), eight as moderate-level evidence, five as low-level evidence, and 15 as very-low-level evidence. For 77 pairs of indirect comparisons, 23 comparisons were rated as moderate-level evidence, 27 as low-level evidence, and 27 as very-low-level evidence. See Supplementary Table S4 for more details.

Discussion

For all interventions and associated pair-wise comparisons, the network meta-analysis results showed that most

TABLE 1 Local inconsistency test based on side-split.

Side	Direct		Indirect		Difference		*P*>|z|
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	
Bupropion - Bupropion + NRT	0.093	0.195	0.249	0.305	−0.156	0.362	0.666
Bupropion - NRT	0.040	0.219	0.081	0.131	−0.041	0.256	0.871
Bupropion - Nortriptyline	−0.151	0.575	0.215	0.398	−0.366	0.698	0.600
Bupropion - Placebo	−0.514	0.099	−0.624	0.228	0.111	0.249	0.658
Bupropion - Varenicline	0.379	0.210	0.432	0.132	−0.053	0.248	0.831
Bupropion + NRT - NRT	−0.240	0.205	0.251	0.279	−0.491	0.349	0.159
Bupropion + NRT - Placebo	−0.469	0.247	−0.826	0.218	0.357	0.333	0.284
Clonidine - NRT	0.941	0.627	0.274	0.399	0.667	0.740	0.367
Clonidine - Naltrexone	−1.117	0.797	0.190	0.459	−1.307	0.937	0.163
Clonidine - Placebo	−0.108	0.403	−0.202	0.594	0.094	0.717	0.896
Cytisine - Placebo	−0.373	0.393	−1.043	0.379	0.670	0.545	0.219
Cytisine - Varenicline	−0.080	0.370	0.590	0.401	−0.670	0.545	0.219
Fluoxetine - Placebo	−0.209	0.439	−1.059	93.837	0.850	93.838	0.993
NRT - NRT + Mecamylamine	1.415	0.749	0.404	1.651	1.011	1.857	0.586
NRT - Naltrexone	−1.929	0.599	−0.397	0.252	−1.531	0.641	0.017
NRT - Placebo	−0.618	0.092	−0.546	0.174	−0.072	0.198	0.714
NRT - Topiramate	−0.518	0.838	−0.158	0.542	−0.359	0.996	0.718
NRT - Varenicline	0.207	0.209	0.392	0.119	−0.185	0.241	0.441
NRT - Varenicline + NRT	0.720	0.421	0.528	0.371	0.192	0.561	0.732
NRT + Mecamylamine - Placebo	−1.268	0.894	−2.673	1.117	1.405	1.493	0.347
Naltrexone - Placebo	−0.188	0.237	1.664	0.685	−1.852	0.725	0.011
Nortriptyline - Placebo	−0.693	0.340	−0.077	1.019	−0.615	1.081	0.569
Placebo - Selegiline	0.135	0.635	1.182	132.188	−1.048	132.190	0.994
Placebo - Topiramate	0.525	0.503	−0.967	1.593	1.492	1.746	0.393
Placebo - Varenicline	0.982	0.086	0.792	0.188	0.189	0.208	0.361
Placebo - Varenicline + Bupropion	1.405	0.676	1.175	0.341	0.230	0.788	0.770
Varenicline - Varenicline + Bupropion	0.225	0.288	1.415	1.332	−1.190	1.363	0.382
Varenicline - Varenicline + NRT	0.188	0.355	0.380	0.434	−0.192	0.561	0.732

NRT: Nicotine replacement therapy.

interventions yielded the benefits of smoking cessation compared with placebo, whether monotherapy or combination therapy. Meanwhile, the results showed that Varenicline, Bupropion, Nicotine replacement therapy, Varenicline + Nicotine replacement therapy, Varenicline + Bupropion, Mecamylamine + Nicotine replacement therapy, and Bupropion + Nicotine replacement therapy were superior to Naltrexone. It was worth mentioning that, in the probability ranking of all interventions, only Naltrexone was similar to placebo, which means that it has the smallest probability of being the best intervention. Therefore, it is necessary to investigate the difference in effect between Naltrexone and placebo. The network meta-analysis in this study showed that no significant differences were found between Naltrexone and placebo. Similarly, as early as 2006, a systematic review published in the Cochrane Library evaluated the efficacy of opioid antagonists (Naltrexone) in promoting long-term smoking cessation, the review failed to detect a significant difference in quit rates between naltrexone and placebo based on the synthesis of the four trials (David et al., 2006). Moreover, a systematic review by David et al. (2014) in 2014 further confirmed no beneficial effect of naltrexone on short-term or long-term smoking abstinence. In the comparison of other monotherapy, it is notable that Varenicline is superior to Nicotine replacement therapy, Clonidine and Bupropion. Among them, a network meta-analysis by Cahill et al. supported our findings, and their results showed that Varenicline was superior to single forms of Nicotine replacement therapy, and to Bupropion (Cahill et al., 2013). For all monotherapies in the analysis, Bupropion, Fluoxetine, and Nortriptyline all are antidepressants, the results showed the antidepressants Bupropion and Nortriptyline aided long-term smoking cessation, the same finding was reported in a review published in the Cochrane Library (Hughes et al., 2014).

TABLE 2 The results of network meta-analysis for all pairwise comparisons.

(A) Overall abstinence rate

VAR + NRT	1.01 (0.47, 2.18)	0.77 (0.45, 1.31)	0.42 (0.15, 1.17)	0.34 (0.09, 1.32)	0.30 (0.17, 0.51)	0.56 (0.24, 1.27)	0.29 (0.15, 0.59)	1.85 (0.45, 7.55)	0.54 (0.31, 0.93)	0.37 (0.13, 1.01)	0.61 (0.29, 1.30)	0.34 (0.15, 0.79)	0.58 (0.31, 1.08)	0.51 (0.29, 0.89)
0.99 (0.46, 2.13)	**VAR + BUP**	0.76 (0.44, 1.31)	0.41 (0.14, 1.18)	0.34 (0.09, 1.32)	0.29 (0.17, 0.52)	0.55 (0.24, 1.28)	0.29 (0.14, 0.60)	1.83 (0.44, 7.56)	0.54 (0.30, 0.96)	0.36 (0.13, 1.01)	0.60 (0.28, 1.30)	0.34 (0.14, 0.80)	0.57 (0.30, 1.09)	0.50 (0.28, 0.90)
1.30 (0.76, 2.23)	1.32 (0.76, 2.29)	**Varenicline**	0.54 (0.22, 1.33)	0.44 (0.13, 1.55)	0.39 (0.33, 0.45)	0.73 (0.38, 1.38)	0.38 (0.24, 0.61)	2.41 (0.65, 8.95)	0.71 (0.58, 0.87)	0.48 (0.20, 1.14)	0.80 (0.47, 1.36)	0.44 (0.23, 0.87)	0.76 (0.54, 1.07)	0.66 (0.53, 0.82)
2.40 (0.85, 6.77)	2.43 (0.85, 6.96)	1.84 (0.75, 4.52)	**Topiramate**	0.82 (0.18, 3.76)	0.71 (0.29, 1.73)	1.34 (0.45, 3.95)	0.71 (0.26, 1.90)	4.44 (0.92, 21.44)	1.30 (0.53, 3.18)	0.88 (0.26, 3.02)	1.47 (0.52, 4.13)	0.82 (0.27, 2.45)	1.39 (0.55, 3.56)	1.21 (0.49, 2.99)
2.94 (0.76, 11.44)	2.98 (0.76, 11.70)	2.26 (0.64, 7.91)	1.23 (0.27, 5.64)	**Selegiline**	0.87 (0.25, 3.03)	1.64 (0.41, 6.59)	0.86 (0.23, 3.24)	5.44 (0.90, 32.99)	1.60 (0.45, 5.59)	1.08 (0.24, 4.89)	1.80 (0.46, 6.97)	1.00 (0.25, 4.08)	1.71 (0.47, 6.16)	1.49 (0.42, 5.22)
3.37 (1.96, 5.80)	3.41 (1.93, 6.02)	2.58 (2.22, 3.01)	1.40 (0.58, 3.40)	1.14 (0.33, 3.97)	**Placebo**	1.87 (1.00, 3.50)	0.99 (0.64, 1.54)	6.22 (1.69, 22.94)	1.83 (1.56, 2.14)	1.23 (0.52, 2.92)	2.06 (1.20, 3.52)	1.15 (0.60, 2.20)	1.95 (1.42, 2.68)	1.70 (1.43, 2.03)
1.80 (0.79, 4.12)	1.82 (0.78, 4.24)	1.38 (0.72, 2.63)	0.75 (0.25, 2.22)	0.61 (0.15, 2.46)	0.53 (0.29, 1.00)	**Nortriptyline**	0.53 (0.25, 1.14)	3.32 (0.78, 14.12)	0.97 (0.51, 1.86)	0.66 (0.23, 1.91)	1.10 (0.48, 2.50)	0.61 (0.25, 1.51)	1.04 (0.52, 2.09)	0.91 (0.48, 1.72)
3.40 (1.69, 6.84)	3.45 (1.68, 7.07)	2.61 (1.64, 4.16)	1.42 (0.53, 3.81)	1.16 (0.31, 4.33)	1.01 (0.65, 1.57)	1.89 (0.88, 4.07)	**Naltrexone**	6.29 (1.59, 24.90)	1.84 (1.16, 2.93)	1.24 (0.47, 3.28)	2.08 (1.04, 4.16)	1.16 (0.54, 2.49)	1.97 (1.15, 3.39)	1.72 (1.07, 2.76)
0.54 (0.13, 2.21)	0.55 (0.13, 2.27)	0.42 (0.11, 1.54)	0.23 (0.05, 1.09)	0.18 (0.03, 1.12)	0.16 (0.04, 0.59)	0.30 (0.07, 1.28)	0.16 (0.04, 0.63)	**NRT + MEC**	0.29 (0.08, 1.08)	0.20 (0.04, 0.95)	0.33 (0.08, 1.35)	0.18 (0.04, 0.79)	0.31 (0.08, 1.19)	0.27 (0.07, 1.02)
1.84 (1.07, 3.18)	1.87 (1.04, 3.35)	1.42 (1.16, 1.73)	0.77 (0.31, 1.88)	0.63 (0.18, 2.20)	0.55 (0.47, 0.64)	1.03 (0.54, 1.96)	0.54 (0.34, 0.86)	3.41 (0.93, 12.54)	**NRT**	0.67 (0.28, 1.62)	1.13 (0.65, 1.97)	0.63 (0.32, 1.22)	1.07 (0.78, 1.47)	0.93 (0.75, 1.16)
2.73 (0.99, 7.57)	2.77 (0.99, 7.76)	2.10 (0.87, 5.03)	1.14 (0.33, 3.92)	0.93 (0.20, 4.22)	0.81 (0.34, 1.92)	1.52 (0.52, 4.41)	0.80 (0.31, 2.11)	5.05 (1.06, 24.12)	1.48 (0.62, 3.56)	**Fluoxetine**	1.67 (0.60, 4.61)	0.93 (0.32, 2.74)	1.58 (0.63, 3.97)	1.38 (0.57, 3.33)
1.64 (0.77, 3.48)	1.66 (0.77, 3.57)	1.26 (0.73, 2.15)	0.68 (0.24, 1.92)	0.56 (0.14, 2.16)	0.49 (0.28, 0.83)	0.91 (0.40, 2.08)	0.48 (0.24, 0.96)	3.03 (0.74, 12.39)	0.89 (0.51, 1.55)	0.60 (0.22, 1.65)	**Cytisine**	0.56 (0.24, 1.30)	0.95 (0.51, 1.77)	0.83 (0.47, 1.45)
2.94 (1.26, 6.83)	2.97 (1.25, 7.05)	2.25 (1.15, 4.39)	1.22 (0.41, 3.67)	1.00 (0.25, 4.06)	0.87 (0.45, 1.67)	1.63 (0.66, 4.03)	0.86 (0.40, 1.85)	5.43 (1.27, 23.26)	1.59 (0.82, 3.08)	1.07 (0.36, 3.16)	1.79 (0.77, 4.17)	**Clonidine**	1.70 (0.83, 3.50)	1.48 (0.76, 2.91)
1.72 (0.93, 3.20)	1.75 (0.92, 3.33)	1.32 (0.94, 1.87)	0.72 (0.28, 1.83)	0.59 (0.16, 2.12)	0.51 (0.37, 0.70)	0.96 (0.48, 1.93)	0.51 (0.30, 0.87)	3.19 (0.84, 12.14)	0.93 (0.68, 1.29)	0.63 (0.25, 1.58)	1.05 (0.57, 1.96)	0.59 (0.29, 1.21)	**BUP + NRT**	0.87 (0.63, 1.20)

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TABLE 2 (*Continued*) The results of network meta-analysis for all pairwise comparisons.

(A) Overall abstinence rate

1.98 (1.13, 3.48)	2.00 (1.11, 3.61)	1.52 (1.22, 1.89)	0.82 (0.33, 2.03)	0.67 (0.19, 2.36)	0.59 (0.49, 0.70)	1.10 (0.58, 2.09)	0.58 (0.36, 0.94)	3.66 (0.98, 13.62)	1.07 (0.86, 1.34)	0.72 (0.30, 1.74)	1.21 (0.69, 2.12)	0.67 (0.34, 1.32)	1.15 (0.83, 1.58)	**Bupropion**

(B) Continuous abstinence rate

VAR + NRT	1.08 (0.51, 2.32)	0.83 (0.51, 1.34)	0.45 (0.17, 1.19)	0.41 (0.12, 1.41)	0.31 (0.19, 0.51)	0.58 (0.28, 1.23)	0.31 (0.15, 0.63)	2.04 (0.53, 7.84)	0.63 (0.38, 1.04)	0.39 (0.15, 0.98)	0.63 (0.32, 1.24)	0.36 (0.17, 0.78)	0.57 (0.31, 1.04)	0.58 (0.35, 0.96)
0.92 (0.43, 1.98)	**VAR + BUP**	0.76 (0.42, 1.39)	0.41 (0.15, 1.17)	0.37 (0.10, 1.37)	0.29 (0.16, 0.53)	0.54 (0.24, 1.24)	0.29 (0.13, 0.63)	1.88 (0.47, 7.61)	0.58 (0.31, 1.09)	0.36 (0.13, 0.97)	0.58 (0.27, 1.25)	0.33 (0.14, 0.78)	0.53 (0.26, 1.07)	0.53 (0.28, 1.00)
1.21 (0.75, 1.95)	1.31 (0.72, 2.37)	**Varenicline**	0.54 (0.23, 1.27)	0.49 (0.15, 1.55)	0.38 (0.33, 0.44)	0.71 (0.39, 1.26)	0.37 (0.22, 0.64)	2.46 (0.69, 8.74)	0.76 (0.62, 0.94)	0.47 (0.21, 1.05)	0.76 (0.48, 1.23)	0.44 (0.24, 0.81)	0.69 (0.47, 1.02)	0.70 (0.56, 0.87)
2.23 (0.84, 5.92)	2.42 (0.85, 6.87)	1.85 (0.78, 4.37)	**Topiramate**	0.91 (0.22, 3.76)	0.70 (0.30, 1.64)	1.31 (0.47, 3.62)	0.69 (0.26, 1.86)	4.56 (1.00, 20.74)	1.41 (0.60, 3.32)	0.87 (0.27, 2.77)	1.42 (0.54, 3.74)	0.81 (0.29, 2.28)	1.28 (0.51, 3.21)	1.29 (0.54, 3.06)
2.47 (0.71, 8.58)	2.68 (0.73, 9.81)	2.05 (0.64, 6.51)	1.10 (0.27, 4.60)	**Selegiline**	0.78 (0.25, 2.44)	1.44 (0.40, 5.18)	0.77 (0.22, 2.69)	5.04 (0.92, 27.67)	1.56 (0.49, 4.97)	0.96 (0.24, 3.87)	1.56 (0.45, 5.41)	0.89 (0.25, 3.26)	1.42 (0.42, 4.71)	1.42 (0.45, 4.55)
3.18 (1.96, 5.17)	3.45 (1.88, 6.34)	2.64 (2.27, 3.06)	1.42 (0.61, 3.32)	1.29 (0.41, 4.06)	**Placebo**	1.86 (1.06, 3.28)	0.99 (0.59, 1.64)	6.50 (1.84, 22.88)	2.01 (1.69, 2.38)	1.23 (0.56, 2.73)	2.02 (1.25, 3.25)	1.15 (0.64, 2.09)	1.82 (1.27, 2.63)	1.83 (1.52, 2.21)
1.71 (0.81, 3.60)	1.85 (0.81, 4.25)	1.42 (0.79, 2.54)	0.77 (0.28, 2.12)	0.69 (0.19, 2.49)	0.54 (0.31, 0.95)	**Nortriptyline**	0.53 (0.25, 1.14)	3.49 (0.88, 13.88)	1.08 (0.60, 1.95)	0.66 (0.25, 1.76)	1.08 (0.52, 2.27)	0.62 (0.27, 1.41)	0.98 (0.50, 1.91)	0.99 (0.55, 1.77)
3.22 (1.60, 6.52)	3.50 (1.58, 7.74)	2.67 (1.57, 4.55)	1.44 (0.54, 3.88)	1.31 (0.37, 4.59)	1.01 (0.61, 1.69)	1.89 (0.88, 4.04)	**Naltrexone**	6.59 (1.70, 25.59)	2.04 (1.20, 3.46)	1.25 (0.49, 3.22)	2.04 (1.02, 4.11)	1.17 (0.55, 2.49)	1.85 (0.99, 3.45)	1.86 (1.08, 3.20)
0.49 (0.13, 1.88)	0.53 (0.13, 2.15)	0.41 (0.11, 1.44)	0.22 (0.05, 1.00)	0.20 (0.04, 1.09)	0.15 (0.04, 0.54)	0.29 (0.07, 1.14)	0.15 (0.04, 0.59)	**NRT + MEC**	0.31 (0.09, 1.09)	0.19 (0.04, 0.84)	0.31 (0.08, 1.19)	0.18 (0.04, 0.71)	0.28 (0.08, 1.03)	0.28 (0.08, 1.01)
1.58 (0.96, 2.61)	1.72 (0.92, 3.21)	1.31 (1.07, 1.61)	0.71 (0.30, 1.67)	0.64 (0.20, 2.04)	0.50 (0.42, 0.59)	0.93 (0.51, 1.67)	0.49 (0.29, 0.84)	3.23 (0.92, 11.36)	**NRT**	0.61 (0.27, 1.39)	1.00 (0.61, 1.66)	0.57 (0.31, 1.06)	0.91 (0.63, 1.31)	0.91 (0.72, 1.15)
2.58 (1.02, 6.55)	2.80 (1.03, 7.62)	2.14 (0.95, 4.80)	1.15 (0.36, 3.69)	1.04 (0.26, 4.22)	0.81 (0.37, 1.80)	1.51 (0.57, 4.00)	0.80 (0.31, 2.06)	5.27 (1.19, 23.36)	1.63 (0.72, 3.67)	**Fluoxetine**	1.63 (0.65, 4.13)	0.93 (0.35, 2.53)	1.48 (0.62, 3.55)	1.49 (0.66, 3.37)
1.58 (0.81, 3.08)	1.71 (0.80, 3.66)	1.31 (0.81, 2.10)	0.71 (0.27, 1.86)	0.64 (0.18, 2.21)	0.50 (0.31, 0.80)	0.92 (0.44, 1.93)	0.49 (0.24, 0.98)	3.22 (0.84, 12.36)	1.00 (0.60, 1.64)	0.61 (0.24, 1.55)	**Cytisine**	0.57 (0.27, 1.22)	0.90 (0.50, 1.64)	0.91 (0.55, 1.51)

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TABLE 2 (*Continued*) The results of network meta-analysis for all pairwise comparisons.

(B) Continuous abstinence rate

2.76 (1.28, 5.94)	2.99 (1.28, 7.01)	2.29 (1.24, 4.22)	1.23 (0.44, 3.47)	1.12 (0.31, 4.07)	0.87 (0.48, 1.57)	1.61 (0.71, 3.67)	0.86 (0.40, 1.82)	5.63 (1.40, 22.61)	1.74 (0.95, 3.20)	1.07 (0.40, 2.89)	1.75 (0.82, 3.74)	**Clonidine**	1.58 (0.79, 3.17)	1.59 (0.85, 2.97)
1.74 (0.96, 3.18)	1.89 (0.93, 3.83)	1.45 (0.98, 2.13)	0.78 (0.31, 1.96)	0.71 (0.21, 2.35)	0.55 (0.38, 0.79)	1.02 (0.52, 1.99)	0.54 (0.29, 1.01)	3.56 (0.97, 13.13)	1.10 (0.76, 1.59)	0.68 (0.28, 1.62)	1.11 (0.61, 2.01)	0.63 (0.32, 1.27)	**BUP + NRT**	1.01 (0.70, 1.45)
1.73 (1.04, 2.90)	1.88 (1.00, 3.53)	1.44 (1.15, 1.79)	0.78 (0.33, 1.84)	0.70 (0.22, 2.24)	0.55 (0.45, 0.66)	1.01 (0.57, 1.82)	0.54 (0.31, 0.93)	3.54 (0.99, 12.61)	1.09 (0.87, 1.38)	0.67 (0.30, 1.52)	1.10 (0.66, 1.82)	0.63 (0.34, 1.17)	0.99 (0.69, 1.43)	**Bupropion**

(C) 7-point continuous abstinence rate

VAR + NRT	0.95 (0.41, 2.19)	0.87 (0.46, 1.62)	0.42 (0.10, 1.73)	0.37 (0.19, 0.70)	0.56 (0.22, 1.46)	0.40 (0.17, 0.97)	0.55 (0.28, 1.08)	0.77 (0.34, 1.75)	0.88 (0.41, 1.87)	0.64 (0.32, 1.25)
1.05 (0.46, 2.43)	**VAR + BUP**	0.91 (0.52, 1.60)	0.44 (0.11, 1.78)	0.39 (0.21, 0.69)	0.59 (0.24, 1.48)	0.43 (0.18, 0.98)	0.58 (0.31, 1.08)	0.81 (0.37, 1.76)	0.92 (0.46, 1.87)	0.67 (0.36, 1.25)
1.15 (0.62, 2.15)	1.09 (0.63, 1.91)	**Varenicline**	0.49 (0.14, 1.74)	0.42 (0.34, 0.52)	0.65 (0.31, 1.35)	0.47 (0.25, 0.88)	0.63 (0.48, 0.84)	0.88 (0.51, 1.52)	1.01 (0.65, 1.58)	0.73 (0.54, 0.98)
2.37 (0.58, 9.77)	2.25 (0.56, 9.04)	2.06 (0.57, 7.39)	**Selegiline**	0.87 (0.25, 3.06)	1.33 (0.31, 5.64)	0.96 (0.24, 3.87)	1.31 (0.36, 4.69)	1.82 (0.46, 7.17)	2.08 (0.56, 7.79)	1.51 (0.42, 5.41)
2.73 (1.43, 5.21)	2.59 (1.44, 4.67)	2.37 (1.92, 2.94)	1.15 (0.33, 4.06)	**Placebo**	1.53 (0.76, 3.10)	1.11 (0.61, 2.01)	1.50 (1.20, 1.88)	2.10 (1.21, 3.62)	2.40 (1.60, 3.58)	1.74 (1.39, 2.16)
1.78 (0.69, 4.63)	1.69 (0.68, 4.23)	1.55 (0.74, 3.22)	0.75 (0.18, 3.18)	0.65 (0.32, 1.32)	**Nortriptyline**	0.72 (0.29, 1.81)	0.98 (0.47, 2.05)	1.37 (0.56, 3.33)	1.56 (0.70, 3.49)	1.13 (0.55, 2.33)
2.47 (1.03, 5.96)	2.35 (1.02, 5.42)	2.15 (1.14, 4.05)	1.04 (0.26, 4.20)	0.90 (0.50, 1.65)	1.39 (0.55, 3.50)	**Naltrexone**	1.36 (0.72, 2.56)	1.90 (0.84, 4.26)	2.17 (1.06, 4.44)	1.57 (0.83, 2.97)
1.82 (0.93, 3.57)	1.72 (0.93, 3.20)	1.58 (1.19, 2.10)	0.77 (0.21, 2.75)	0.66 (0.53, 0.83)	1.02 (0.49, 2.13)	0.73 (0.39, 1.38)	**NRT**	1.39 (0.78, 2.50)	1.59 (1.08, 2.36)	1.15 (0.87, 1.53)
1.30 (0.57, 2.97)	1.24 (0.57, 2.69)	1.13 (0.66, 1.95)	0.55 (0.14, 2.16)	0.48 (0.28, 0.82)	0.73 (0.30, 1.78)	0.53 (0.23, 1.18)	0.72 (0.40, 1.29)	**Cytisine**	1.14 (0.58, 2.24)	0.83 (0.46, 1.49)
1.14 (0.54, 2.43)	1.08 (0.53, 2.19)	0.99 (0.63, 1.54)	0.48 (0.13, 1.80)	0.42 (0.28, 0.62)	0.64 (0.29, 1.43)	0.46 (0.23, 0.94)	0.63 (0.42, 0.93)	0.87 (0.45, 1.71)	**BUP + NRT**	0.72 (0.49, 1.08)
1.57 (0.80, 3.10)	1.49 (0.80, 2.78)	1.37 (1.02, 1.84)	0.66 (0.18, 2.38)	0.58 (0.46, 0.72)	0.88 (0.43, 1.82)	0.64 (0.34, 1.20)	0.87 (0.65, 1.15)	1.21 (0.67, 2.17)	1.38 (0.92, 2.06)	**Bupropion**

BUP: Bupropion; NRT: Nicotine replacement therapy; MEC: Mecamylamine; VAR: Varenicline.

Note: All effect sizes were presented using OR values and 95% confidence intervals.

In each column, each effect size was the result of that intervention compared to any other intervention.

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TABLE 3 Meta-analysis of smoking cessation effects of different interventions in specific populations of smokers.

Population	Comparison	Relation	Study	OR	95% CI	*p* Value
COPD	VAR vs. PLA	Direct	2	4.46	(3.21, 6.21)	$p < 0.05$
	BUP vs. PLA	Direct	1	2.26	(1.07, 4.81)	$p < 0.05$
	NOR vs. PLA	Direct	1	1.95	(0.90, 4.23)	$p > 0.05$
	NOR vs. BUP	Direct	1	0.53	(0.09, 3.00)	$p > 0.05$
	VAR vs. BUP	Direct	1	2.47	(1.23, 4.92)	$p < 0.05$
	VAR vs. NOR	Indirect	—	1.9	(0.33, 10.82)	$p > 0.05$
Mental illness	VAR vs. PLA	Direct	5	3.03	(2.04, 4.51)	$p < 0.05$
	BUP vs. PLA	Direct	4	2.56	(1.40, 4.68)	$p < 0.05$
	BUP + NRT vs. NRT	Direct	1	3	(0.52, 17.16)	$p > 0.05$
	NRT vs. PLA	Direct	1	3.42	(1.78, 6.56)	$p < 0.05$
	VAR vs. BUP	Direct	1	2.29	(1.34, 3.88)	$p < 0.05$
	VAR vs. NRT	Direct	1	1.35	(0.83, 2.19)	$p > 0.05$
	BUP vs. NRT	Direct	2	2.08	(0.12, 36.42)	$p > 0.05$
	BUP + NRT vs. PLA	Indirect	—	16.14	(2.91, 89.58)	$p < 0.05$
	BUP + NRT vs. VAR	Indirect	—	4.75	(0.88, 25.51)	$p > 0.05$
	BUP + NRT vs. BUP	Indirect	—	6.86	(1.23, 38.29)	$p < 0.05$
Cardiovascular disease	BUP vs. PLA	Direct	4	1.94	(1.03, 3.66)	$p < 0.05$
	VAR vs. PLA	Direct	2	2.47	(1.07, 5.70)	$p < 0.05$
	NRT vs. PLA	Direct	1	1.97	(0.97, 4.01)	$p > 0.05$
	VAR vs. BUP	Indirect	—	1.88	(0.44, 8.04)	$p > 0.05$
Cancer	VAR vs. PLA	Direct	1	1.16	(0.58, 2.30)	$p > 0.05$
	BUP vs. PLA	Direct	1	1.07	(0.56, 2.06)	$p > 0.05$
HIV	VAR vs. PLA	Direct	1	2.51	(1.05, 6.01)	$p < 0.05$
Posttraumatic Stress Disorder	BUP vs. PLA	Direct	1	2.67	(0.21, 33.49)	$p > 0.05$
	NRT vs. PLA	Direct	1	2.07	(0.35, 12.22)	$p > 0.05$
Substance Use Disorders	VAR vs. NRT	Direct	2	3.61	(1.17, 11.13)	$p < 0.05$
Asthma	VAR vs. PLA	Direct	1	1.25	(0.29, 5.31)	$p > 0.05$
Tuberculosis	CYT vs. PLA	Direct	1	1.09	(0.93, 1.28)	$p > 0.05$
Medical illnesses smokers	BUP + NRT vs. NRT	Direct	1	2.33	(1.03, 5.25)	$p > 0.05$
Alcohol dependence	VAR vs. PLA	Direct	6	2.71	(1.32, 5.58)	$p < 0.05$
	NAL vs. PLA	Direct	4	1.36	(0.81, 2.28)	$p > 0.05$
	BUP vs. PLA	Direct	3	0.73	(0.41, 1.29)	$p > 0.05$
	TOP vs. PLA	Direct	2	1.3	(0.56, 3.02)	$p > 0.05$
	NRT vs. PLA	Direct	1	3.09	(1.12, 8.54)	$p < 0.05$
	VAR + NRT vs. NRT	Direct	1	2.06	(0.97, 4.37)	$p > 0.05$
	VAR vs. CYT	Direct	1	0.65	(0.31, 1.38)	$p > 0.05$
	NRT vs. NAL	Indirect	—	2.18	(0.57, 8.37)	$p > 0.05$
	BUP vs. NAL	Indirect	—	0.5	(0.18, 1.36)	$p > 0.05$
	NAL vs. VAR	Indirect	—	0.7	(0.23, 2.14)	$p > 0.05$
	NAL vs. VAR + NRT	Indirect	—	0.22	(0.04, 1.15)	$p > 0.05$
	NAL vs. TOP	Indirect	—	0.41	(0.34, 3.59)	$p > 0.05$
	NRT vs. VAR	Indirect	—	1.53	(0.36, 6.53)	$p > 0.05$
	NRT vs. TOP	Indirect	—	2.4	(0.54, 10.70)	$p > 0.05$
	BUP VS. VAR + NRT	Indirect	—	0.11	(0.02, 0.57)	$p > 0.05$
	BUP VS. VAR	Indirect	—	0.35	(0.11, 1.11)	$p > 0.05$
	BUP VS. TOP	Indirect	—	0.54	(0.16, 1.80)	$p > 0.05$
	VAR vs. VAR + NRT	Indirect	—	0.32	(0.06, 1.79)	$p > 0.05$
	TOP vs. VAR + NRT	Indirect	—	0.2	(0.03, 1.18)	$p > 0.05$

(Continued on following page)

TABLE 3 (*Continued*) Meta-analysis of smoking cessation effects of different interventions in specific populations of smokers.

Population	Comparison	Relation	Study	OR	95% CI	*p* Value
	TOP vs. VAR	Indirect	—	0.64	(0.17, 2.34)	$p > 0.05$
	BUP vs. NRT	Indirect	—	0.23	(0.06, 0.88)	$p > 0.05$
	PLA vs. VAR + NRT	Indirect	—	0.16	(0.04, 0.69)	$p > 0.05$
	BUP vs. CYT	Indirect	—	0.23	(0.05, 1.00)	$p > 0.05$
	CYT vs. TOP	Indirect	—	2.41	(0.49, 11.86)	$p > 0.05$
	CYT vs. PLA	Indirect	—	3.11	(0.87, 11.17)	$p > 0.05$
	CYT vs. NAL	Indirect	—	2.19	(0.51, 9.34)	$p > 0.05$
	CYT vs. NRT	Indirect	—	1.01	(0.18, 5.63)	$p > 0.05$
	CYT vs. VAR + NRT	Indirect	—	0.49	(0.07, 3.46)	$p > 0.05$

COPD: Chronic Obstructive Pulmonary Disease; Bupropion: BUP; NRT: Nicotine replacement therapy; Cytisine: CYT; Naltrexone: NAL; Topiramate: TOP; Placebo: PLA; Nortriptyline: NOR; Varenicline: VAR.

In addition, the smoking cessation effect of some combined interventions was worthy of attention. In this network meta-analysis, four combined interventions were reported, including Varenicline + Nicotine replacement therapy, Varenicline + Bupropion, Nicotine replacement therapy + Mecamylamine, and Bupropion + Nicotine replacement therapy. For Varenicline + Nicotine replacement therapy, our analysis showed that it was superior to the six monotherapies, and it was third in the probability ranking. Differently, in a recent network meta-analysis, the authors determined the clinical effectiveness of smoking cessation medicines and e-cigarettes, and the results revealed that Varenicline plus nicotine replacement therapy was ranked first for sustained abstinence (Thomas et al., 2021). Although there were some differences in these two reviews, this also illustrated the potential smoking cessation benefits of the varenicline plus nicotine replacement therapy. As for Varenicline + Bupropion, the treatment was ranked second in all interventions, and the findings in this network meta-analysis showed that compared with Bupropion monotherapy, combination treatment with Varenicline and Bupropion could significantly improve the abstinence rate, but no statistical difference was found compared with Varenicline. However, a meta-analysis published in 2019 assessing the effects of the combination therapy of varenicline and bupropion in smoking cessation, the results showed the combination treatment was superior to Varenicline monotherapy (Zhong et al., 2019). This difference may be due to the incorporation of newer trials in our analysis, as well as potential heterogeneity (inconsistencies in populations and interventions) between studies.

In subgroup analyses, we investigated the effect of smoking cessation in 11 specific populations, in these populations, more trials reported smokers with chronic obstructive pulmonary disease, mental illness, cardiovascular disease, and alcohol dependence. For chronic obstructive pulmonary disease, our network meta-analysis showed that both Varenicline and Bupropion were superior to Placebo. Similarly, a review by

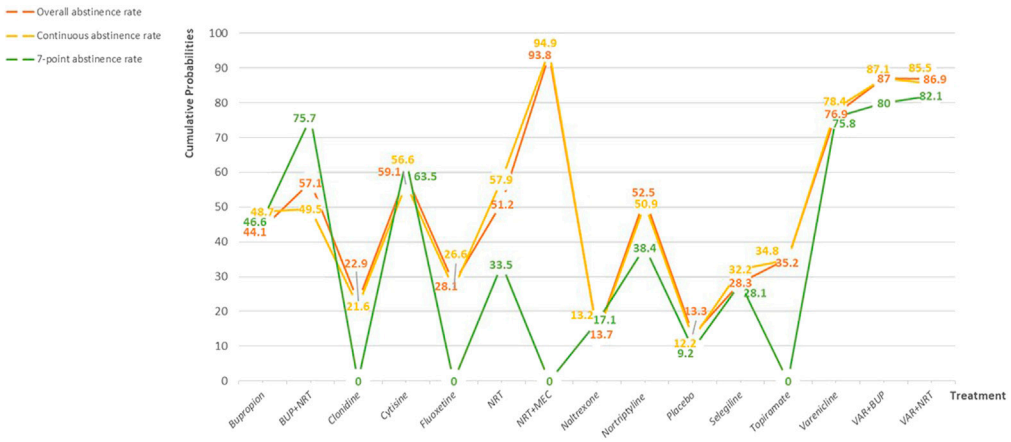

FIGURE 3
Probability ranking for all interventions. NRT: Nicotine replacement therapy; VAR: Varenicline; BUP: Bupropion.

Antoniu et al. (2021) showed the benefits of these two interventions for smoking cessation. However, in an earlier systematic review, the authors showed that Bupropion did not result significantly higher prolonged abstinence rates. In patients with mental illness, the results of this analysis showed that Varenicline, Bupropion, Nicotine replacement therapy, and Bupropion + Nicotine replacement therapy showed better withdrawal effects than placebo. A network meta-analysis by Roberts et al. (2016) also demonstrated that bupropion and Varenicline are effective and tolerable for smoking cessation in adults with severe mental illness. Interestingly, compared to the above studies, our study also found that Bupropion + Nicotine replacement therapy exhibited better withdrawal effects in psychiatric patients, which was significantly better than Bupropion, but no difference compared with Varenicline and Nicotine replacement therapy. Given that direct comparisons between these interventions are based on a limited number of studies, the quality of the evidence for this finding needs to be validated by more trials. For smokers with cardiovascular disease, our results found a significant withdrawal advantage for varenicline and bupropion, which is consistent with Karine's findings (Suissa et al., 2017). For alcohol dependent smokers, more types of comparisons were reported, including seven pairs of direct comparisons and 21 pairs of indirect comparisons. The results showed that both Varenicline and Nicotine replacement therapy were superior to Placebo. Noteworthy, Guo et al. (2021) study also found that Varenicline can promote smoking cessation in alcohol-dependent people, while Naltrexone, Topiramate and Bupropion have no significant effect. In addition, withdrawal benefits of varenicline have been found in limited trials in patients with AIDS and substance use disorders, and are inconclusive in tuberculosis, asthma, post-traumatic stress disorder, and medical conditions. More high-quality studies are needed to validate this in the future.

Furthermore, assessing the quality of evidence for the findings is an important basis for practice. The first is that potential risk of bias of the included studies might be a critical determinant (Guyatt et al., 2011c). The risk of bias assessment revealed that over 80% of studies included in the review were rated as unclear risk of bias due to insufficient information and unclear reporting. These results directly lead to more trials being judged to be at high risk of bias, which can affect the reliability of the synthetic effects. Therefore, in the evaluation of the quality of evidence, it will lead to different degrees of downgrading, and while reducing the quality of the evidence, it may also affect the generalizability of the evidence (Guyatt et al., 2011c). In addition, other factors such as inconsistency and imprecision also contributed to weakening the quality of the evidence for the outcomes. For inconsistency, the heterogeneity on population, intervention, and confirmation of outcomes between included trials might be the main sources (Guyatt et al., 2011b). Moreover, there were significant differences in sample size between included trials, especially with small sample sizes in some trials, which could result in wide confidence intervals (imprecision) in the combined effect sizes (Guyatt et al., 2011a). These issues should receive further attention from future research and in health practice.

Based on this network meta-analysis, certain detailed improvements were found to be more promising for future research. Firstly, when conducting clinical trials, more details can be considered in the selection of smokers. For example, the physical condition of the smokers (with or without disease), the number of cigarettes smoked per day, and age may affect the effectiveness of the intervention. For example, some published studies showed that smokers with chronic obstructive pulmonary disease to have specific smoking characteristics that differentiated them from the rest of smokers and which complicated smoking cessation (Jiménez Ruiz et al., 2012; Zhang et al., 2022). In addition, smoker's psychological conditions or preparation may influence withdrawal, Ussher et al. proposed measuring dependence and motivation of smokers to predict both short-term and medium-term outcomes of attempts to stop smoking in treatment-seeking smokers involved in a clinical trial, while Watson et al. assessed the effectiveness of anxiety and depression levels in predicting smoking cessation, these attempts have shown the importance of quitting intention and psychological state of smokers (Ussher et al., 2016; Watson et al., 2020). Therefore, researcher can minimize the differences between these factors in the participant selection process. Secondly, clarifying the details of intervention implementation plays an important role in practice. For example, a systematic review by Lindson et al. (2019) determined the effectiveness and safety of different forms, deliveries, doses, durations and schedules of nicotine replacement therapy, for achieving long-term smoking cessation, there was high-certainty evidence that using combination treatment vs. single-form nicotine replacement therapy, and high dose vs. low dose nicotine gum, could increase the chances of successfully stopping smoking. Overall, detailed reports on the dosage, frequency, and duration of specific pharmacological interventions should be fully considered. Finally, in terms of biochemical verification of tobacco abstinence, Benowitz et al. (2020) pointed out that biochemical verification could increase right and validity compared to self-reported smoking abstinence. However, for biomarkers such as exhaled carbon monoxide level, it needs to be assessed in the context of potential environmental exposures. As the degree of air pollution will affect the measurement of carbon monoxide level, it will lead to differences in the setting of parts per million value among researchers in different regions (Tual et al., 2010; Zhang et al., 2013; Maga et al., 2017), so future researchers could fully consider environmental factors when conducting biochemical verification.

The impact of some limitations on this study needs to be clarified. Although many clinical trials were included in this

study, there is a possibility that some trials and interventions may be missed, considering the need for each intervention in the network meta-analysis to be interconnected. In addition, the included trials differed in follow-up time and types of outcome measures. In general, most trials reported a follow-up period of more than 6 months, but in some trials the follow-up period was insufficient. Collectively, these differences introduce potential bias to the level of evidence for the findings of this network meta-analysis. Moreover, from the network graph formed by all interventions, there are indirect comparisons between more interventions, which also means that direct comparisons between these interventions are lacking in clinical trials. Therefore, future trials of more intervention types are recommended to further clarify and validate existing findings.

Conclusion

The results of this network meta-analysis showed that most pharmacological interventions demonstrated a benefit in smoking cessation compared with placebo, whether monotherapy or combination therapy. Among all monotherapies, Varenicline showed a higher level of evidence of smoking cessation. Furthermore, confirmed evidence suggested that some combination treatments, such as Varenicline plus Bupropion and Nicotine replacement therapy plus Mecamylamine have a higher probability of being the best smoking cessation interventions.

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.

Author contributions

All authors contributed to the conception, search terms and methodology of the review. XS, KG, and WL came up with the study idea. XS, KG, and FE designed the study. YNW and MX completed the database searches and study selection. CQ-Y and YNW completed the assessment of bias of the included studies. XD, YSW and ZW extracted data from the included studies. XS, KG, and FE completed the meta-analyses. XS and KG wrote the first draft of the manuscript. KY and XL completed the critical revision of the manuscript. All authors contributed to the writing or revision of the final manuscript. And all authors have read and approve the final version submitted to this journal.

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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.2022.1012433/full#supplementary-material

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Comprehensibility of a personalized medication overview compared to usual-care prescription drug labels

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Poor understanding of prescription drug label (PDL) instructions can lead to medication errors, suboptimal treatment (side) effects, and non-adherence. A personalized medication hard-copy overview listing PDL instructions and visual information may support patients in their medication use. This study aimed to investigate the comprehensibility of PDL instructions on a personalized medication overview compared to usual-care PDL instructions presented on a medication box. A hypothetical-online-experiment was set up, comparing groups of respondents exposed vs not exposed to the medication overview and who received PDL instructions for three, five, or eight medications. Participants were divided randomly in six groups. Online questionnaires were sent to a stratified sample of 900 members from the Nivel Dutch Healthcare Consumer Panel. Outcome measures included comprehension of instructions for medication use, e.g. how often, dose timing, usage advice and warnings for a medication with simple use instructions (omeprazol) and more complex use instructions (levodopa/carbidopa (L/C)). To analyze differences between experimental conditions ANOVA testing was used. 604 respondents (net response 67%) completed the questionnaires. Respondents exposed (E) to the overview gave a higher proportion of correct answers compared to non-exposed (NE) respondents for usage advice (L/C: mean 0.83, SD 0.4 E; 0.03, SD 0.2 NE, $p < 0.001$; omeprazol: mean 0.85, SD 0.4 E; 0.10, SD 0.3 NE, $p < 0.001$). Both groups gave the same proportion of correct answers (mean 0.80, SD 0.4, $p = 1.0$) for dose timing of omeprazol. More NE respondents gave correct answers for how often (mean 0.85, SD 0.4 NE; mean 0.76, SD 0.4 E, $p = 0.02$) and dose timing (mean 0.92, SD 0.3 NE; mean 0.86, SD 0.4 E, $p = 0.04$) of L/C. No differences were found regarding number of medications nor were interaction effects found between the number of medications and information type. As a medication overview contains additional information, it can be a good addition in supporting patients in their medication use compared to usual-care

PDLs. Future research should focus on identifying patient groups who might benefit more from a medication overview, by testing the effect of such overview on this group.

KEYWORDS

comprehensibility, (usual-care) prescription drug labels, medication overview, patient-tailored medication information, treatment adherence

Introduction

Poor understanding of prescription drug label (PDL) instructions can lead to medication errors, side effects, suboptimal treatment effects and non-adherence (Davis et al., 2009; Bailey et al., 2015). PDLs are often the most read source of information before a patient starts using the medication (Webb et al., 2008), and they contain dosing instructions, usage recommendations and warnings (Wolf et al., 2007). On the PDL, there is only limited space, making it difficult to provide additional information (Maghroudi et al., 2020). Consequently, the information on the PDLs is often not comprehensible, as up to 50% of the adult population show limited understanding of PDLs, precautions, and medication warnings (Davis et al., 2006a; Davis et al., 2006b; Wolf et al., 2006; Wolf et al., 2007; Bailey et al., 2009; Wolf et al., 2010; Wolf et al., 2011; Bailey et al., 2012; Bailey et al., 2014).

Problems understanding medical information seem to be more common in certain patient groups, such as the elderly, people with limited health literacy, and people with language barriers (van Dijk et al., 2016). However, when it comes to PDLs also some with adequate health literacy skills find it difficult to understand and apply the usage instructions on PDLs. Previous research by Davis et al. (2006) showed that 37% of the interviewed patients, including those with adequate health literacy scores, did not understand instructions on the PDLs correctly (Davis et al., 2006a). To ensure understanding of instructions it is important to formulate instructions as clearly and explicitly as possible (Davis et al., 2006b; Bailey et al., 2012).

Researchers have long studied how to best provide comprehensive medication information related to medication use and understanding in a simplistic and practical manner. As such, numerous studies related to this topic have been published (Maghroudi et al., 2021). Studies have focused on factors such as, complexity of dosing instructions particularly in relation to patient health literacy (Beckman et al., 2005; Shrank et al., 2007; European Commission, 2009; Bailey et al., 2012; Emmerton et al., 2012; Koster et al., 2014; Patel et al., 2018), requirements concerning content an comprehensibility of the text (Raynor and Bryant, 2013; Pires et al., 2016; Yuan et al., 2019), precision of writing dosing instructions (Borgsteede and Heringa, 2019), and the use of icons, graphics and pictograms (Kheir et al., 2014; van Beusekom et al., 2017). As a result, guidelines have been drawn up with standards on how information should be presented on the PDL (i.e. simple language, one message per PDL line, formulated text as concretely as possible) (Houts et al., 2006; Blake et al., 2010). Also, studies have focused on communication of medicines information, format and organization of the medicines label, as well as number of medicines dispensed (Wolf et al., 2007; Bailey et al., 2012; Emmerton et al., 2012; Samaranayake et al., 2018). There is attention for improving the PDL texts (Maghroudi et al., 2018; Maghroudi et al., 2021), which has improved the labels. However, the ideal approach to bundle these aspects still remains unclear.

Tools have been developed to clarify prescription medication label texts in order to facilitate medication use. For example, medication overviews have been developed using illustrations and icons to support label texts (Dowse et al., 2010; Dowse et al., 2014). These information aids are intended to increase understanding of the usage instructions of prescribed medications (Payne and Avery, 2011; Masnoon et al., 2017), however, there is not yet a good simple solution for patients using multiple medications. A medication overview listing the patient's medications and use instructions can support patients with polypharmacy to keep a clear overview of their medication use, which in return may lead to better treatment adherence (Nair et al., 2011).

The aim of this study was to understand whether such a personalized medication overview can support patients in their medication use compared to the usual-care PDLs. Our hypotheses were that: 1) patients better understand the medication instructions when they have a personalized medication overview rather than PDLs-only, 2) this understanding increases with the number of medications (the more medications, the greater the benefit from the overview), and 3) a personalized medication overview has influence on the comprehensibility of the medication-use instruction, as it is intended to help patients better process the information on PDL instructions, particularly patients with low health literacy skills.

Materials and methods

Design and procedure

2 × 3 between-subjects experimental design

A hypothetical online experiment was set up, comparing groups of respondents exposed vs not exposed to a medication overview and who received PDL instructions for three, five, or

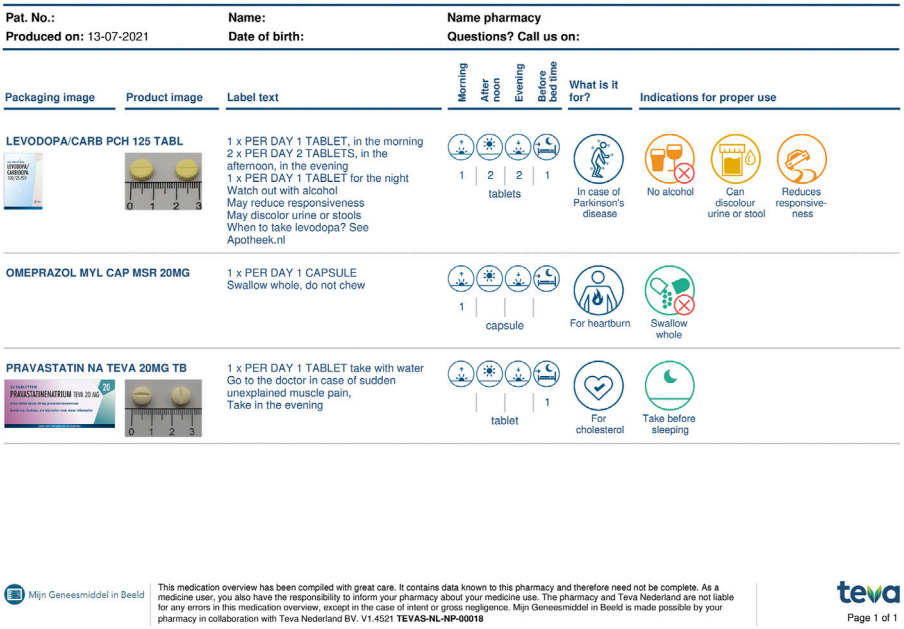

FIGURE 1
Example of MijnGiB overview for three medications.

eight medications. Participants were divided randomly in six groups (each receiving one of the six questionnaires, for one of the six conditions; n = 150 participants per questionnaire).

Participants

Online questionnaires were sent out to panel members of the Nivel Dutch Health Care Consumer Panel, which collects the general population's experiences and opinions on different matters regarding to healthcare (Brabers et al., 2012). This panel, of approximately 11,500 people (2021) who are 18 years and older from the Netherlands, is an access panel where members have given permission to be contacted to fill in questionnaires on regular basis. The background characteristics of the panel members, such as their gender, age, level, self-reported health status, and education are known. The panel is renewed on a regular basis to ensure that representative samples of the Dutch population can continue to be drawn, with regard to age and gender. Participants are recruited via bought addresses from an address supplier. Panel members are approached about four to five times a year to complete questionnaires, from the approximately eight times to ten per year a survey is distributed on all kinds of topics within the healthcare sector. The respondents are given the choice to fill in a paper or online questionnaire. Respondents can withdraw themselves from the panel at any time, but cannot sign up on own

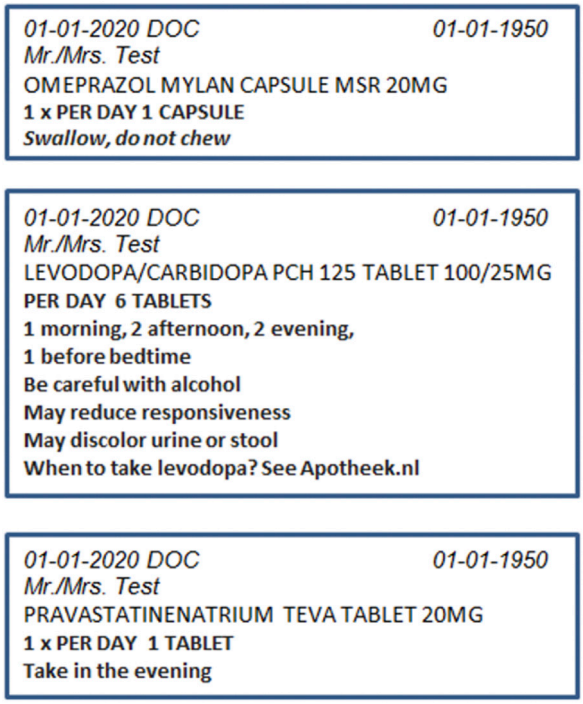

FIGURE 2
Prescription drug label 1–3 (translated from Dutch to English).

BOX 1 Hypothetical case: situation where three medications are prescribed and MijnGiB and PDLs were provided (translated from Dutch to English) (PDLs and MijnGiB followed after this hypothetical case).

Imagine being prescribed a new medication by your general practitioner. You go to the pharmacy to pick up this medication. The pharmacy technician (PT) tells you how to take the medication and says that you can also read the instructions on the PDL on the medication box. The PT also gives you two other medications that you have already been using for some time. You can also read on the PDL how to take these medications. In addition, the PT gives you an overview whereby the information is presented in a different way. This overview is called 'Mijn Geneesmiddel in Beeld' (MijnGiB). You decide to read this at home. See below the three PDLs and MijnGiB.

initiative to become member of the panel. Panel members do not receive financial compensation for filling out questionnaires nor is there a membership fee, though by answering the questionnaires they can save up for a gift card.

For the purpose of this study, we approached a sample of 900 members from the Nivel Dutch Health Care Consumer Panel (Brabers et al., 2012). An expert-based opinion was used to determine the appropriate number of respondents, which has also been done in a study with a similar study design (Struikman et al., 2020). First, we selected respondents from previous surveys (2019 and 2020) who indicated they were taking prescription medications, and from the 2019 sample in which health literacy scores were assessed, we also selected respondents who had limited health literacy skills according to their answers/scores on a health literacy scale. This resulted in 811 eligible panel members. Secondly, to complete the total sample of 900, another 89 respondents were sampled at random from the panel. All 900 respondents indicated online as their preference for completing the questionnaire.

Stimulus materials

The three 'exposure' groups received both the PDLs as used in usual-care as well as the medication overview, My Medication Review (in Dutch: Mijn Geneesmiddel in Beeld® (MijnGiB)) (Figure 1), and the three 'non-exposure' groups received PDL instructions only as presented on the medication boxes (Figure 2). Within the conditions, the same medication order was used. The order of the stimulus was also fixed for the participants who received PDL or PDL + MijnGiB.

Since 2019, the pharmaceutical company Teva has been offering MijnGiB, a complete paper version, personalized overview of all medications of the patient in addition to the regular PDL provided by the pharmacy. MijnGiB includes the following information: name of medication, PDL text, moment of intake, the number of tablets per day time, for which condition or disease the medication is used, advice and warnings for use, photos of Teva products to recognize the medication and pictograms/icons of the instructions for proper use.

Both PDLs on medication boxes and MijnGiB communicate dosage instructions and usage advice and warnings. MijnGiB gives more information on the moment of intake, for which condition or disease the medication is taken, as well as photographs of the prescribed medications and tablets/capsules. The additional information on MijnGiB is intended to help patients better process the information on PDL instructions, particularly patients with low health literacy skills.

The respondents were asked to read a hypothetical case (Boxes 1, 2) and to imagine that this hypothetical situation was applicable to them. During the online questionnaire, participants could scroll back to the stimuli material. However, they could not print the stimulus, or at least, this was not presented as an option. The participants were not timed when filling in the questionnaire or viewing the stimulus materials. Questions were asked for a medication with simple (i.e. 1 dose moment per day, 1 tablet) use instructions (omeprazol) and a medicine with more complex instructions (levodopa/carbidopa (L/C)).

Data collection and ethical considerations

The online questionnaire was sent out to the sample of panel members on the 1st of December, 2020, and two reminders were sent on the 8th and 15th of December. The questionnaires closed on the 22nd of December.

According to Dutch legislation, neither obtaining informed consent nor approval by a medical ethics committee is obligatory for carrying out research using the Dutch Healthcare Consumer Panel (CCMO, 2022). Data are analyzed pseudomized, and processed according to the privacy policy of the Dutch Healthcare Consumer Panel, which complies with the General Data Protection Regulation (GDPR) (Supplementary Appendix S1, Data availability). A privacy regulation is accessible for the Nivel Dutch Health Care Consumer Panel (Jong and Brabers, 2022). The research team who analyzed the data had no access to any identifiable information of the respondents, such as name and address. Participation is voluntary and members are not forced to participate in surveys. They can stop their membership at any time without giving a reason.

Measurements

Experiment outcome measures

The online questionnaire had four experimental outcome measures (Supplementary Appendix S2, for outcome measure questions from questionnaire with 3 medications, for the MijnGiB + PDLs group). Full questionnaires can be requested from the corresponding author. These were: dosage instructions; 1) how often (x times per day or "I do not know"), 2) dose timing

BOX 2 Hypothetical case: situation where three medications are prescribed and PDLs only are provided (translated from Dutch to English) (PDLs followed after this hypothetical case).

Imagine being prescribed a new medication by your general practitioner. You go to the pharmacy to pick up this medication. The pharmacy technician (PT) tells you how to take the medication and says that you can also read the instructions on the PDL on the package. The PT also gives you two other medications that you have been taking for some time. You can also read on the PDL how to take these medications. You decide to read this at home. See below the three PDLs.

(morning, afternoon, evening, before bedtime, "I do not know"), 3) whether it was clear which condition or disease the medication is for (yes/no), and 4) usage advice and warnings. The advice and warnings questions consisted of: which aspects does one need to pay attention to when taking these medications (respondents could select multiple answers, including the options "other", or "none of the above"). We asked the outcome measures for a medication with simple instructions for use (omeprazol) and a medication with more complex instructions (levodopa/carbidopa). At the end we asked if it was clear for which condition or disease the respondent had to hypothetically take the medication (answer options: yes or no).

TABLE 1 Distribution of participants per condition.

Condition	N (%)
3 medications + MijnGiB	95 (15.7)
5 medications + MijnGiB	101 (16.7)
8 medications + MijnGiB	100 (16.6)
3 medications without MijnGiB	108 (17.9)
5 medications without MijnGiB	98 (16.2)
8 medications without MijnGiB	102 (16.9)

Given that medication instructions are either followed correctly or incorrectly, we grouped the answers into dichotomous variables. The "I do not know" option was combined with the incorrect answer, with the exception of the question regarding the moment of intake of omeprazol for the condition PDL-only. In practice the PDL text on the medication box corresponds to the PDL text on MijnGiB. In this experiment, the PDL-only did not state at which moment of the day the patient should take their medication. Therefore, the PDL-only group could not have known the answer. Thus, for the respondents who stated "I do not know," this was also classified as a correct answer.

Background characteristics

Gender, age, education level (low, middle, high) (CBS, 2019), household composition (one person household or multiple person household), ethnicity (native Dutch or (non-) western foreigners), income and perceived general and psychological health on a scale from 1 to 5 (bad, fair, good, very good, excellent) were already known from the panel members. The questions used for the perceived general and psychological health were: In general, how would you describe your general/mental/psychological health? The five-point Likert-scale participants used to answer the questions are based on the categorization of the SF-12 questionnaire (Stewart, 1992).

In addition, questions were asked related to medication use (yes, currently taking one or more prescription medications; no, not at the moment; or no, never used a prescription medication), whether the patient has 1) chronic condition(s) (yes/no), and whether the patient is familiar with MijnGiB (yes (either received from pharmacy or heard of), or no).

Health literacy score

Chew's Brief questions to identify patients with inadequate health literacy (SBSQ) tool was used to assess the health literacy of the respondents. Three questions provided insight into their understanding of health information: 1) how often respondents receive assistance in reading health information, 2) their confidence in filling medical forms, and 3) how often the respondents find it difficult to learn more about their health because they do not understand written information. The respondent's health literacy score was calculated by taking the sum of the three 5-point Likert scale questions, a scale from 0 to 4 (always have problems/not confident to never have problems/confident) (Fransen et al., 2011). An average score of 2 or lower indicates inadequate health literacy, and a score greater than 2 indicates adequate health literacy (Chew, Bradley, Boyko; Chew et al., 2008).

Statistical analysis

The statistical analysis software STATA version 16 was used to perform the statistical analysis. A p-value of <0.05 was considered statistically significant. Descriptive statistics were used to describe the sample population. A randomization check using one-way ANOVA test (F-test) (Goodall and Appiah, 2008) and chi-square tests (for dichotomous proportions) were performed to examine whether the participant characteristics were equally divided across experimental conditions. One-way ANOVAs were used to analyze differences in proportion of correct answers regarding dosage instructions and advice/warnings between the experiment conditions. Thereby it became it apparent whether there was a statistically significant difference between amount of incorrect and correct answers in the exposed and non-exposed

TABLE 2 Background characteristics of respondents (N = 604).

Characteristics	Values	N	Randomization check, p-value
Age (years), mean (SD: range)	62.7 (12.9; 28–90)	604	χ^2 (5) = 3.8, p = 0.6
Gender, n (%)	—	604	χ^2 (5) = 1.3, p = 0.9
Male	305 (50.5)	—	—
Female	299 (49.5)	—	—
Education, n (%)	—	595	χ^2 (10) = 13.7, p = 0.2
Low	56 (9.4)	—	—
Middle	281 (47.2)	—	—
High	258 (43.4)	—	—
Household, n(%)	—	595	χ^2 (5) = 6.3, p = 0.3
One-person household	148 (24.8)	—	—
Multiple-persons household	447 (75.1)	—	—
Migrant status, n(%)	—	597	χ^2 (5) = 4.5, p = 0.5
Non-migrant	546 (91.5)	—	—
Migrant	51 (8.5)	—	—
Health status, n(%)	—	585	χ^2 (20) = 22.6, p = 0.3
Excellent/very good	139 (23.8)	—	—
Good	293 (50.1)	—	—
Fair/bad	153 (26.2)	—	—
Psychological status, n(%)	—	585	χ^2 (20) = 18.5, p = 0.6
Excellent/very good	314 (53.7)	—	—
Good	218 (37.3)	—	—
Fair/bad	53 (9.1)	—	—
Use of prescription medication(s), n(%)	—	604	χ^2 (1.8) = 1.8 p = 0.9
Yes	527 (87.2)	—	—
Has at least one chronic condition, n(%)	—	604	χ^2 (5.6) = 5.6, p = 0.4
Yes	477 (79.0)	—	—
Familiarity with MijnGiB, n(%)	—	599	χ^2 (14.4) = 14.4, p = 0.01
Have heard of MijnGiB	25 (4.2)	—	—
Received MijnGiB from the pharmacy	18 (3.0)	—	—
Never heard or received MijnGiB	556 (92.3)	—	—
Health literacy score, n(%)	—	604	χ^2 (5) = 7.8, p = 0.2
Adequate health literacy (score >2)	579 (95.9)	—	—
Inadequate health literacy (score 2 or lower)	25 (4.1)	—	—

group. The outcome measures were coded dichotomously (0 = incorrect, 1 = correct). Tukey post-hoc tests revealed the difference in means in the groups of respondents with the different experimental conditions. In the case there is a statistically significant difference, the summary of means (SD) gave insight in how much variance there is, e.g. which group (exposed vs non-exposed) had a higher proportion of correct answers than the other group. Two-way full-factorial ANOVA tests were used to analyze interactions.

Results

Of the 900 invited panel members, 661 responded to the questionnaire and 604 panel members completed the questionnaire fully (response rate 67%). The respondents were almost equally distributed over the six groups, see Table 1. Mean age was 63 years (SD 13). As selected for, most had a chronic condition (79%) and used prescription medications (87%), also almost equally divided over the six groups. The majority had a self-perceived adequate health literacy (96%), implying that the hypothesis on the role of health literacy cannot further be analyzed as the number of respondents with an inadequate health literacy score was too small.

The randomization check presented no significant differences between the six experimental conditions and the participant characteristics. The small group of participants who were familiar with MijnGiB (n = 43) were not equally spread across the six conditions (χ^2 (5) = 14.4, p = 0.01). The

TABLE 3 Differences in means (SD) between the groups of respondents exposed and non-exposed to MijnGiB (N = 561).

Questions	Non- exposure to MijnGiB (N = 296)	Exposure to MijnGiB (N = 308)	*p*-value
	Correct answers	Correct answers	
	Mean (SD)	Mean (SD)	
levodopa/carbidopa			
How often should you take levodopa/carbidopa?	0.85 (0.4)	0.76 (0.4)	0.02
At what moment of the day should you take levodopa/carbidopa?	0.92 (0.3)	0.86 (0.4)	0.04
Is it clear for which condition, disease or ailment you should use levodopa/carbidopa?	0.03 (0.2)	0.83 (0.4)	<0.001
Which of the following should you watch out for while taking levodopa/carbidopa?	0.91 (0.3)	0.89 (0.3)	0.5
omeprazol			
How often should you take omeprazol?	0.96 (0.2)	0.96 (0.2)	0.9
At what moment of day should you take omeprazol ?	0.80 (0.4)	0.80 (0.4)	1.0
Is it clear for which condition, disease or ailment you should use omeprazol ?	0.10 (0.3)	0.85 (0.4)	<0.001
Which of the following should you watch out for while taking omeprazol ?	0.93 (0.3)	0.93 (0.3)	0.8
Medications received			
If you look at all PDLs, for which conditions, diseases or ailments have you have received medications?	0.04 (0.2)	0.66 (0.5)	<0.001

participants were therefore excluded from the sample for the data analysis of the experiment, but not for the questions for background characteristics of the sample population. See Table 2 For background characteristics of the respondents.

2 × 3 experimental design results

The effect of the instruction type, number of hypothetically prescribed medications, and the interaction effect between the increasing number of medications and instruction type were investigated. No statistically significant differences were found regarding number of medications (three, five, or eight) nor were interaction effects found between the number of medications and instruction type. There were statistically significant differences between the instruction type (non) exposed to the medication overview (Table 3).

Dosage instructions

How often one takes medication

In total, there was a high proportion of correct answers (mean 0.81, SD 0.4) for how often one should take L/C per day in the exposed (E) and non-exposed (NE) groups to MijnGiB (n = 541). There was a significant difference in the proportion of correct answers amongst the two groups. The non-exposed group gave a slightly higher proportion of correct answers for how often (mean 0.85, SD 0.4 NE; mean 0.76, SD 0.4 E, $p = 0.02$) one should take L/C per day. There were no significant differences for how often one should take omeprazol. In both groups of the respondents (n = 535), there was the same proportion of respondents who gave the correct answer (mean 0.96, SD 0.2) for the non-exposed and exposed group to MijnGiB.

Moment of intake per day

There was also a high proportion (mean 0.89, SD 0.3) of the total respondents (n = 542) who gave the correct answer on the question about at which moment of the day one should take L/C. The non-exposed group had a slightly higher proportion of correct answers (mean 0.92, SD 0.3 NE; mean 0.86 SD, E, $p = 0.04$). Of the total group respondents (n = 533) who answered the question on which moment of the day they should take omeprazol, there was an overall high proportion of correct answers given (mean 0.8, SD 0.4). This correct answer includes respondents in the PDL-only group who stated "I do not know" given that the information was not present on the PDL. There was no significant difference in the proportion of the correct answers between the two groups (mean 0.80, SD 0.4 E; mean 0.80, SD 0.4 NE, $p = 1.0$).

Medication use for type of condition or disease

In total, respondents (n = 539) gave a lower proportion of correct answers (mean 0.40, SD 0.5) for which condition or disease the medication is used. There was a significant difference in the proportion of correct answers between the two groups. The exposed respondents gave a higher proportion of right answers for which condition or disease they should use L/C (mean 0.83,

SD 0.4 E; mean 0.03, SD 0.2 NE, $p < 0.001$). In comparison, the respondents (n = 540) also gave a lower proportion of right answers (mean 0.45, SD 0.5) regarding for which condition or disease omeprazol is used. There was a significant difference between the groups. MijnGiB-exposed respondents gave a higher proportion of correct answers for which condition or disease they should use omeprazol (mean 0.85, SD 0.4 E; 0.10, SD 0.3 NE, $p < 0.001$).

Medication usage advice and warnings

Overall, there was a high proportion (mean 0.9, SD 0.3) of correct answers amongst the respondents (n = 409) who answered the question on what they should pay attention to when using L/C. Also, for omeprazol, of the total respondents (n = 496) a high proportion gave the correct answer (mean 0.93, SD 0.3). No significant differences in the proportion of the correct answers between the exposed and non-exposed group were found.

Overview of medications respondents received

At the end of the experiment questions, respondents were asked for which conditions, diseases or ailments they had received the instruction labels. A small proportion (mean 0.3, SD 0.5) of the total respondents (n = 545) gave the right answer. There was a significant difference in the proportion of the correct answers between the exposed and non-exposed group. MijnGiB-exposed (E) respondents gave a higher proportion of correct answers for the questions regarding for which medications they received the instruction labels compared to the non-exposed group (mean 0.66, SD 0.5 E; mean 0.04, SD 0.2 NE, $p < 0.001$).

Discussion

In this study, we reported on the added value of a personalized medication overview to support patients in their medication use compared to usual-care PDLs. The majority of the respondents gave a high proportion of correct answers, despite the type of PDL instruction, indicating high comprehensibility of both the usual-care PDL instructions and on the personalized medication overview. Respondents exposed to the medication overview gave a higher proportion of correct answers compared to non-exposed for instructions on usage advice (additional information presented on the medication overview) for both a medication simple and complex use instructions. Regarding dose timing (how much and at what moment) of the simple medication both groups gave the same proportion of correct answers. A greater proportion of respondents exposed to the usual-care PDL only gave correct answers for how often and dose timing of the more complex medication. No differences were found regarding number of medications nor were interaction effects found between the number of medications and information type. The results show that a medication overview can be a good addition (as it contains additional information) to support patients in their medication use compared to usual-care PDLs.

Problems understanding medical information seem to be more common in certain patient groups, such as the elderly, people with limited health literacy, and people with language barriers (van Dijk et al., 2016). In this study, not all these factors were investigated. We had a selective population with older medication users with adequate health literacy skills, making it not comparable to the literature that up to 50% of the adult population incorrectly understands the dosage information on PDLs (Davis et al., 2006a; Davis et al., 2006b; Wolf et al., 2006; Wolf et al., 2007; Bailey et al., 2009; Wolf et al., 2010; Wolf et al., 2011; Bailey et al., 2012; Bailey et al., 2014).

The medication overview had beneficial effects on understanding for which condition or disease the medication should be used. This turned out to be the case regardless of whether it was a medication with simple or more complex instructions for use, and regardless of the number of other medications someone is taking according to the hypothetical scenario. It is thereby important to mention that on the PDL, there is only limited space, making it difficult to provide additional information (Maghroudi et al., 2020).

Including specifically the medicine use information (intake, dosing moment) on the PDL is important for patient safety. An additional overview, such as the MijnGiB, is a good way to provide more information that does not fit on the prescription medication label.

The effects of the medication overview on understanding how to take the medication depended on whether it was a medication with simpler or more complex instructions for use. For the medication with simpler instructions for use (omeprazol), the addition of the medication overview had no effect for understanding how the medication should be taken. For the medication with more complex instructions for use (L/C), the addition of the medication overview had less of an effect than the PDL-only, as the group respondents with the usual-care PDL-only had higher percentages of correct answers. It might be plausible that the participant has an information preference and chooses one information type over the other. Hence, in the situation that the participant received both types of information, it could have been possible they choose the PDL over the medication overview.

There are different reasons that could explain why respondents with the usual-care PDL-only had a higher proportion of correct answers. For example, there is less information on the usual-care PDL, and thus less information to understand, whereby the core information is highlighted more easily. Respondents may also be used to using the usual-care PDLs as the majority of the respondents use medications in their own day-to-day lives. Thus, the usual-care PDLs may have been easier to use during the experiment than a medication overview

like MijnGiB as it is new. This latter may be specifically applicable to the older respondents, who were overrepresented in this study due to our sample stratification. Research conducted on how elderly think about change indicates that they often want things to stay the way they are (Molenaar, 2022). Therefore, as long as an older person can still get away with their way of doing things, like the use of the usual-care PDLs, they will probably opt for this rather than a new development like a personalized medication overview.

Moreover, we hypothesized that patients better understand the medication instructions when they have a personalized medication overview rather than PDLs-only, and that this understanding increases with the number of medications. However, there were no significant differences found regarding number of medications, nor were interaction effects found between the number of medications and instruction type. A possible explanation might be linked to the setup of the experiment as all respondents were asked how well they understand the instructions for use (at what moment and how often) of one specific medication at a time and not all three, five or eight. The results show this is slightly easier to do with the PDL-only of this specific medication than when the personalized medication overview is added. This may be the case because the personalized medication overview provides information about the use of several medications at the same time, which may suggest that use of specifically one of these medications (omeprazol or L/C) becomes more omitted. When measuring how well people understand the use of one medication at a time, the medication overview may be less beneficial as opposed to only the PDL with one medication.

Strengths and limitations

A strength of this study is that we used a controlled experimental design, in which the respondents were randomly assigned across the six conditions, and the groups were equally spread with regard to the background characteristics (i.e. age, education level, *etc.*) of the respondents. Another strength is the use of the Dutch Health Care Consumer Panel, which includes people who cannot register themselves, but have to be invited to join the panel. In panels that are formed by people signing up on their own to join, there is higher risk of selection bias. Our panel includes people who do accept an invitation, but would not register themselves.

There were also limitations to this study. A limitation of this study can be the hypothetical situation of this experiment. Respondents were asked to imagine a situation in which they are prescribed several medications. This might have been difficult for some respondents, especially since most of them already use medication in their own daily life, and answered the questions based on their own experiences. They might have responded differently if it was their own medication they were asked about. Nevertheless, as shown in the meta-analysis by Van Vliet et al. (Van Vliet et al., 2012), results of actual patients would not have been stronger than using analog patients/fictive examples, as in this study.

Another limitation of this study is that there was little or no variation in the health literacy (on the health literacy scale used for this study) of the respondents in this sample. This sample was selected for limited health literacy, yet the vast majority self-identified adequate health literacy. The small group of people with inadequate health literacy may be related to ease or difficulty that people with a lower health literacy may experience when completing questionnaires.

In addition, a limitation is that respondents were not given an instruction on how to use the medication overview. In the pharmacy one does receive an explanation on how to use the medication overview, which might make it easier to use the overview, and prevent potential misunderstandings of medicine use information. Furthermore, a limitation is that it was not known whether people in the experiment sample took the specified medications as we present in the experiment.

Lastly, a limitation of this study could be reflected on the setup of the experiment and the outcomes on how well the participants understood the medicine use information for three, five, or eight medicines. All respondents were asked how well they understood the instructions for use (when and how often) of one specific medication at a time. Measuring how well people understand the use of one medication at a time, MijnGiB may be less beneficial as opposed to the prescription medication label only with one medication. However, more positive effects from MijnGiB may be expected from how well people understand the use of all medications together when comparing MijnGiB and the prescription medication label only.

Implications for research

The results of this study do not fully assess how the medication overview may help people with low literacy given the small group of respondents (4%) with low literacy. Future research can focus on better identifying patient groups for whom the personalized medication offers the most support. Also, the medication overview appears to be less beneficial when measuring how well people understand the use of one of the medications. However, more positive effects can be expected from how well people understand the use of all medications together. The latter has not been measured, but is a suggestion for further research. For further research it is also important to test in real life conditions. For example, with patients using their own personalized medication overview, how do they understand the usage information and what are their impressions for their own medication use. Moreover, this study focused on oral medicines (tablets), and could be extended to dosage forms with more complex instructions (e.g. variable dosing) or mastery of

technique for self-administration of the medicine in future studies.

Conclusion

Both the respondents who were shown the personalized medication overview and the respondents who only saw the PDLs showed a high level of comprehensibility of the use instructions for the hypothetically prescribed medications. However, the medication overview increased respondents' comprehension of the instructions regarding the usage advice and for which condition or disease one should use the medication, which is extra information on this overview. The overview can be a good addition to the prescription drug labels to support patients in their medication use. Future research should focus on identifying patient groups who might benefit more, by testing the use of a medication overview among different patients.

Data availability statement

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

Author contributions

LS, MV, and LV contributed to the conceptualization and design of this project. Data analysis were led by LS under the supervision of SZ and MV. Data interpretation and critical review of the results were discussed with all the authors. LS wrote the first draft of the paper under the supervision of MV; All authors contributed to reviewing and editing subsequent drafts and reviewed the final manuscript.

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Conflict of interest

LD received funding from Biogen, the Dutch Ministry of Health, Zilveren Kruis, ZonMw, and EIT Health for studies not related to this study. MV received funding from AstraZeneca, Biogen, ZonMw, EIT Health, and the Royal Dutch Pharmacists Association for research not related to this study. LS received funding from EIT Health and the Royal Dutch Pharmacists Association for research not related to this study.

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.

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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.2022.1004830/full#supplementary-material

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Artificial intelligence-based internet hospital pharmacy services in China: Perspective based on a case study

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Background: Recently, internet hospitals have been emerging in China, saving patients time and money during the COVID-19 pandemic. In addition, pharmacy services that link doctors and patients are becoming essential in improving patient satisfaction. However, the existing internet hospital pharmacy service mode relies primarily on manual operations, making it cumbersome, inefficient, and high-risk.

Objective: To establish an internet hospital pharmacy service mode based on artificial intelligence (AI) and provide new insights into pharmacy services in internet hospitals during the COVID-19 pandemic.

Methods: An AI-based internet hospital pharmacy service mode was established. Initially, prescription rules were formulated and embedded into the internet hospital system to review the prescriptions using AI. Then, the "medicine pick-up code," which is a Quick Response (QR) code that represents a specific offline self-pick-up order, was created. Patients or volunteers could pick up medications at an offline hospital or drugstore by scanning the QR code through the window and wait for the dispensing machine or pharmacist to dispense the drugs. Moreover, the medication consultation function was also operational.

Results: The established internet pharmacy service mode had four major functional segments: online drug catalog search, prescription preview by AI, drug dispensing and distribution, and AI-based medication consultation response. The qualified rate of AI preview was 83.65%. Among the 16.35% inappropriate prescriptions, 49% were accepted and modified by physicians proactively and 51.00% were passed after pharmacists intervened. The "offline self-pick-up" mode was preferred by 86% of the patients for collecting their medication in the internet hospital, which made the QR code to be fully applied. A total of 426 medication consultants were served, and 48.83% of them consulted outside working hours. The most frequently asked questions during consultations were about the internet hospital dispensing process, followed by disease diagnosis, and patient education. Therefore, an AI-based

medication consultation was proposed to respond immediately when pharmacists were unavailable.

Conclusion: The established AI-based internet hospital pharmacy service mode could provide references for pharmacy departments during the COVID-19 pandemic. The significance of this study lies in ensuring safe/rational use of medicines and raising pharmacists' working efficiency.

KEYWORDS

internet hospital, artificial intelligence, prescription preview, medication pick-up code, online medication consultation

Introduction

Telemedicine services are a growing technology that promotes quality in healthcare worldwide (Qiu et al., 2018; Bokolo, 2021). With the increasing use of internet and decreasing cost of telemedicine services, the internet hospital has greatly impacted many developing countries where healthcare services are concentrated in large cities (Tu et al., 2015). Ever since "Opinion on promoting the development of internet + medical and health care" was issued by the state council of the People's Republic of China (PRC) (The State Council of the People's Republic of China, 2018), internet plus healthcare centers have been emerging. These centers significantly saved patients' time and economic costs and played a crucial role in the prevention and control of COVID-19 epidemic (Li et al., 2020; Gong et al., 2020; Sun et al., 2020). As patients' medical behavior patterns are shifting from on-site to online, the demand for internet hospitals has increased (Ge et al., 2022). According to incomplete statistics, over 1,600 hospitals in China obtained the business license of internet hospital by June 2021 (Zhang, 2022). There are three types of internet hospitals in China—those independently operated by entity medical institutions (e.g., public hospitals and private hospitals), government-sponsored internet hospitals, and those sponsored by internet medical enterprises (e.g., Hao Daifu, WeMed, and Ping An Good Doctor, *etc.*) (Han et al., 2020; Jiang et al., 2021; Xu et al., 2021). A cross-sectional survey showed that Chinese patients were more likely to use public hospital-sponsored internet hospitals (Liu and Shi, 2021). Therefore, China's internet hospitals gradually formed a model that entity hospitals led along with technology companies providing the main technical support under the general trend of government management and patients' choice. Moreover, pharmacy services acted as a link between doctors and patients, which is essential in improving patient satisfaction, assuring safe and rational drug use, *etc.*

Eye & ENT Hospital of Fudan University is a grade 3A specialized hospital in Shanghai that represents the advanced medical level in China. Its otolaryngology has been ranked number one in the specialty rankings for 11 consecutive years and ophthalmology has been firmly in the top three. The pharmacy service of Eye & ENT Hospital of Fudan University has been at the forefront of the internet + services. However, the existing pharmacy service mode of internet hospitals is primarily manual, making it cumbersome, inefficient, and high-risk. In March 2022, Shanghai faced the most severe test after the normalization of prevention and control of the COVID-19 epidemic. Therefore, there is an urgent need to build an AI-based internet hospital pharmacy service mode during the COVID-19 pandemic.

To strictly implement the prevention and control of the COVID-19 epidemic and further meet patients' needs, we leveraged the internet hospital services, including online follow-up, dispensing, "offline pick-up" and "logistics delivery," and online patient medication consultation. Additionally, to ensure patients' safe, fast, convenient, and efficient access to pharmacy services, we combined pharmacy services in conjunction with artificial intelligence (AI), which simultaneously provided new insights for internet hospitals during the COVID-19 pandemic.

Meterials and methods

Design of the AI-based internet hospital pharmacy services

This study was carried out at Eye & ENT Hospital of Fudan University. In April 2020, its internet hospital was approved for a business license and officially launched on 23 June 2020. Initially, it was limited to self-pay patients and gradually expanded its range of users by realizing Shanghai medical insurance settlement. Thus far, there have been over 200,000 internet prescriptions, providing pharmacy services to over 100,000 people nationwide in China.

Before launching internet hospital, we learned from the experiences of the top ten hospitals in the 2020 Fudan edition of China's best comprehensive hospital ranking (Hospital Management and Fudan Institute., 2020; Li et al., 2022). Information was obtained through the official websites, Alipay Life, WeChat and published literature of these hospitals (Li et al., 2020; Li et al., 2020; Hu et al., 2020; Li et al., 2021; Zhi et al., 2021; Zhang, 2022). Thus, the framework of the AI-based internet

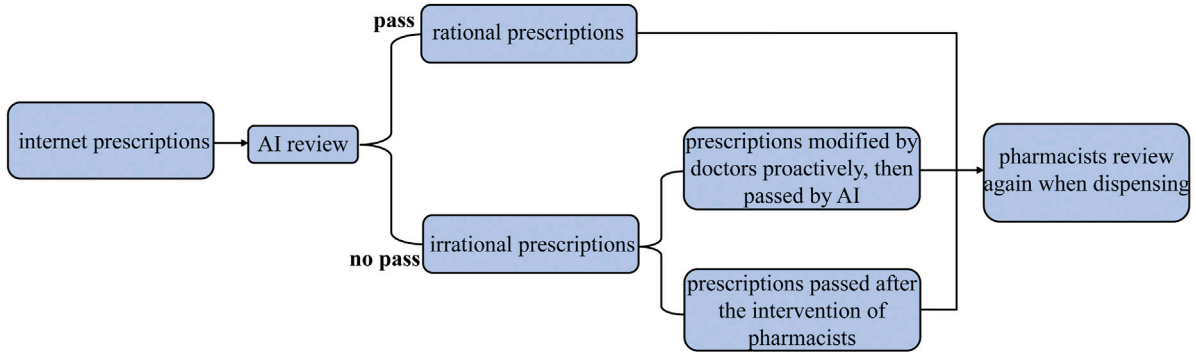

FIGURE 1
Prescriptions preview process.

hospital pharmacy services was concentrated on improving prescription review, convenient drug collection and medication consultation. The data interface was accomplished by our hospital's information technology department and the corresponding software company.

Prescription preview with AI

The preparation of prescription preview can be traced back to September 2020. First, prescription preview rules were formulated based on drug labels, clinical protocols and guidelines, clinical pathways, national formulary, national prescription laws and regulations *etc.* Then, AI preview was realized using a rational medication monitoring system developed by Beijing Puhua health technology Co., Ltd. The prescription preview process is shown in Figure 1. Three steps were designed to ensure the accuracy of prescriptions, including AI preview, pharmacists preview and double check when dispensing. Moreover, unreasonable prescriptions would be rejected and recorded. Two different levels of problem prescriptions were highlighted, namely, alerts, and interceptions. Absence of a reasonable indication and overdose were defined to be warned, as well as drug-drug interactions and repeated medication. However, those prescriptions cannot be sent when there were any contraindications. After that, the rational medication monitoring system was embedded into the internet hospital system to test the effectiveness of AI-preview. Prescriptions approved by AI were required to be 100% qualified before going live with it.

Picking up medicine and medicine pick-up code

To ensure the safety and effectiveness of patient medications, refrigerated drugs, fragile drugs, drugs with high risks, and drugs requiring special management and storage requirement at 2–8°C, must be picked up offline based on the "Guidelines for the Construction of Internet Hospitals in Shanghai Municipal Hospitals." Therefore, the list of drugs that must be picked up offline was made. Other deliverable drugs were entrusted to a third-party pharmaceutical company for delivery. Based on the drug availability in the third-party pharmaceutical company, the drug distribution has two modes: "Large warehouse" and "storage." The "large warehouse" mode refers to the direct delivery from the warehouse of the pharmaceutical company when the drug is available in the warehouse; the "storage" mode refers to the delivery mode when the drug is unavailable in the warehouse of the pharmaceutical company, and they must pick up drugs from the hospital first and store these drugs in their drugstore. When drugs are dispatched, the logistics information is updated in real-time and patients can check the logistics information on the internet hospital system. Also, the way patients chose to pick up their medications was recorded in the internet hospital. Then the data could be exported in xlsx format and analyzed. Additionally, the idea of quick response (QR) code that represented a specific offline self-pick-up order was proposed on the occasion of zone lockdown in April 2022 and carried out by the information technology department of EENT hospital. The prescription details that directly associated with the offline self-pick-up order number were then written into the QR code and could be read through the dispensing system.

Medication consultation service

The medication consultation service was supported by Shanghai Liankong network technology Co., Ltd. A volunteer team of licensed pharmacists with extensive clinical experience provided free medication consultation services online. Prior to beginning this service, all pharmacists received standardized

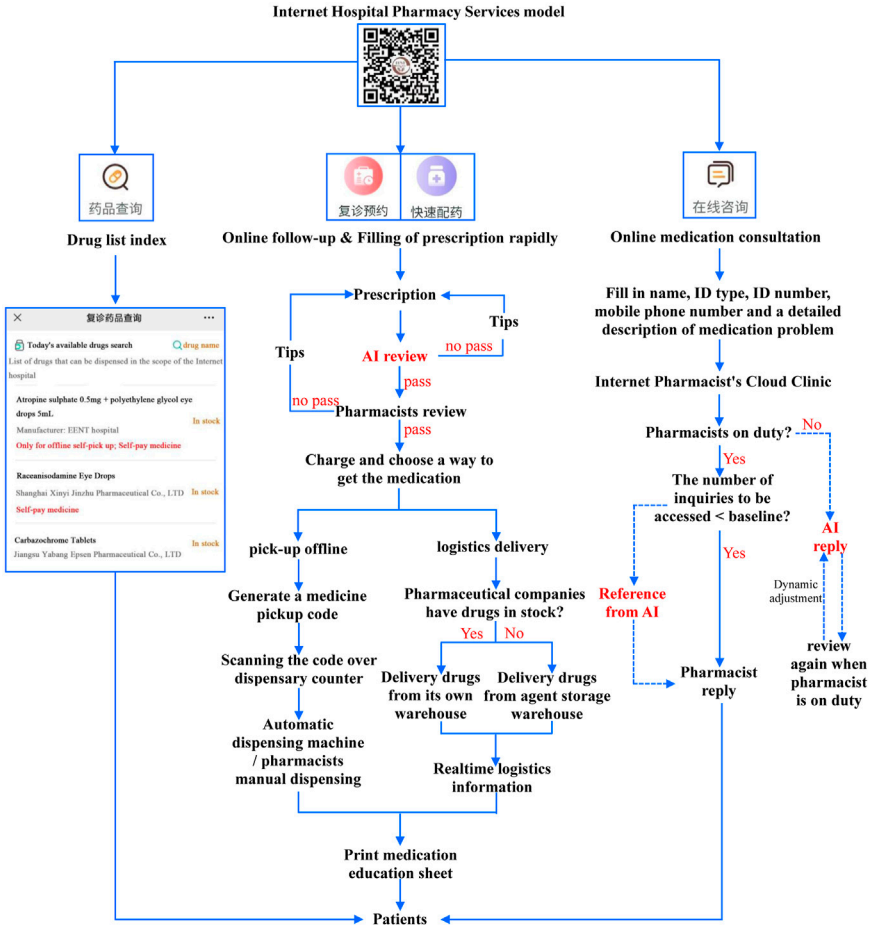

FIGURE 2
Established AI+ internet hospital pharmacy services mode.

training to handle patient questions. If a patient asked questions regarding a disease diagnosis, the pharmacist would guide the patient to consult a clinician. For complex questions, pharmacists would discuss with other pharmacists to ensure that the answers were correct. The basic information of medication consultants and the questions they asked can be recorded, which can be exported to xlsx format. Further analyses were performed to understand the effectiveness of medication counseling.

Results

The established AI+ internet hospital pharmacy services mode

The development of pharmacy service in domestic Internet hospitals was shown in Supplementary Table S1. Only the General Hospital of the Chinese People's Liberation Army (PLA) was remaining to open its internet hospital services. In the remaining nine hospitals, the preview of prescriptions was carried out manually. All nine hospitals offered patients a variety of choices when it comes to picking up their medication. For online medication consultation, three hospitals provided free services, and six hospitals charged fees according to the pharmacist's title or the type of consultation. Accordingly, as demonstrated in Figure 2, there were four main pharmacy services in our proposed AI-based internet hospital, including drug list indexing, online follow-up, rapid filling of prescriptions, and online medication consultation. People could search the drug lists online without registering and consulting doctors for a specific drug. Additionally, the generic drug names, manufacturers, and information on the offline pickup drugs were listed in detail.

Patients with medication records in our hospital or other medical institutions in Shanghai in the past 6 months could follow up online, and doctors could then prescribe for them. To ensure safe and rational drug use, the formulated prescription rules were embedded into the internet hospital system to review

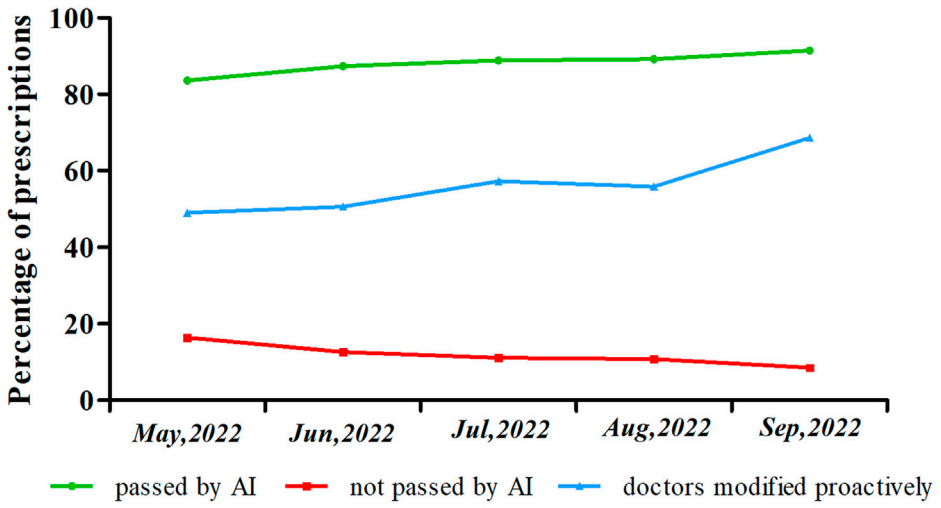

FIGURE 3
Results of prescriptions pre-reviewed by AI and modified by doctors proactively. (Green line: represents the percentage of prescriptions passed by AI; Blue line: represents the proportion of irrational prescriptions modified by doctors proactively; Red line: represents the percentage of prescriptions intercepted by AI).

the prescriptions by AI. There were two steps in the prescription preview process, namely AI automatic and pharmacist manual reviews. Meaning, the prescription was prechecked by AI first, and then AI would tip doctors on whether the prescription was rational. If physicians did not modify their prescriptions accordingly, pharmacists would review the prescription again until the prescriptions were qualified; only the prescriptions that are passed could be charged. After payment, patients could choose a way to pick up their drugs: "Offline self-pick up" or "logistics delivery." By interconnecting internet hospital patients' data with social pharmacies, we realized the flow of prescriptions, allowing patients to pick up their medications at a social pharmacy, in addition to picking them up at a hospital pharmacy. Finally, the offline pick-up orders would generate a QR code; the patients or volunteers could pick up medications at the offline hospital or social pharmacies by scanning the QR code through the window, and the machine or pharmacists would dispense the drugs. People who choose "logistics delivery" could have access to real-time drug logistic information.

In the online medication consultation, people could scan the medication consultation two-dimensional code to enter a quick consultation page or select a dedicated pharmacist. Then, they presented a brief description of their medication doubts. When the consultation information was submitted, the message would be sent to the cloud consultation room on the internet. If the pharmacist was online and the number of inquiries to be accessed was below a certain threshold (e.g., 10), the pharmacist would answer the question directly. If there were many inquiries to be accessed, AI would provide references for pharmacists. If pharmacists were unavailable, the AI would reply instead.

TABLE 1 The classification of inappropriate prescriptions not passed by preview system.

Classification	Proportion (%)
Absence of a reasonable indication	59.99
Long-term prescriptions	26.73
Repeated medication	4.51
Incorrect routes of administration	2.75
Overdose	2.42
Inappropriate dosing frequency	2.24
Presence of contraindication	1.36
Total	100

Qualified rate of prescription preview by AI

Data of prescriptions pre-review from May to September 2022 was shown in Figure 3. The percentage of internet prescriptions passed by AI was always above 80%, which increased month by month. Also, leaving less than 20% of prescriptions to be handled by pharmacists. The proportion of irrational prescriptions modified proactively by doctors was also improving. Considering May 2022 as an example, the percentage of internet prescriptions passed by AI was 83.65% (Supplementary Figure S1). Among the 83.65% prescriptions passed by AI, 100% were double checked by pharmacists when dispensing. More importantly, there was zero prescription that has been rejected when dispensing in May 2022. Among the 16.35% not passed prescriptions, 49% were modified by doctors proactively and 51% were passed after

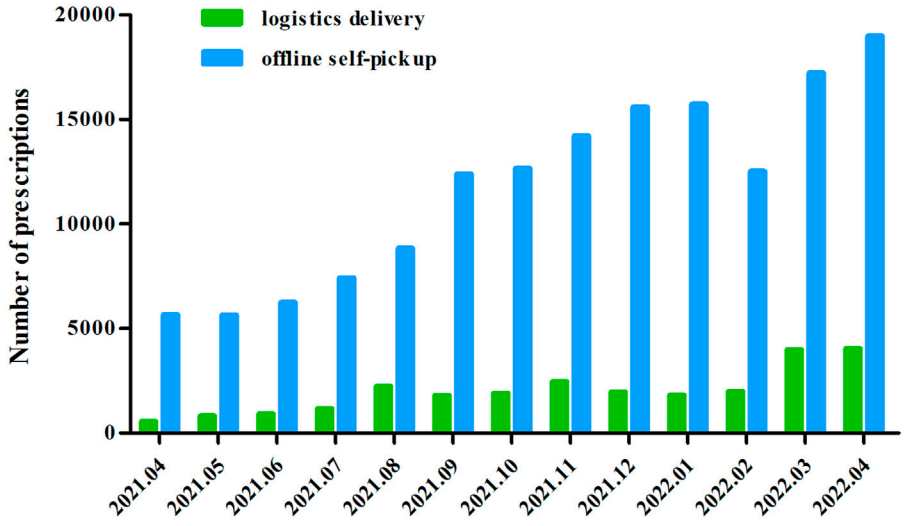

FIGURE 4
Comparison of the number of prescriptions between "logistics delivery" and "offline self-pick up."

the intervention of pharmacists, as shown in. For instance, the prescription of tropicamide phenylephrine eye drops was intercepted because this patient was suffering from glaucoma. To sum up, the classification of inappropriate prescriptions not passed by preview system was shown in Table 1. The most common inappropriate prescriptions intercepted by this preview system were related to the absence of a reasonable indication, long-term prescriptions (more than 4 weeks), repeated medication, incorrect routes of administration and overdose.

Comparison on the delivery modes patients chose to pick up their medication at internet hospitals

Prescriptions from the internet hospital had been increasing month by month since it was put into use, especially during the most severe period of the COVID-19 pandemic in Shanghai (March and April 2022). Figure 4 shows that from April 2021 to April 2022, 86% of the internet hospital prescriptions were distributed in the "offline self-pick up" mode on average. Therefore, the "offline self-pick up" was the predominant mode in the internet hospital.

Internet hospital medication consultation

We served 426 visits of medication consultants from April 24 to 17 June 2022, during the most severe period of the COVID-19 pandemic in Shanghai. Table 2 shows the basic information about medication consultants. The mean age of patients was 29 years with the youngest age being 2 and the oldest being 89. Medication counseling for patients under 18 years old was primarily carried out by their parents. Moreover, 48% of the consultations were submitted outside working hours. Among the 426 visits, the most frequent questions were about the internet hospital dispensing process, followed by the diagnosis of disease and patient education. Figure 5 displays the detailed classification and ranking involved in the consultation content.

Vision of AI-based medication consultation

To meet the demands of medication consultation around the clock, an AI-based medication consultation mode was raised. The proposed model was an AI module that was based on the internet hospital and consisted of three parts: patient client, data processing center, and pharmacist client, as shown in Figure 6. The data processing center comprised a "question and answer bank" and logical operations that match patient questions with AI answers. The AI module library, which contained all the information in drug labels, could be dynamically adjusted and customized by users to reply more accurately and efficiently. For example, when a patient submitted an inquiry "what are the adverse reactions if the 0.01% atropine eye drops are withdrawn," the data would be transmitted to a processing center. Then,

TABLE 2 Basic information of the medication consultants.

Classification	Number of consultants	No (%)
Gender		
Male	200	46.95
Female	226	53.05
Age		
<18	176	41.31
18–40	135	31.69
41–65	87	20.42
>65	28	6.57
Consultation time		
Working hours	218	51.17
Non-working hours	208	48.83

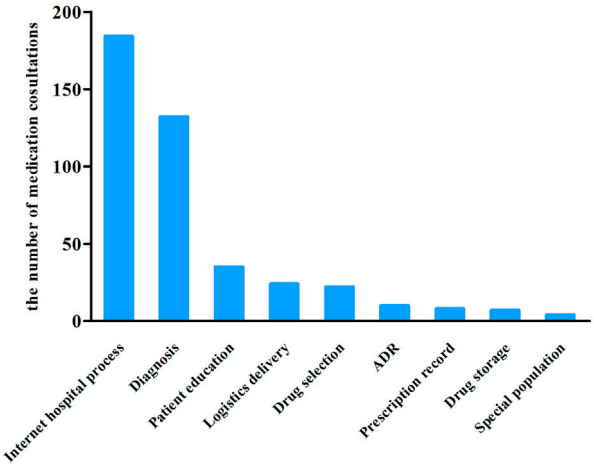

FIGURE 5
The number of medication consultation categories.

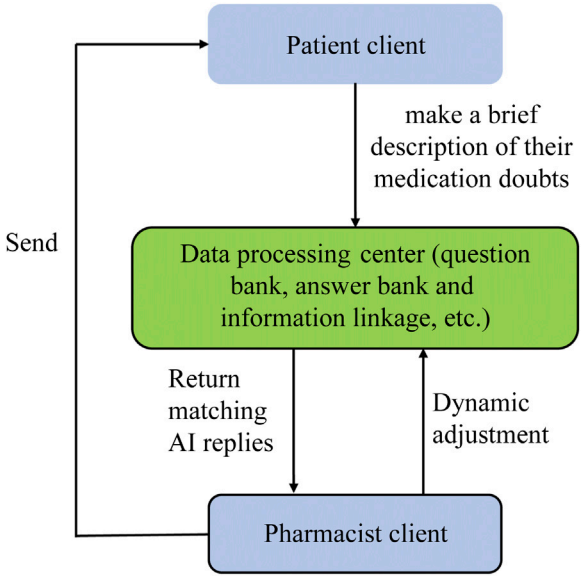

FIGURE 6
Technology roadmap of medication consultation module.

the question would be divided into three connected entries: "0.01% Atropine drops," "withdraw" and "Adverse reactions." When these three entries existed side by side, AI will return "Myopia rebound may occur after withdrawal of 0.01% atropine eye drops, and it is recommended to gradually reduce the dosage when discontinuing the drug to avoid myopia rebound." If "0.01% atropine eye drops" and "adverse reactions" just appeared together, the AI response would be "Some children may experience adverse reactions, such as photophobia and blurred vision, while taking 0.01% atropine eye drops."

Discussion

In this article, we reported on our initiatives in internet hospital pharmacy service combined with AI. Cloud-based medical research is growing rapidly worldwide, and its technologies are simultaneously differentiating and becoming more intelligent (Gu et al., 2020). The established AI-based internet hospital pharmacy services have four major functional segments: online drug list retrieval, prescription preview, drug dispensing and distribution, and online medication consultation, which are essential in ensuring safe and rational use of drugs as well as saving patients' money and time.

The online drug list search function makes it more convenient for patients. Currently, most internet hospitals lack this function, which can be observed in Supplementary Table S1. Moreover, prescription preview was mainly handled manually by pharmacists in many internet hospitals. After "prescription checking specifications for medical institutions" was announced in July 2018 by the national health commission of the PRC (National health commission of the PRC, 2018), all prescriptions must be reviewed and approved before charging and dispensing. Additionally, we introduced a rational medication monitoring system and applied it to control rational drug use, which partly reduced the workload of pharmacists and increased the prescription preview efficiency. This rational medication monitoring system was widely used in prescription checks and known as a clinical decision support system (Corny et al., 2020; Hashemi et al., 2022). However, there is lack of a uniform criteria for the validation evaluation of such AI systems. In this study, prescriptions passed by AI were double checked by pharmacists and required to be 100% qualified before the

launch of the system. As a result, there were no rejected prescriptions when dispensing. But for the pass rate of AI, there was no compulsory requirement. Actually, the pass rate of AI-preview was above 80%. From May to September 2022, the percentage of internet prescriptions passed by AI increased gradually, as well as the proportion of irrational prescriptions modified proactively by doctors. These results suggested that the physicians' prescribing behavior was altered after the introduction of AI based prescription preview system.

We developed a QR code to use in offline medicine pick-up that has significantly reduced the risk of cross-infection and protect patients' privacy. Especially, in March 2022, when Shanghai implemented the zone lockdown to control the COVID-19 epidemic, it restricted the logistics and delivery, and many patients could only entrust volunteers to pick up their medications offline from the nearest hospital (Hall et al., 2022). In traditional offline self-pickup mode, patients must present their medical insurance card, self-payment card, or medical insurance electronic certificate to pharmacists to pick up their medications. Although we have two alternatives for collecting medication, the data show that 86% of patients choose the offline pickup mode. However, for general hospitals in China, 61% of patients preferred getting their medicine through a delivery service (Ding et al., 2020). Compared with general hospitals in China, drug delivery service was also more popular during lockdown in foreign countries (Mash et al., 2021; Hammour et al., 2022). This is because that we are a specialized hospital and the characteristic medicines for disease treatment are hospital preparations. Furthermore, most hospital preparations in our hospital must be stored at 2–8°C and picked up offline.

Apart from drug dispensing, medication consultation service is another important component of internet and pharmacy service. We found that 48% of the consultations were submitted outside working hours. Presently, the traditional online medication consultation is responded to by pharmacists who are usually on duty from 8 a.m. to 5 p.m. and it is difficult for them to stay online always (Li et al., 2021). It is also difficult for pharmacists to remember all the information about indications, dosage, adverse reactions, and drug-drug interactions; it is also time-consuming to search for this information when responding. Accordingly, a combination of AI and manual mode of medication consultation will make it possible to give an immediate reply whenever necessary.

In general, the mode that combined AI with internet hospital pharmacy services could be a megatrend in developing internet hospitals and interconnecting these internet hospitals together. For example, during the COVID-19 epidemic prevention and control, to better meet the demand of residents seeking medical and pharmacy services, the "health cloud" platform (An, 2022) launched medical and pharmacy services online in April 2022 with joint efforts of the Shanghai municipal commission of health and family planning, the medical insurance platform, and a majority of hospitals in Shanghai that have launched internet hospitals. Similarly, AI enabled pharmacists to access the medical data across different health care providers (Roosan et al., 2022). Moreover, it provides people the flexibility to choose a certain doctor and pharmacist in the internet hospital to consult. However, the government guidelines are still needed for the following: 1) to supervise the whole process of internet hospital; 2) to archive the service information and realize the whole process traceability and ensure the security of relevant information; a secure and private framework must be adopted to record and administer extremely sensitive data (Mittal et al., 2022). 3) to establish a uniform charging standard for internet pharmacy service; presently, most pharmacy services are free of charge, and only a few hospitals charge fees according to the pharmacist's title or the type of consultation.

Limitations and future work

There are still some deficiencies of this AI system to be improved. For example, the operation interfaces of the patient client are all in Chinese, which is not friendly to foreigners. For the elder people, they often need the support from their family members to access pharmacy services in internet hospitals. What's more, this AI system needs to be maintained regularly to avoid being unable to handle it when it goes beyond the settings. Finally, a new AI-based pharmacy service function such as "medication housekeeper" will be developed in the near future, including medication reminders (WeChat push message, short messaging service, AI voice call reminders, *etc.*), medication record (check-in and clock-in, medication adherence record), and medication tracking.

Conclusion

We developed an AI-based pharmacy service mode of internet hospital. This mode realized drug list indexing, AI prescriptions reviewing, multiple medicine delivery methods, medication consultation, and patient education. This study suggests that the AI-based internet hospital pharmacy service ensures safe and rational drug use, saves patients' time and

economic costs, and is crucial in COVID-19 epidemic prevention and control.

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.

Author contributions

FB, HS, and TH contributed to the conception and design of the study. LL and FT contributed to formulating the rules of prescription preview. XZ and JY contributed to data collection and statistical analysis. ZY developed and tested the quick response code. FB wrote the first draft of the manuscript. HS and TH revised the manuscript. All authors contributed to interpretation of the results and final approval of the manuscript.

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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.2022.1027808/full#supplementary-material

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Medication non-adherence and associated factors among older adult stroke survivors in China

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Aim: Medication non-adherence has remained a common and costly global health issue of growing importance among older adults. This study aims to determine the prevalence and associated factors related to medication non-adherence among older adult stroke survivors in China.

Methods and results: In this cross-sectional study, a total of 402 older adult stroke survivors were recruited from three tertiary hospitals in China. The results of the survey showed that 61.4% exhibited medication non-adherence. The chances of medication non-adherence among older adult stroke survivors who had primary school or less educational levels were higher than those who had senior secondary and junior college educational levels [OR (95% CI) = 0.440(0.249, 0.778)] as well as those who had a bachelor's degree or above educational levels [OR (95%CI) = 0.367(0.202, 0.667)]. Moreover, the probability of medication non-adherence with 4–5 and ≥6 types of total prescription medications per day increased by 1.993 times [OR (95% CI) = 1.993(1.190, 3.339))] and 2.233 times [OR (95%CI) = 2.233(1.159, 4.300)], respectively, as compared to when there were ≤3 types. Furthermore, medication non-adherence decreased with the increase in health literacy scores (β = −0.641 (95% CI; (0.913, 0.965)) and BMQ specific-necessity scores (β = −0.131 (95% CI; 0.806, 0.995)). On the other hand, when the BMQ specific-concerns score increased by one unit, medication non-adherence increased by 11.1% [OR (95% CI) = 1.111(1.044, 1.182)].

Conclusion: The present study found that patient medication adherence among older adult stroke survivors in China is problematic and associated with educational levels, total prescribed drugs per day, beliefs about medication, and health literacy scores. This indicates that measures should be taken to enhance medication adherence among such higher-risk populations.

KEYWORDS

medication, non-adherence, older adults, stroke survivors, associated factors

Introduction

Globally, stroke remains the second leading cause of death and the third leading cause of disability in adults (Zhang et al., 2021; Feigin et al., 2022). In 2019, stroke was responsible for 143 million disability-adjusted life-years and 6·55 millions of deaths (Feigin et al., 2022). In this context, many published studies have concluded that multiple modifiable or non-modifiable factors may increase the risk of stroke occurrences. Here, it is worth mentioning that approximately three-quarters of all strokes occur in persons older than 65 years (Yousufuddin and Young, 2019). Additionally, Gorelick (2019) suggested that to relieve the future global burden of strokes, prevention among older adults would be an important objective.

Stroke survivors are at an elevated risk of having recurrences (Del et al., 2019), which make up 25–30% of all strokes (Hankey, 2014). As recurrent strokes are associated with high mortality and more disabling (Wu et al., 2019), prescribed medications are recommended for secondary prevention of stroke by guidelines (Coutts et al., 2015; Ahmed et al., 2019). Moreover, several sources of evidence indicate that secondary prevention medications tend to reduce the risk of stroke recurrence (Bushnell et al., 2014; Flach et al., 2020; Yeo et al., 2020). For example, it has been conclusively shown that higher adherence to antithrombotic or statin treatments is associated with a decreased risk of stroke recurrence and mortality (Yeo et al., 2020; Rodriguez-Bernal et al., 2021). In the same vein, Toyoda et al. (2019) reported that the combination of cilostazol with aspirin or clopidogrel resulted in a reduced recurrence of ischemic strokes. In addition, a review conducted by Katsanos and Hart (2020) indicated that an important protection against recurrent strokes is provided by the current triad of pharmacologic mainstays for secondary stroke prevention: blood-pressure lowering drugs, statin drugs, and antiplatelet agents. Meanwhile, there is consensus among scientists that non-medication adherence is a potential modifiable risk factor for poor BP control (Boima et al., 2015; Burnier and Egan, 2019), which is itself a well-established and modifiable risk factor for strokes.

However, patient adherence to medication is largely accounted for the effect of medical management to prevent recurrent strokes and other adverse outcomes (Zhang et al., 2021). Medication adherence is generally defined as the extent to which patients take their medication in line with the recommendations of their healthcare provider (Sabaté, 2003). A large and growing body of literature has reported that post-stroke medication adherence and persistence rates are low in stroke survivors (Kim et al., 2020; Ruksakulpiwat et al., 2020; Zhang et al., 2021). These results, therefore, suggest that improving medication adherence among survivors of stroke should be a growing concern to clinicians, healthcare systems, and other stakeholders (e.g., payers).

There is no doubt that a key step in the creation of an appropriate strategy to improve medication adherence is first understanding stroke survivors' non-medication adherence and its associated factors. Although several studies have shown the prevalence and factors associated with medication adherence among stroke survivors (Pan et al., 2017; Wei et al., 2017; Ruksakulpiwat et al., 2020), they are not specific to older adults. Furthermore, it is important to note that medication adherence is of a particular concern in older persons. A recent systematic review indicated factors negatively associated with adherence in this population: complex regimens with multiple prescribing physicians; problems with medication storage and formulation; and multimorbidity and cognitive impairment (Smaje et al., 2018). On the other hand, non-medication adherence rates among older adults in other chronic diseases (e.g., diabetes mellitus and hypertension patients) have been found to be alarmingly high (Saqlain et al., 2019; Xu et al., 2020). Meanwhile, older adult stroke survivors are likelier to have other chronic medical conditions (e.g., hypertension, history of cardiac-related comorbidities, diabetes, etc.) (Gruneir et al., 2016; Maresova et al., 2019), which means they have to take more medications to meet their broader health needs, thus further challenging their adherence to medications and an increase in the possibilities of worse health-related risks when non-adherence occurs. However, little is known about the prevalence of non-medication adherence and the factors associated with it among older adult stroke survivors, which this study aims to examine among older adult stroke survivors in Chenzou, Hunan, China.

Methods

Study design

We conducted a cross-sectional study from June 2022 to August 2022. The study was approved by the ethics committee of three tertiary hospitals (Affiliated Hospital of Xiangnan University, Chenzhou No. 1 People's Hospital, and Chenzhou Third People's Hospital) before the initiation of this study.

Participants

Participants were recruited using a systematic sampling method from three tertiary hospitals in Chenzhou, Hunan Province, China. They were eligible for inclusion based on the following criteria: if they were aged 60 years or older; had a history of strokes confirmed by neuroimaging at the time of the episode; taken at least one medication in the previous month such as (but not limited to) anti-platelets, statins, and anti-hypertensives to control risk factors for strokes; it had been more than a month since the last stroke episode; were able to read Chinese and communicate in Mandarin Chinese or the local

TABLE 1 Demographic characteristics of total participants (*N* = 402).

Variable	*n*	(%) OR mean ± SD
Age, y		72.16 ± 7.43
Gender		
Male	243	60.4
Female	159	39.6
Marital status		
Unmarried	1	0.2
Married	293	72.9
Divorced or widowed	108	26.9
Educational level (missing = 1)		
Primary school or less	157	39.2
Junior school	121	30.2
Senior secondary and junior college	97	24.2
Bachelor degree or above	26	6.5
Duration of disease, month		49.37 ± 51.99
Living conditions		
Living alone	73	18.2
Living with spouse	205	51.0
Living with children	48	11.9
Living with a nanny	1	0.2
Living with spouse and children	75	18.7
Ethnic groups (missing = 2)		
Han nationality	350	87.5
Others	50	12.5
Payment methods		
Self-pay	2	0.5
Urban resident basic medical insurance	81	20.1
Rural cooperative medical insurance	175	43.5
Urban employee basic medical insurance	141	35.1
Public medical care	3	0.7
Monthly household income per capita, ¥[a]		
≤1,000	90	22.4
1,001–3,000	184	45.8
3,001–4999	103	25.6
≥5000	25	6.2
Occupation status		
Employed	29	7.2
Unemployed	211	52.5
Retired	162	40.3
Residence (missing = 1)		
Rural areas	107	26.7
Town and county	119	29.7
City	175	43.5
Comorbidity		
No	68	16.9
Yes	334	83.1
Total prescription medications per day		3.96 ±1.68
Frequency of daily doses		
1	169	42.0
2	96	23.9
3	129	23.9
4	8	2.0
Ischemic stroke	341	84.8
Hemorrhagic stroke	61	15.2

[a]As of 30 August 2022, 1¥ = 0.145US$.

Chenzhou dialect. We excluded the following patients who: had psychiatric illness or deafness, aphasia, or other language barriers; had cognitive impairment (Mini-Mental State Examination score ≤17 [for illiterate] or ≤20 [individuals with 1–6 years of education] or ≤24 [individuals with 7 or more years of education]).

Sample size calculation

Sample size calculations were conducted to determine the prevalence of medication non-adherence using a single proportion formula and the associated factors using PS Power and Sample Size software version 3.1.6 for a dichotomous two-proportion formula. Based on the calculations, the highest sample size of 416 was chosen. This sample size was based on a precision of 0.05 and power of 80%; the proportion of permanent employment being 0.448 was based on the study by Kim et al. (2020). However, after considering the non-response level of 10%, the calculated sample size is 458.

Survey instrument

The study protocol included one set of demographic questions and three validated instruments—the General Medication Adherence Scale (GMAS-C), Beliefs about Medicines Questionnaire (BMQ), and Health Literacy Scale for Stroke Patients.

Demographic data were self-reported by the participants and included gender, age, marital status, educational level, duration of disease, living conditions, membership in ethnic groups, payment method for medical expenses, per-capita monthly household income, occupation status, number of prescribed medicines, frequency of daily doses, types of strokes, residence, and existence of comorbidities.

The GMAS-C is a self-report tool containing 11 items that measure medication adherence among patients with chronic diseases, including strokes. It consists of three dimensions: 1) patient behavior-related non-adherence (five items), 2) additional disease and pill burden (four items), and 3) cost-

TABLE 2 Medication adherence among patients.

GMAS score	Mean ± SD	High adherence no. (%)	Good adherence no. (%)	Partial adherence no. (%)	Low adherence no. (%)	Poor adherence no. (%)	Non-adherence no. (%)	Adherence no. (%)
Patient behaviour related non-adherence	15.00 ± 9.83	129(32.1)	82(20.4)	80(19.9)	55(13.7)	56(13.9)	–	–
Additional disease and pill burden	12.00 ± 8.19	109(27.1)	100(24.9)	115(28.6)	38(9.5)	40(10)	–	–
Cost-related non-adherence	6.00 ± 4.60	179(44.5)	40(10.0)	129(32.1)	37(9.2)	17(4.2)	–	–
Overall adherence	22.62 ± 7.77	91(22.6)	64(15.9)	149(37.1)	55(13.7)	43(10.7)	247(61.4)	155(38.6)

related non-adherence (two items). All items are answered on a four-point Likert scale: responses of "always," "mostly," "sometimes," and "never" are scored as 0, 1, 2, and 3, respectively. The total GMAS-C score is the summation of the scores for the 11 items and ranges from 0 to 33: high adherence (30–33), good adherence (27–29), partial adherence (17–26), low adherence (11–16), and poor adherence (0–10). Patients with a total score of 26 and below are considered medication non-adherent, while a score of 27 and above indicates adherence (Naqvi et al., 2019).

Moreover, Wang et al. (2021) undertook validity and reliability studies of the Chinese version of the GMAS-C in 2021 and found that the exploratory factor analysis extracted three factors with eigenvalues >1 and that 60% of the total variance was explained by a three-factor solution. Next, confirmatory factor analysis showed acceptable fit indices (χ^2/df = 1.58, IFI = 0.96, TLI = 0.94, CFI = 0.96, and RMSEA = 0.05). Thus, it was concluded that the scale was a valid and reliable instrument for the assessment of medication adherence.

The BMQ was developed to assess personal beliefs and worries about taking medications for diseases (Horne and Weinman, 1999a). It consists of two domains—the BMQ-Specific and BMQ General—that are independently validated and can be used in combination or separately. In this study, we used only the BMQ-Specific because Horne and Weinman (1999a) reported that it is a flexible instrument that can be adapted to assess beliefs about all medicines for a particular condition or individual components of a regimen. The Chinese version of the BMQ-Specific has been proved to be a good instrument with acceptable reliability and validity. The Cronbach's α coefficients of the necessary and concerns dimensions were 0.813 and 0.706, respectively, and the test–retest reliability coefficients were 0.743 and 0.786, respectively (Yang, et al., 2014). The BMQ-Specific has two subscales (specific-necessity and the specific-concerns) with five questions each, which aim to assess beliefs about the necessity of prescribed medication and concerns about them based on beliefs about the danger of dependence, long-term toxicity, and the disruptive effects of medication (Verhagen, 2018).

The Chinese version of the Health Literacy Scale for Stroke Patients has been used to assess the health literacy of patients who have had a stroke and proved to be a good instrument with acceptable reliability and validity (Jiru, et al., 2020). It has three subscales and a total of 20 items. The first subscale is basic knowledge of strokes, which consists of six items. A five-point Likert scale is used, and responses are assigned to a score of 5 for "strongly agree," 4 for "agree," 3 for "neutral," 2 for "disagree," and 1 for "strongly disagree." For two items (4,5), reverse scoring is applied. The second subscale with nine items evaluates the healthy lifestyles and behaviors of stroke survivors: it is responded to as follows: 1—"never"; 2—"rarely"; 3—"sometimes"; 4—"often"; and 5—"always." Reverse coding was carried out for item 2 because it is a negative statement. The third subscale is related to the basic skills of stroke survivors and consists of five items, for which a five-point Likert score method is used. The response options are "never," "rarely," "sometimes," "often," and "always," which corresponds to the scores of 1, 2, 3, 4, and 5 points, respectively. A higher score indicates better health literacy.

Data collection procedure

Data were collected using a questionnaire-guided interview method. Written informed consent was received prior to the respondents answering the questionnaire. This study was conducted in full accordance with the principles of the Declaration of Helsinki. The participants were informed that their participation was voluntary and that they had the right to withdraw from the study at any time without any influence, coercion, or persuasion. Questionnaires were distributed and completed by participants (it took approximately 20 min to complete the questionnaires) who

were in rehabilitation settings, at the departments of neurology, or at the out-patient clinics during the investigation period. A total of 458 stroke survivors who were admitted to hospitals were approached. Five trained health professionals who speak the local language and did not work at the study hospital were recruited to distribute and collect questionnaires. In order to familiarize data collectors the data collection tool, we conducted training prior to the study. Regarding illiterate participants or those with eye problems, the question items were read word by word exactly as they appeared on the questionnaires by the researchers. Responses were then recorded on the questionnaire. Upon completion, the questionnaires were collected immediately and checked for any missing information, after which follow-ups were undertaken with the participants if needed.

Statistical analysis

All statistical analyses were performed using the Statistical Program for the Social Sciences (SPSS version 26). The data were checked, explored, and cleaned. Descriptive statistics was used to calculate the frequency and percentage (categorical data) or the mean and standard deviations (continuous data). The prevalence of medication adherence was calculated using the aforementioned cutoff scores and reported as the percentage of cases in different populations. The 95% CIs were produced using exact binomial methods. The chi-squared test method was used for univariate analysis. To explore factors that are potentially associated with medication non-adherence, binary logistic regression analyses were performed, and odds ratios (ORs) and 95% CIs were presented. p-values less than 0.05 were considered statistically significant throughout the analysis.

Results

Characteristics of participants

A total of 458 older adult stroke survivors were approached, with 402 giving consent and being enrolled in the study (response rate of 87.8%). Most participants were male (243 [60.4%]), were married (293 [72.9%]), were of Han nationality (350 [87.5%]), and had comorbidities (334 [83.1%]). Of the 402 responding participants, 341 (84.8%) had ischemic strokes, while 61 (15.2%) had hemorrhagic strokes. Meanwhile, 43.5% resided in city areas, and 42.0% took medicine only one time a day. Almost half the participants (211 [52.5%]) were unemployed. Approximately one-third (39.2%) only had a primary school education or less. Those living with spouses represented 51.0% of the sample, and 43.5% used rural cooperative medical insurance. A total of 184 participants (45.8%) had a monthly per-capita income between 1,001 and 3,000 ¥. The mean age of participants was 72.16 ± 7.43 SD, the mean (SD) duration of stroke disease was 49.37 (51.99) months, and the mean total types of prescription medications per day was 3.96 (1.68). The characteristics of the study participants are shown in Table 1.

Participants' medication adherence

Of the 402 responding participants, 247 (61.4%) exhibited medication non-adherence. In total, 22.6% of the participants had high adherence, approximately 64 (15.9%) of the participants had good adherence, and 149 (37.1%) had partial adherence. Meanwhile, low adherence and poor adherence were 13.7% and 10.7%, respectively. The participants' medication adherence is detailed in Table 2.

Relationship of non-adherence with related factors

Table 3 shows the univariate analysis of the factors associated with medication non-adherence, which are as follows: educational level ($p < 0.001$), payment methods ($p < 0.001$), total prescription medications per day ($p = 0.002$), monthly income per capita ($p < 0.001$), occupation status ($p < 0.001$), residence ($p < 0.001$), BMQ specific-necessity score ($p < 0.001$), BMQ specific-concerns score ($p = 0.002$), and health literacy score ($p < 0.001$).

Risk factors for medication non-adherence

All variables with a p-value < 0.05 in the univariate analysis were included in the logistic regression analysis. Table 4 shows the results of the multivariable analyses. Results from logistic regression suggest that educational level and total prescription medications per day as well as the BMQ specific-necessity, BMQ specific-concerns, and health literacy scores were associated with medication non-adherence.

Compared to stroke survivors who had primary school or less educational levels, those with senior secondary and junior college educational levels [OR (95% CI) = 0.440(0.249, 0.778)] as well as those who had bachelor's degree or above [OR (95% CI) = 0.367(0.202, 0.667)] had significantly decreased risks of medication non-adherence. Those with 4–5 types of total prescription medications per day had 1.993 times the risk of medication non-adherence as compared to those with ≤3 types [OR (95% CI) = 1.993(1.190, 3.339)]. On the other hand, those with ≥6 types of total prescription medications per day were 2.233 times likelier to be

TABLE 3 Relationship of non-adherence with related factors.

Variable	Non-adherence	Adherence	Total, no. (%)	χ^2	*p*
Age				0.781	0.677
≤70	108 (60.7)	70 (39.3)	178 (44.3)		
71~79	99 (63.9)	56 (36.1)	155 (38.6)		
≥80	40 (58.0)	29 (42.0)	69 (17.2)		
Gender				0.004	0.949
Male	149 (61.3)	94 (38.7)	243 (60.4)		
Female	98 (61.6)	61 (38.4)	159 (39.6)		
Marital status				0.487	0.485
Married	177 (60.4)	116 (39.6)	293 (72.9)		
Unmarried, divorced, or widowed	70 (64.2)	39 (35.8)	109 (27.1)		
Educational level				29.926	<0.001
Primary school or less	121 (77.1)	36 (22.9)	157 (39.2)		
Junior school	69 (57)	52 (43)	121 (30.2)		
Senior Secondary and junior college	47 (48.5)	50 (51.5)	97 (24.2)		
Bachelor degree or above	10 (38.5)	16 (61.5)	26 (6.5)		
Duration of disease, month				4.370	0.112
≤12	74 (55.2)	60 (44.8)	134 (33.3)		
13~36	79 (68.1)	37 (31.9)	116 (28.9)		
≥37	94 (61.8)	58 (38.2)	152 (37.8)		
Living conditions				0.002	0.969
Living alone	45 (61.6)	28 (38.4)	73 (18.2)		
Living with others[a]	202 (61.4)	127 (38.6)	329 (81.8)		
Ethnic groups				0.151	0.698
Han nationality	214 (61.1)	136 (38.9)	350 (87.5)		
Others	32 (64.0)	18 (36.0)	50 (12.5)		
Payment methods				21.144	<0.001
Self-pay	1 (50.0)	1 (50.0)	2 (0.5)		
Urban resident basic medical insurance	52 (64.2)	29 (35.8)	81 (20.1)		
Rural cooperative medical insurance	126 (72.0)	49 (28.0)	175 (43.5)		
Urban employee basic medical insurance	67 (47.5)	74 (52.5)	141 (35.1)		
Public medical care	1 (33.3)	2 (66.7)	3 (0.7)		
Monthly household income per capita, ¥[a]				30.150	<0.001
≤1,000	69 (76.7)	21 (23.3)	90 (22.4)		
1,001–3,000	123 (66.8)	61 (33.2)	184 (45.8)		
3,001–4999	46 (44.7)	57 (55.3)	103 (25.6)		
≥5000	9 (36.0)	16 (64.0)	25 (6.2)		
Occupation status				26.804	<0.001
Employed	19 (65.5)	10 (34.5)	29 (7.2)		
Unemployed	153 (72.5)	58 (27.5)	211 (52.5)		
Retired	75 (46.3)	87 (53.7)	162 (40.3)		
Residence				15.904	<0.001
Rural areas	78 (72.9)	29 (27.1)	107 (26.7)		
Town and county	80 (67.2)	39 (32.8)	119 (29.7)		
City	89 (50.9)	86 (49.1)	175 (43.6)		
Comorbidity				3.436	0.064
No	35 (51.5)	33 (48.5)	68 (16.9)		
Yes	212 (63.5)	122 (36.5)	334 (83.1)		

(Continued on following page)

TABLE 3 (*Continued*) Relationship of non-adherence with related factors.

Variable	Non-adherence	Adherence	Total, no. (%)	χ^2	*p*
Total prescription medications per day				12.708	0.002
≤3	99 (52.4)	90 (47.6)	189 (47.0)		
4–5	96 (68.1)	45 (31.9)	141 (35.1)		
≥6	52 (72.7)	20 (27.8)	72 (17.9)		
Frequency of daily doses				3.478	0.324
1	110 (65.1)	59 (34.9)	169 (42.0)		
2	59 (61.5)	37 (38.5)	96 (23.9)		
3	75 (58.1)	54 (41.9)	129 (32.1)		
4	3 (37.5)	5 (62.5)	8 (2.0)		
Stroke subtype				0.188	0.664
Ischemic stroke	208 (61.0)	133 (39.0)	341 (84.8)		
Hemorrhagic stroke	39 (63.9)	22 (36.1)	61 (15.2)		
BMQ specific-necessity score	16.22 ± 3.16	17.86 ± 2.75	16.85 ± 3.11	−5.497	<0.001
BMQ specific-concerns score	14.97 ± 3.64	13.74 ± 3.91	14.50 ± 3.79	3.140	0.002
Health literacy score	59.11 ± 8.78	66.19 ± 9.53	61.84 ± 9.70	−7.477	<0.001

[a]Living with others includes living with spouse, children, and nanny.

TABLE 4 Factors associated with medication non-adherence using logistic regression.

Variable	B	S.E.	Wald χ^2	*p*	OR (95%CI)
Educational level					
Primary school and below	-		13.646	0.003	–
Junior school	-0.821	0.291	7.971	0.005	0.440 (0.249, 0.778)
Senior Secondary and junior college	−1.002	0.305	10.823	0.001	0.367 (0.202, 0.667)
Bachelor degree or above	−1.039	0.494	4.425	0.035	0.354 (0.134, 0.932)
Total prescription medications per day					
≤3			9.679	0.008	
4~5	0.690	0.263	6.861	0.009	1.993 (1.190, 3.339)
≥6	0.803	0.334	5.771	0.016	2.233 (1.159, 4.300)
Health literacy score	−0.064	0.014	20.006	<0.001	0.938 (0.913, 0.965)
BMQ specific-necessity score	−0.131	0.043	9.058	0.003	0.878 (0.806,0.955)
BMQ specific-concerns score	0.105	0.032	11.134	0.001	1.111 (1.044, 1.182)

B, B coefficient; SE, standard error; Wald, Wald chi-squared test; *p*, *p*-value; OR, odds ratio; CI, confidence interval. Significance taken at $p < 0.05$.

medication non-adherent as compared to those with ≤3 types [OR (95% CI) = 2.233(1.159, 4.300)]. Furthermore, when the BMQ specific-concerns score increased by one unit, the medication non-adherence increased by 11.1% [OR (95% CI) = 1.111(1.044, 1.182)]. Meanwhile, for every one-unit increase in the Health Literacy Scale for Stroke Patients score, there will be a 0.938 times decrease in the GMAS-C score (β = −0.641 (95% CI; (0.913, 0.965)). Lastly, for every one-unit increase in the BMQ specific-necessity score, there will be a 0.878 times decrease in the GMAS-C score (β = −0.131, (95% CI; 0.806, 0.995)).

Discussion

To the best of our knowledge, this cross-sectional study is the first to evaluate medication non-adherence among older adult stroke survivors in China. Our findings showed that medication non-adherence was observed in 61.4% of the 402 sampled patients. Specifically, partial adherence, low adherence, and poor adherence were found to be 37.1%, 13.7%, and 10.7%, respectively. Moreover, the findings in terms of the non-adherence rates in the current study were much higher than those previously published in a meta-analysis of observational

studies regarding post-stroke patients. The latter indicated that the overall non-adherence rate to secondary preventative medication among stroke survivors was 30.9%–35.9% (Al et al., 2016; Zhang et al., 2021). A possible explanation for this is that the aforementioned studies included all stroke patients aged over 18 years, while the present study focused on patients over 60 years of age. In this context, Yuvaraj et al. (2019) found that being part of the elderly age group is a determinant of non-adherence to medications after adjusting for possible confounding variables. Older adults are prone to multiple comorbidities and use more medications than their younger counterparts and may therefore present with a higher risk of medication non-adherence (Chiang-Hanisko et al., 2014). Taken together, our findings present concerns about the alarming rate of non-medication adherence among older adult stroke survivors in Chenzhou, Hunan Province, China, which requires further attention. This finding, while preliminary, suggests that strategies to promote medication adherence among this group are urgently needed.

Meanwhile, the educational level was found to be a predictor of medication non-adherence among older adult stroke survivors. According to our findings, patients who had higher educational levels were less likely to be non-adherent as compared to those who had attended only primary school or less. These results are consistent with those of other studies and suggest that higher education levels are associated with adherence (Kirkman et al., 2015; Jin et al., 2016; Bandi et al., 2017). This could be explained by the fact that those with higher educational levels may be less likely to have negative beliefs about medications (Lemay et al., 2018), which would promote medication adherence. Therefore, when seeking strategies to improve medication adherence among stroke survivors, educational-level factors must be considered. Meanwhile, it is worth noting that the average duration of education for stroke patients was significantly lower in patients aged ≥65 years than in patients aged <65 years (Lu et al., 2018). Such findings help shed light on the educational level as an important challenge for medication adherence interventions among older adult stroke survivors.

Among the common concerns, we found that the medication non-adherence of stroke survivors increased with that of total prescription medications per day. These results are congruent with the findings of earlier studies that indicate older adults are more adherent to a simplified medication regime (Jin et al., 2016). A possible explanation of this result is that patients may be less likely to forget to take medicine if the number of pills is low (Napolitano et al., 2016). However, Kim et al. (2020) reported that optimal medication adherence was associated with more prescribed medicines. This rather contradictory result could be attributed to the study including chronic diseases, while our study only considered elderly stroke patients.

Another important finding was that low needs or high concern regarding medication were associated with medication non-adherence. This finding is in agreement with previous studies on medication adherence among elderly people with chronic diseases (Lemay et al., 2018; Park et al., 2018), which revealed that as compared to patients with high needs and low concerns about medication, those with low needs and high concerns had significantly high medication non-adherence. Our results corroborated that of Horne and Weinman (1999b) who suggested that beliefs in medication may offer accurate predictability about adherence. Additionally, concerns about prescribed medications and unawareness of the rationale for treatments were expressed as primary reasons for non-adherence by stroke survivors (Bauler et al., 2014). Hence, for medical professionals, it is of great importance to outline and educate patients on the necessity of treatments rather than simply providing information about medication, while also managing patients' concerns by sharing the known side effects of prescribed drugs and helping them recognize and cope with side effects to improve their confidence.

Overall, the most important clinically relevant finding was that health literacy is significantly associated with medication non-adherence. Here, health literacy refers to the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to understand and use information to promote, maintain, or improve their health (Ratzan, 2001). According to this finding, lower health literacy has a greater likelihood of being associated with non-medication adherence. This result matches those observed in earlier studies (Lee et al., 2017; Mayo-Gamble and Mouton, 2018). This may be attributable to the fact that low health literacy is associated with less understanding of prescribed medication instructions (Mayo-Gamble and Mouton, 2018) and problems in using preventive services (Stormacq et al., 2019). As health literacy is considered the most important modifiable risk factor of socioeconomic differences in health (šedová et al., 2021), future work should investigate tailored interventions considering health literacy among older adult stroke survivors.

Strengths and limitation

The most important strength of this study is that to the best of our knowledge, it provides invaluable information on the prevalence and factors associated with medication non-adherence by using standardized rating scales among older adult stroke survivors in Chenzhou, Hunan Province, China. Furthermore, our findings may provide a comprehensive picture of medication non-adherence among stroke survivors, which may lay the groundwork for interventions aimed at increasing adherence among this population. Here, it should be noted that our participant population was older adult stroke survivors, who have been frequently left out of studies. Hence, our study addresses an understudied group.

However, this study has limitations that are worth considering. First, information on medication adherence was collected for the previous months prior to the survey, so some degree of recall bias cannot be ruled out. This could lead to inaccurate estimations of the prevalence of medication non-adherence. Additionally, the data relied on self-reported practices of medication adherence, which might have been over- or under-reported by participants. Second, it was limited in scope. Participants were from three tertiary hospitals in Chenzhou, Hunan Province, China, which limits its generalizability to the broader regions in China. Third, this was a cross-sectional study. Therefore, associations between medication non-adherence and risk factors cannot necessarily be considered causal relationships.

Conclusion

Our findings emphasize that medication adherence among older adult stroke survivors is problematic in this sample of study participants from Chenzhou, Hunan Province, China. Specifically, we found that medication non-adherence was significantly associated with educational levels, number of prescription medications to be taken per day, low needs or high concerns for medication, and health literacy. Building on this, we have offered specific recommendations for proposing population-specific medication adherence interventions among older adult stroke survivors. Our findings also suggest that efforts are needed to explore the prevalence and associated factors of medication non-adherence among older adult stroke survivors in other countries.

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 human participants were reviewed and approved by the ethical committees of the Affiliated hospital of Xiangnan University (Linyan K2022—003—01), Chenzhou No. 1 People's Hospital (Yu2022033)and Third People's Hospital (Lunshen 2022—10). All participants gave written consent.

Author contributions

IIH and AAK conceived and proposed the idea. JW and WC designed the work. WC, LC, LP, and NL contributed to the data collection. WC and LH contributed to data analysis and the interpretation of data for the work. WC wrote the first draft of the manuscript. IIH, AAK, and JW helped revise the manuscript. All authors read and approved the submitted version.

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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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Community pharmacists' views and experiences toward over-the-counter medicines misuse and abuse in Saudi Arabia: A qualitative study

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Background: Community pharmacists are uniquely positioned to identify and address the issue of misuse and abuse of over-the-counter (OTC) medicines. To date, no study has explored the Saudi community pharmacists' views and experiences regarding aspects of OTC medicines' misuse and abuse.

Objective: To explore the views and experiences of the Saudi community pharmacists towards OTC medicines misuse and abuse. Furthermore, we aimed to identify frequently misused and abused medicines, the reasons and contributing factors, the role of pharmacists, and potential risk-mitigating strategies.

Methods: Semi-structured interviews were conducted with a convenient sample of sixteen community pharmacists recruited from community pharmacies across the AL-Baha region, Saudi Arabia. Interviews were conducted using a pilot-tested interview guide in the Arabic language. All interviews were audio-recorded, transcribed verbatim, translated from Arabic into English, and then thematically analysed.

Results: Analysis of interviews generated five main themes, including the commonly misused and abused OTC medicines, reasons and factors contributing to misuse and abuse of OTC medicines, pharmacists' interventions to manage misuse and abuse, challenges and barriers to pharmacists' interventions in misuse and abuse issues; and potential strategies to reduce the risk of OTC medicines misuse and abuse and improve pharmacists' practice. Sedative antihistamines, cough products containing dextromethorphan, codeine-based analgesics, and non-codeine-based analgesics were commonly misused and abused OTC medicines. Managing ongoing medical conditions was the main reason for misusing OTC analgesics while recreational use and inducing sleep were the common reasons for abuse. Several factors contributing to misuse and abuse were reported, including unprofessional advice sought from other people, lack of awareness about medicines, and commercial advertisement of OTC products.

Community pharmacists identified misuse and abuse among customers by judging their behaviours and attitudes and using structured questioning techniques. Counselling customers on the appropriate use of medicines, providing safe alternatives, and refusing to sell products were among the commonly used actions of pharmacists to address misuse/abuse. Pharmacists proposed several strategies to reduce the risk of OTC medicines misuse/abuse but believed that rescheduling OTC medicines with abuse potential to prescription-only medicine was the best option.

Conclusion: Community pharmacists believed that the misuse and abuse of OTC medicines amongst pharmacy customers was common. A multidimensional strategy consisting of upskilling community pharmacists, a comprehensive review of OTC medicines sale regulations, and patient education to limit the risks of OTC medicines misuse/abuse is required.

KEYWORDS

community pharmacist, over-the-counter, medicines, misuse, abuse

Introduction

Over-the-counter (OTC) medicines, also known as non-prescription medicines, can be obtained without a prescription from a physician. They are frequently used in the prevention and treatment of various conditions such as common cold, headache, musculoskeletal pain, and heartburn (Bowman et al., 2020). Although they provide benefits to patients, their use is not without risks. These risks may include improper patient understanding of the underlying condition, wrong dosage, dependence or addiction, adverse reactions, and drug-drug interactions (Wazaify et al., 2005). Unlike prescription medicines, OTC medicines are safe in general when used as recommended, but there is potential for misuse and abuse as well. Misuse of medicines refers to the use of OTC medicines for medical purposes but inappropriately, such as taking higher doses than recommended (Cooper, 2013b). However, abuse refers to the use of medicines for non-medical reasons such as recreational purposes (Hall et al., 2012). As community pharmacists are often the primary contact for patients requiring OTC medicines, they can take proactive actions in preventing and managing misuse and abuse issues by exploiting their clinical skills, offering oral and written medicine information, and establishing trust among patients (Roussin et al., 2013). However, pharmacists face multiple challenges in identifying and managing the problematic use of OTC medicines such as a lack of access to patient medication history, making patient counselling challenging (Griese et al.).

Unlike other countries, OTC medicines are not available in Saudi Arabia for sale in supermarkets or groceries, and their provision is restricted to only community pharmacies. A number of studies have been undertaken in Saudi Arabia exploring the public's attitude toward OTC medicines. Al-Khamees et al. (2018) reported that OTC analgesics were the most commonly used OTC medicines with diclofenac being the most commonly used analgesic. A study estimating the prevalence of OTC medicine misuse among Saudi female university students reported the lifetime prevalence of misuse to be 29.1%. Diphenhydramine and Paracetamol were the most frequently misused medicines while pain relief and inducing sleep were the main reported reasons (Dabbagh et al., 2021). In another study, 6.6% of the study participants reported daily use of OTC analgesics (Qahl et al., 2020).

Since community pharmacists are the only point of contact for individuals seeking OTC medicines, they can play an important role in detecting and managing misuse/abuse incidents. To date, no study has sought to explore community pharmacists' views and experiences on various aspects of OTC medicine's misuse and abuse. Therefore, this study aimed to explore the views and experiences of community pharmacists in Saudi Arabia towards OTC medicines misuse and abuse, particularly to identify: OTC medicines commonly misused/abused, reasons and contributing factors, pharmacists' roles in identification and management, barriers to pharmacists' interventions and potential strategies to reduce the risks of OTC medicines misuse/abuse and improve pharmacists' current practice to ensure safe and effective use of OTC medicines.

Methods

Design

This was an exploratory qualitative study using in-depth semi-structured interviews. The use of semi-structured interviews as a data collection method allowed researchers to gain spontaneous expressions from participants, minimise pre-conceptualised boundaries, and stay close to the study objectives (Smith, 1998).

Setting

The research was conducted among community pharmacists working at a national pharmacy chain (X) across different locations in the Al Baha region, Saudi Arabia. The participating chain pharmacy is one of the largest national chains in Saudi Arabia, operating more than 1,000 pharmacies. Al Baha is one of the thirteen regions of Saudi Arabia and is located in the Southwest of the country. There are 96 community pharmacies across this region (Saudi Ministry of Health, 2022). Pharmacists working in other pharmacy chains and independent pharmacies in the region were also approached, but none responded to our invitation to participate in the study.

Interview guide development

The Interview guide was developed based on the study objectives, the reviewed literature, and discussion among the research team (Cooper, 2013a; Algarni et al., 2021). The interview guide comprised open-ended questions and further probing questions to seek information about participants' characteristics and perspectives towards various aspects of OTC medicines misuse/abuse. These aspects involved the commonly implicated medicines in misuse/abuse and pharmacists' experiences with recent misuse/abuse cases, reasons, and factors contributing to misuse/abuse, methods of identifying and addressing misuse/abuse incidents, barriers to pharmacists' interventions, and potential strategies to minimise the risk of OTC medicines misuse/abuse and improving pharmacists' practice in this respect. Face and content validation for the interview guide were conducted. The research team reviewed the interview guide to ensure its clarity, relevance, and reasonableness. A faculty member with research experience in medication use and misuse checked the content of the interview guide to ensure that it was logical and balanced. The interview guide was piloted with two community pharmacists. Piloting the interview guide indicated that conducting the interviews in the participants' first language (Arabic) rather than in English would allow participants to express their thoughts easily and freely and provide more in-depth data. In addition, it showed the need to refine the interview guide with more probing questions. Subsequently, the interview guide was translated into the Arabic language.

Sampling and recruitment

As the research team was unable to purposively recruit pharmacists from other local and national chains or independent pharmacies, convenience sampling was used to recruit pharmacists who expressed their willingness to participate in the study after receiving the initial invitation sent by the company's regional supervisor. However, we considered the area of practice (urban vs. rural), working experience as community pharmacists, and qualifications to ensure diversity in the experiences of pharmacists. Out of the 38 pharmacists working in (X) chain pharmacies across the Al Baha region, 22 agreed to participate in the study. Sampling and recruitment of participants continued until data saturation was reached.

Data collection

Pharmacists who agreed to participate in this study were emailed a participant information sheet (PIS) stating the study's objective and expected time commitment. They were asked to inform the research team about the suitable date, time, and location for conducting the interview. The participants were sent an overview of the questions in advance to allow for reflection before conducting the interview. For safety purposes during the COVID-19 pandemic, the first six interviews were conducted face-to-face, and the remaining were conducted over the phone. For the face-to-face interviews, the interviewer (MA) met the pharmacists at their workplace. Interviews were conducted in Arabic (the National language of Saudi Arabia) and took, on average between 19 and 45 min. Interviews were conducted between March and July 2020 and were digitally audio-recorded. Using the approach proposed by Francis et al. (2010), data saturation was ensured after no new themes emerged from the last three consecutive interviews (Francis et al., 2010).

Data generation and analysis

Data were transcribed verbatim and independently checked for transcription accuracy. Participants were permitted to review their transcripts to allow further review and editing of the transcripts. The interview transcripts were translated into English by a certified company. To ensure the translation accuracy, an independent expert in Arabic-English translation checked the translation of three randomly selected interviews. The translated interviews were then entered into the qualitative software NVivo 12 plus (QSR International) for initial coding. The analysis was interpretative, focused on the participants' experience, and relied on the interaction between the researcher and the data. Thematic analysis was guided by the six steps developed by Braun and Clarke, including familiarisation with the data, coding, generating initial themes, reviewing themes, defining and naming themes, and writing up (Braun and Clarke, 2006). Data familiarisation was conducted simultaneously with data collection through listening to the recordings and reading the produced transcripts. Transcripts

TABLE 1 Demographic details of participants.

Characteristic	N (%)
Gender	
Male	16 (100)
Education	
B.Sc	15 (94)
PharmD	1 (6)
Years of practice	
Less than 5 years	4 (25)
5–10 years	8 (50)
11–15 years	3 (19)
More than 15 years	1 (7)
Pharmacy location	
Urban area	10 (63)
Suburban area	3 (19)
Rural area	3 (19)

were read thoroughly to shape initial impressions and develop potential themes. The first author (MA) coded each transcript and created a set of codes pursuant to careful reading of all transcripts. A randomly selected sample of interviews were coded by another investigator of the research group (ZJ). Codes from individual transcripts were checked line-by-line, then compared, discussed, and changes were made as applicable until a consensus was reached. Categories were derived from combining codes to create an analytical framework, and the primary themes were formed. The analytical framework was refined iteratively over the analysis through discussions among the research members experienced in qualitative research (MH and SA).

To ensure rigour and trustworthiness in our study, strategies like member checking, reflexivity, and a detailed audit trail were used.

Ethics

The ethics approval for this study was obtained from the University of Birmingham Science, Technology, Engineering, and Mathematics Ethics Committee (Ref# ERN_19_1636). Permission and approval were also obtained from the participating chain pharmacy. All participants signed a paper or electronic informed consent, agreed to audio record the interview, and gave verbal consent prior to conducting the interviews.

Results

A saturation of data was reached after interviewing sixteen pharmacists. All the respondents were male, while the majority had work experience ranging from 5 to 10 years and worked in pharmacies located in urban areas. Further demographic details of the participants are presented in Table 1. The coding process and subsequent analysis of the findings generated five main themes, including the commonly misused and abused OTC medicines, reasons and factors contributing to misuse and abuse of OTC medicines, pharmacists' interventions to manage misuse and abuse, challenges and barriers to pharmacists' interventions in misuse and abuse issues and potential strategies to reduce the risk of OTC medicines misuse and abuse and improve pharmacists' practice (Figure 1). Pseudonyms were developed to show information relevant to each participant, such as pharmacist participant number (e.g., PH 1); pharmacy location (urban 'ur' or suburban 'sub ur' or rural 'ru'); and the number of years the participant had been working as a pharmacist (e.g., 5 years).

Theme 1: OTC medicines commonly misused and abused

The participating pharmacists nominated various OTC products commonly misused/abused or suspected to be misused/abused by their customers. These products largely belonged to the following classes; sedative antihistamines, dextromethorphan-based cough products, codeine-based analgesics, non-codeine-based analgesics, cortisone-based skin preparations, and nasal decongestants. All quotes are [sic].

> *"Well. At first place comes (Diphenhydramine combined with Paracetamol), then comes (codeine-based analgesics). We may place Dextromethorphan in the second place, and then come (codeine-based analgesics) in the third place. We may place the analgesics in the fourth order because you cannot judge whether or not the customer is a misuser"* PH8 Sub Ur (11 yr).

Most pharmacists reported that they predominantly encounter misuse/abuse among male customers as they are frequent visitors to their local pharmacies requesting medicines for themselves or their female partners.

> *"Our pharmacy, here on the South Line location and that's why the majority of the customers I have, may be 80–90%, of them are males"* PH11 Ur (6 yr)

However, specific products such as cortisone-based topical preparations were reported to be heavily abused by women for skin whitening purposes.

> *"For example, Cortisone cream is recently misused by some women in a skin whitening mixture because of the cortisone side effects is that it can bleach skin"* PH6 Ur (9 yr).

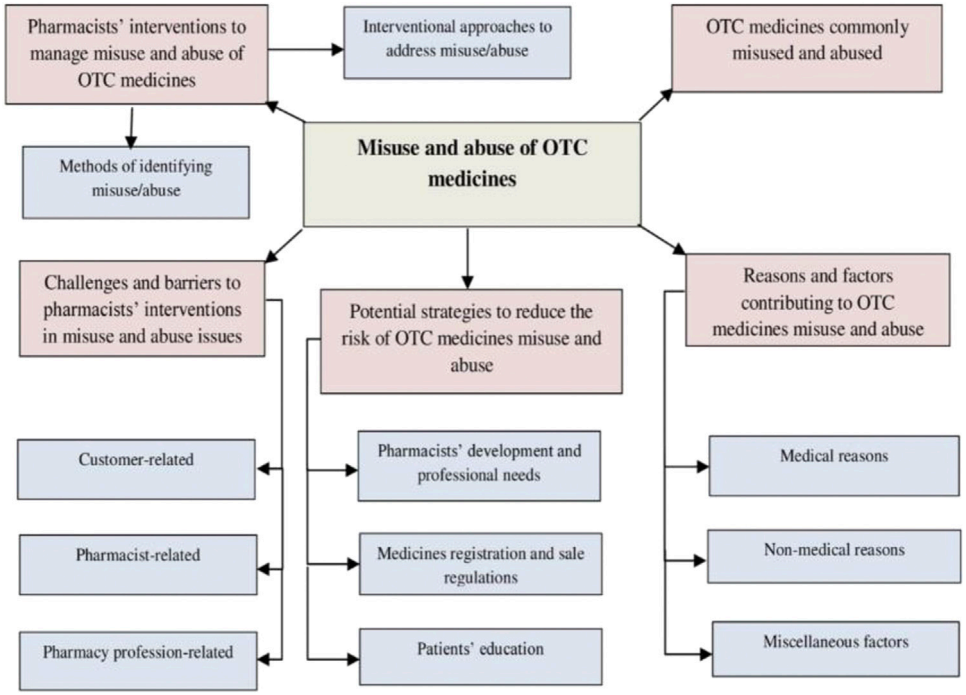

FIGURE 1
Emerged themes and subthemes.

Regarding customers' age, products with abuse potential were mainly perceived to be abused by young people, while misuse was more experienced in older people, particularly with analgesics

> *"Painkillers are mostly misused by the old-aged while these antihistaminic drugs and these containing codeine like [codeine-based painkiller] are mostly abused by young adults"* PH6 Ur (9 yr).

Community pharmacists also noticed some patterns in the shopping behaviour of prospective abusers of OTC medicines. For example, customers craving sedative antihistamines frequently visits the pharmacy at night.

> *"for (Diphenhydramine) and (codeine), people come at the end of the night while consumers of other things may come in the middle of the day and the afternoon at the crowded times"* PH16 Ur (1 yr).

Others try to visit the pharmacy when it is busy to avoid being questioned by pharmacy staff.

> *"they come at the time when pharmacy is crowded with customers exploiting, for example, that I have no free time to spend with them. They aspire to win their request and leave right away"* PH10 Ru (9 yr).

Theme 2: Reasons and factors contributing to OTC medicines misuse and abuse

Pharmacists perceived several medical and non-medical reasons and other factors precipitating OTC medicines misuse/abuse. Pharmacists perceived that managing ongoing medical conditions such as toothache, migraine, and osteoarthritis is the main reason for customers to consume higher doses of OTC analgesics or use them for a more extended period of time.

> "they misuse very big quantities of them (painkillers) to relieve toothache to the extent that someone may take 1200 or 1800 mg of (Ibuprofen) per day. But you do not talk about for one-time use but for long-term use" PH5 Ru (7 yr).

Numerous non-medical reasons for abusing OTC medicines were also reported such as abusing codeine-based analgesics or dextromethorphan-containing products for recreational purposes and sedative antihistamines to induce sleep.

> *"secondly, we are also asked, of course, about [codeine-based painkiller]. It is either used for getting high which has nothing to do with the prescribed medication or for its analgesic effect for a long time"* PH5 Ru (7 yr).

Two pharmacists reported a more dangerous practice with sedative antihistamines as some parents administer syrups to their children to induce sleep.

> *"Others may misuse them to get sedated and that's why they resort to taking Chlorpheniramine maleate in the form of pills or syrups"* PH13 Ur (8 yr).

Female customers in particular abuse skin creams containing cortisone for skin whitening purposes and sometimes mix them with Hydroquinone and Tretinoin.

> *"Despite the availability of alternatives, [Cortisone containing cream] is still famous among some people who misuse it in mixtures for the purpose of whitening skin as it happens when used with Hydroquinone and Retinoid in this famous mixture"* PH10 Ru (9 yr).

Among customer-related factors, seeking unprofessional advice from others and searching on the internet for information were the most commonly reported contributor to misuse/abuse

> *"look, the reason could be that one of his relatives tells him about that medicine and how good it is, and how it helps him to sleep well, so he imitates him, or he uses it profusely so he will be misusing the medicine and he will get used to it like [product combines diphenhydramine and paracetamol] "* PH12 Ur (12 yr).

In addition, lack of awareness about medicines, low education, and cultural influence were other important factors reported by many participants. Pharmacists illustrated that highly-educated individuals appeared more amenable to accepting advice once problematic use of OTC medicines was identified.

> *"Of course, educational level makes a great difference. When some customer is educated person, he listens to my advice and even thanks me. When the customer sometimes has low educational level, he can enter into an argument shouting impolitely at me in order to give him the medication and stop admonishing him"* PH9 Ur (8 yr).

Pharmacists reported that previous experience of using the medicine as well as previous medical prescribing urged customers to repeat using medicines when they experience the same symptoms without following up with the prescriber

> *"Some patients may, for example, go to hospital and physician prescribes some medications including these OTC medicines for him. That patient by himself keeps repeating the dosage when having the same previous symptoms"* PH3 Ur (10 yr).

Pharmacists described the importance of peer pressure in driving individuals to behave similarly toward medicine use. For instance, pharmacy visitors from a specific nationality or the same age group, such as young individuals, share the same misuse/abuse practices.

> *"many of these people of non-Arab nationalities especially Indians and Bengalis, sometimes ask about medicines for coughing, which is a cough suppressant like [dextromethorphan product] and [dextromethorphan product] which are very well-known"* PH14 Sub Ur (8 yr).

Pharmacists perceived that the inability to access General Practitioners (GPs) and hospitals due to cost entails some people using OTC medicines without proper medical diagnosis or supervision.

> *"yes, the point of preferring to visit pharmacy to visiting a doctor has more than one reason, including the financial side that he is not able to go to hospital and pay for the doctor's costs"* PH6 Ur (9 yr).

Pharmacists reported two factors related to OTC products that precipitate their misuse/abuse. Firstly, advertising products on television and social media, and secondly, affordable price of generic medicines with abuse potential.

> *"let me give you an example.[Xylometazoline] has some specific usages; it must be used for 5 days only at maximum; otherwise, it can cause a rebound effect which has many more harmful effects than the benefits. It is actually advertised on TV and as a result, people ask for it a lot"* PH7 Sub Ur (17 yr).

Theme 3: Pharmacists' interventions to manage misuse and abuse of OTC medicines

Pharmacists described how they identify misuse/abuse incidents through customers' behaviours and attitudes and procedures they have in place. Most pharmacists reported that misusers/abusers could initially be judged by observing their facial expressions, physical appearance, and reactions during conversations

> *"another sign is the behavior some of those people show when first visiting pharmacy; they may a little bit confused or*

> *perplexed in his speech or movements. You may find them apparently unnatural"* PH9 Ur (8 yr).

Many pharmacists also regarded frequent visits requesting the same product, requesting a large quantity at once, visiting the pharmacy during busy times, exploiting the crowd to avoid being asked by pharmacists, and refusing any alternative as usual behaviours aiding in the identification of misuse and abuse incidents.

> *"the pharmacy here, especially in the Al-Baha region, is considered a neighborhood pharmacy, so customers almost daily frequent at it. Therefore, I can mostly identify them by frequently visiting pharmacy and asking for the same drug"* PH5 Ru (7 yr).

Few pharmacists indicated that some customers disclose to them the non-legitimate use of the medication.

> *"when they visit me, they tell frankly that they want that comforting syrup, such as [product combines pseudoephedrineand and triprolidine], for example, or any antihistaminic syrup"* PH6 Ur (9 yr).

Concerning the procedures used by pharmacists to identify problematic use with OTC medicines, nearly half of pharmacists specified the pharmacy mnemonics WWHAM (which stands for five questions W = Who is the patient? = What are the symptoms? H = How long have the symptoms been present? A = Action taken, M = Medication being taken) as the main procedure for gathering essential clinical information from customers.

> *"you should use the regular WWHAAM questions with anyone visiting you. Before dispensing the medications for him, you should ask why he gets the medications and what the symptoms are"* PH13 Ur (8 yr).

Some pharmacists stated that they get notified about misuse/abuse incidents by their colleagues or a nearby pharmacy

> *"In case some of them frequently request the medication from other pharmacies and we are told and warned of them that they were, for example, searching Al-Baha city for getting the same medication"* PH16 Ur (1 yr).

Regarding the actions taken by pharmacists to address misuse/abuse, advising customers on the appropriate use of medications and the wise handling of objections were the initial actions taken by most pharmacists.

> *"Someone may have recommended for the visiting customer a medication for cough that the customer even does not know anything about it. The customer may not be an addict at all; in that case, you can counsel him about it" PH14 Sub Ur (8 yr).*

However, offering safe alternative products was the most reported action by pharmacists when the requested medications were being surely misused/abused

> *"I have the Codiene shown outside because it is among the OTC medications. As pharmacist, I try to play my role in order to know why the customer is taking it and try to shift him to another alternative."* PH5 Ru (7 yr).

Pharmacists dealt with those who used OTC medicines for medical reasons but in wrong ways by providing a limited quantity of the product or reducing its dose and frequency

> *"I can decide the action taken; I can urge him to decrease the used dosage so as to minimize the side effects and thus reduce the rate with which he takes the drug in the wrong way"* PH5 Ru (7 yr).

Community pharmacists, when left with no other option to prevent misuse/abuse of OTC medicines, had to refuse to sell the product or deny its availability. Community pharmacists would also notify their colleagues or the nearby pharmacies about customers with the potential of abusing OTC medicines, especially pharmacists working in rural areas who had better communication with local pharmacies of different groups, whereas those working in urban areas exchange information only with the same chain pharmacies.

> *"I am here talking about Al-Aqiq as we created a group on WhatsApp for our group of pharmacies. That group not only includes (Our company), but also includes (Another chain pharmacy) as they are four pharmacies or four companies. We have a group for all of them so that we can tell each other what happens"* PH4 Ur (10 yr).

As a precautionary procedure, pharmacists kept products with misuse/abuse potential out of customers' sight to prevent abusers from picking them directly from the shelves

> *"generally, I keep these well-known abused/misused drugs, such as [product contains diphenhydramine and paracetamol], [codeine-based painkiller] or [topical cortisone] behind the counter so that no one else can see them"* PH10 Ru (9 yr).

Lastly, pharmacists stated that they often signpost customers requiring further care or those non-responsive to their advice to GPs and hospitals.

> *"in case he was not to accept my advice, I would recommend visiting any physician so that he could have some examinations and blood tests"* PH8 Sub Ur (11 yr).

Theme 4: Challenges and barriers to pharmacists' interventions in misuse and abuse issues

Pharmacists reported multiple barriers and challenges relating to customers, pharmacists, and the pharmacy profession that hinder their interventions. Failure to change customers' perceptions about OTC medicines was the most common challenge mentioned by pharmacists

> *"we offer the alternative, but almost 98% of people do not get convinced" PH11 Ur (6 yr).*

> *"On the other hand, there are some experienced customers who can answer all questions in such a way that convince us to dispense the medications for him. I mean he can circumvent to take the medications and that happens a lot"* PH6 Ur (9 yr).

Pharmacists were concerned about raising the issue of misuse/abuse among women and the elderly especially.

> *"the first main challenge is keeping the privacy of females; I cannot investigate deeply the whole matter. I would talk to her as a pharmacist; in case there was rigidity from the person before me, I would not enter into this debate or in the discussion"* PH5 Ru (7 yr).

Some pharmacists complained that the customer would easily obtain the medicine from another pharmacy once their request was denied.

> *"In fact, we did not; he went, unfortunately, to the other pharmacies and they were selling quantities of the medications he wanted"* PH4 Ur (10 yr).

One pharmacist mentioned that purchasing medicines online limits the contact with the customer and gives no opportunity to identify any problematic use.

> *"up till now, we and my colleagues can control the question of the OTC abuse/misuse because we want to do that. But we have some electronic service in [our company] which can enable the visitor to shop online. It also enables him to know his credit in the pharmacy and it is his right to order the medications. In this case, you are forced to get the medications ready for shipment for him"* PH14 Sub Ur (8 yr).

Pharmacists stressed that identifying misuse/abuse in new customers was challenging. This was especially challenging among pharmacists with limited experience and little sociocultural awareness.

> *"As for us working here in a community pharmacy and thanks for long experience, we have become very acquainted with most of our guests. Therefore, it is normal to have some unfamiliar customer whom you did not see before"* PH1 Ur (4 yr).

Concerning the work environment and pharmacist-related barriers, personal safety was the most often reported barrier. In particular, it limits those working in rural areas from dealing with aggressive customers.

> *"of course, the first barrier is taking care of your own safety as a pharmacist or of the person you are dealing with. I mean, if someone in a state of drunkenness or intoxication with some illegal drug visited you to ask for some medication, then it would be natural for you to be afraid of clashing with him"* PH10 Ru (9 yr).

Workload was noted by many pharmacists as it forces them to reduce their contact time with customers during busy times

> *"Moreover, workload and rush hour make me so occupied that I have no enough time to talk freely with the patient so as to completely advise him as possible as I can"* PH5 Ru (7 yr).

Pharmacists indicated that the lack of standardised protocol for OTC medicines sale and scarcity of training designed for abuse management limited their capability in managing abuse issues.

> *"of course, there are no clear statements from the Ministry of Health concerning OTC medications. Thus, you cannot abstain from dispensing these medications for customers because the Ministry of Health cannot support you in case you do"* PH13 Ur (8 yr).

Only a few pharmacists considered business targets, lack of experience, and initiative to deal with abuse issues as barriers. A majority of pharmacists reported that drug distributors often pressured them to display products with misuse/abuse potential in a visible location for customers.

> *"the salesperson or the one who are in the pharmacy waits for such pretext for selling more and more of analgesics"* PH2 Ur (4 yr).

Some pharmacists referred to the poor connection with other local pharmacies as limiting information sharing about medicines abusers

> *"No, frankly speaking. There is no contact with other pharmacists who work in other pharmacies outside (X) group"* PH9 Ur (8 yr).

Theme 5: Potential strategies to reduce the risk of OTC medicines misuse and abuse

Pharmacists perceived several strategies and professional development requirements to help mitigate OTC medicines misuse/abuse. Switching abuse susceptible medicines from OTC to prescription-only or behind-the-counter status by health authorities was considered the most robust strategy. For instance, rescheduling codeine-based analgesics to prescription-only status was suggested by most pharmacists.

> *"Yes, codeine and Chlorpheniramine contained in [product X] are really supposed to be prescriptions only"* PH13 Ur (8 yr).

Half of the pharmacists perceived that developing a nationwide standard protocol for OTC medicines sales would uniform the procedures followed by all pharmacists. Similarly, pharmacists showed the need for training programs on abuse and dependence management and providing continuous informational updates about abuse issues

> *"You may encounter dangerous situations in which you can deal with some serious addicted person. You may not know how to deal with him. That's why it is so important to learn- even if you have reached a very high degree of experience- how to manage such people and how to guide and counsel them"* PH1 Ur (4 yr).

Pharmacists emphasised that raising public awareness about OTC medicines' safe use is crucial to reducing their risks. Two pharmacists stressed that lessons could be learned from a previous campaign, which successfully raised public awareness about antibiotics' rational use

> *"that's why when the media talked about antibiotics and their bad side effects, it affected people. That' s why I have told you earlier that there has to be an awareness among people, and it should not be by one side"* PH12 Ur (12 yr).

Monitoring the advertisement of OTC products *via* different media means was suggested by some pharmacists

> *"of course, I see that it is necessary to restrictions to be imposed. I do not know whether or not they can be applied. When you make advertisements for some drug, you mean to say that it has no side effects. In Europe, they tell people about all pros and cons of the product. That is no applied here in Saudi Arabia"* PH4 Ur (10 yr).

Some pharmacists suggested regulations to determine a maximum pack size for medications susceptible to misuse/abuse and restrict the number of packs at the time of sale

> *"of course, it is possible to reduce number of pills in each medication box. You as customer should get but one box. That can already help in minimizing abuse"* PH7 Sub Ur (17 yr).

Other strategies less often mentioned by pharmacists were enhancing cooperation between local pharmacies, allowing pharmacists to access patient medical records, tracking the sale of medicines to identify the frequently misused/abused medicines, and convening workshops for pharmacists and GPs to share experiences about medicines abuse and inform GPs prescribing decisions.

Discussion

The aim of this qualitative study was to explore the views and experiences of the Saudi community pharmacists towards OTC medicines misuse and abuse, specifically aiming to identify the implicated medicines, reasons, and contributing factors, the role of pharmacists and potential risk-mitigating strategies. In the present study, the common OTC medicines reported by pharmacists to be misused/abused were first-generation antihistamines, codeine-based analgesics, and antitussive preparations. These findings are in line with previously published literature in other countries (Wazaify et al., 2006; Cooper, 2013a; Abood and Wazaify, 2016; Wazaify et al., 2017). Pharmacists stressed that OTC analgesics, including codeine-based, nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol, are misused to manage pain, especially by the elderly. Therefore, the potential risks in such vulnerable groups are highly anticipated due to comorbidities and polypharmacy. Other studies have also identified painkillers as the most common OTC medicines misused by older people and their chronic use was the most common form of misuse (Elhoseeny et al., 2013; Stone et al., 2017). On the other hand, abusing OTC medicines to obtain mind-altering effects was usually encountered in young people. Sometimes, such medicines are used concurrently with illegal substances or as alternatives to the inaccessible abused prescription medications.

In the present study, pharmacists often attribute misusing OTC medicines by customers to not seeking professional advice. Instead, people tend to take advice from friends and family or use the internet as a source of information about medicines. In an Egyptian study, pharmacists illustrated that customers do not seek advice on OTC medicines as the majority trust the safety of these medicines, and the others believe that seeking advice is unnecessary (Elhoseeny et al., 2013). Seeking advice for self-medication from friends and parents is the secondary source of information in Middle Eastern countries (Khalifeh et al., 2017). Pharmacists perceived that misuse/abuse is influenced by geographic, educational, cultural, and ethnic disparities among customers. An earlier cross-sectional survey conducted in the United States revealed that people with low income and low

education show significantly less risk awareness about OTC and prescribed NSAIDs, with significant racial/ethnic disparities in risk awareness, communication, and behaviour (Fry et al., 2007). Among OTC product-related factors, direct-to-consumer advertising (DTCA) was perceived by pharmacists as strongly influencing the abuse of certain products and making consumers unresponsive to professional advice. Australian pharmacists believed that DTCA of OTC medicines disempowered them, undermining their role in protecting the community from inappropriate medicine use (Chaar and Kwong, 2010). Pharmacists also considered the affordable price of OTC medicines with abuse potential to drive abuse among young people. In contrast, the high cost of healthcare services necessitates low-income patients to use OTC products for long periods without a proper medical diagnosis. The low price and availability of OTC cough mixtures facilitated the recreational use among young people in China and the abuse of topical corticosteroids among women in India (Lam et al., 1996; Rathi, 2006). Pharmacists deemed the past experience of using the medicine and previous medical prescribing to precipitate frequent use for recurrent symptoms without seeking professional consultation. Previous or ongoing medical prescribing was associated with abusing OTC codeine by some users (Cooper, 2013b).

The common ways reported by pharmacists to identify misuse/abuse are, to some extent, similar to what has been reported in other studies (Eickhoff et al., 2012; Cooper, 2013a; Barrett and Costa, 2018). Pharmacists initially judge abusers by observing their behaviours and attitudes. In the United Kingdom, pharmacists commented that behaviours such as avoiding eye contact with the pharmacist, being agitated, and giving inconsistent answers are indications helping identify those abusing codeine analgesics (Carney et al., 2016). Pharmacists in the present study emphasised the use of the specific pharmacy mnemonic WWHAM to gather clinical when high-risk OTC medicines are requested. However, such standardised approaches do not necessarily improve consultation performance, possibly because the collected information is not always adequate for the decision-making process (Sinopoulou et al., 2019).

Pharmacists respond differently to each misuse/abuse situation. Resolving the situation through counselling, providing a limited quantity of the product, reducing the dose and frequency, and offering alternatives are actions usually taken with customers who misuse medications. Those customers generally accept the pharmacist's advice. However, pharmacists require to take further actions against those abusing medicines for non-medical purposes, including refusing the sale or denying the availability of the product, referral to physicians, and notifying fellow pharmacists. It was shown that pharmacists successfully addressed 73.3% of OTC medicines-related problems, including misuse/abuse, in the pharmacies with no need for referral, while counselling and drug switching were the most commonly made interventions. (Ylä-Rautio et al., 2020).

Although pharmacists showed readiness to identify and resolve misuse and abuse issues, they face multiple barriers to intervening in such issues. Pharmacists face customers' objections when medicine shifting is the appropriate choice to tackle the problematic use. Customers tending to abuse medicines for illicit purposes showed more resistance to medicine shifting. Also, those customers usually use different scenarios to circumvent obtaining their medicines. In a United Kingdom study, pharmacists showed that younger customers abusing OTC laxatives respond more defensively when questioned about the intended purchase as they think that they have the right to pick a General Sale List (GSL) medicine without being questioned by a pharmacist (Kelly and White, 2016). Pharmacists could refuse or deny the availability of the product when abuse is confirmed. However, customers can obtain the medicine easily from another pharmacy. Pharmacists can fairly identify and resolve misuse/abuse issues with their regular customers, but it is not the case with irregular ones. This advocates that loyalty and a good customer-pharmacist relationship could result in better outcomes when pharmacists intervene to tackle problematic use. Among barriers relevant to pharmacists and the work environment, lack of initiative to monitor the inappropriate use of OTC medicines and prioritising business interests could result in higher abuse opportunities. Nevertheless, workload, high-stress prescription processing, and low staffing make pharmacists less pharmacovigilant when the intervention is significant in preventing OTC medicines' misuse/abuse (Sansgiry et al., 2017).

Worldwide, several strategies and programmes have been considered to mitigate the misuse and abuse of prescription medicines and in turn little attention paid to OTC medicines. In the present study, pharmacists highlighted the importance of standerdising national protocol to facilitate their role in OTC medicines counselling and provision. At present, pharmacists use their own informative guidelines to support the advice-giving role. Such protocols are intended to guide pharmacists in identifying ailments, selecting medicine, counselling, following up with the patient, and referring for further care (Cavaco and Pereira, 2012). However, extending such protocol to include medicines abuse management could be beneficial. Pharmacists raise the need for specific training programmes in the area of abuse management as well as access to informational updates about abuse issues. An expert panel rated providing training for pharmacists and pharmacy staff as the most important and effective approach to reducing the inappropriate use of OTC medicines (McBride et al., 2003). In terms of regulations, pharmacists call for rescheduling OTC medicines with abuse potential into prescription-only or into a third-class that requires pharmacists' assessment upon dispensing. Currently, in Saudi Arabia, medicines are classified into prescription-only and OTC medicines. However, a third class of medicines, those with abuse potential, are currently defined in several countries, such as the pharmacist-only list in the

United Kingdom and the behind-the-counter class of medicines in the United States. Medicines in this class are provided upon the pharmacist's assessment after considering the required tests, preliminary screening, and appropriate counselling (Sansgiry et al., 2017). Moving codeine-combined analgesics from OTC to the pharmacists only category in Ireland and to prescription-only in Australia resulted in a misuse rate reduction (Cairns et al., 2016; Kennedy et al., 2019; Cairns et al., 2020). Because of its notable contribution to abuse, pharmacists emphasised that authorities should monitor the direct advertising of OTC products. Banning public advertising in addition to restricting pack sizes, limiting product visibility and customer self-selection, and increasing visibility of warnings on labels have been utilised in other countries to reduce codeine abuse (VAN and NORMAN, 2016). Eventually, pharmacists proposed raising public awareness about the safe use of OTC medicines. As some of the reported misuse/abuse practices in this study were attributed to illiteracy and lack of knowledge about medicines, considering health education is imperative to improve public knowledge about medicines.

Study limitations

There are some limitations to this research. First, the method of interviewing participants varied, with six pharmacists interviewed face-to-face and nine by telephone. This is because the interviewer was not able to meet face-to-face with the remaining participants due to COVID-19 restrictions. Consequently, this could have impacted the quality of the data collected from interviewees over the phone since the interviewer could not grasp the participants' body language. On the other hand, the increased sense of anonymity may have improved the quality of the data collected. Second, although the recruitment of participants considered a range of pharmacists working in urban, suburban, and rural areas, the study was conducted within one chain pharmacy in one region. Therefore, findings may not reflect the experiences of pharmacists working in independent or other chain pharmacies across the country. Third, medicines that are licenced in Saudi Arabia as OTC and the regulations for their sale may differ from those available in other countries. As a result, the study's findings cannot be generalised to other countries with different healthcare systems and drug regulations.

Conclusion

This study has provided unique insights into community pharmacists' experiences and views regarding the misuse and abuse of OTC medicines. Pharmacists identified the commonly misused and abused OTC medicines amongst different sets of pharmacy customers besides the reasons and factors precipitating the problematic use. Pharmacists also described the current strategies adopted to identify and manage misuse/abuse cases. However, they raised multiple challenges and barriers to effectively managing the misuse/abuse of OTC medicines. Pharmacists proposed several strategies with regard to OTC medicine regulations, pharmacists' professional needs, and patient education to mitigate the risk of OTC medicines misuse/abuse.

Data availability statement

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

Ethics statement

Approval for this study was obtained from the University of Birmingham Science, Technology, Engineering and Mathematics Ethics Committee (Ref# ERN_19_1636). The patients/participants provided their written informed consent to participate in this study.

Author contributions

MA and ZJ designed the study and developed the interview guide. SA recruited participants. MA conducted the interviews. MA, ZJ, and MH Co-analysed the interviews. MA wrote the initial draft, and ZJ and MH edited the document. All the authors made extensive contributions to the final draft of this manuscript.

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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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Pharmacist-led olaparib follow-up service for ambulatory ovarian cancer patients: A prospective study in a tertiary specialized cancer hospital in China

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Purpose: To establish a pharmacist-led olaparib follow-up program for ovarian cancer patients, provide patient education, get information on adverse drug reactions (ADRs), and identify and manage drug-related problems.

Methods: Ambulatory adult patients with ovarian cancer receiving olaparib were enrolled. At least one follow-up session was conducted by clinical pharmacists. Pharmacists collected data on the type and grade of ADRs, drug adherence, olaparib dosing, concomitant medications, and pharmacists' suggestions.

Results: 83 patients were enrolled with the median age of 58. The average number of the follow-up sessions provided to each patient was 1.31, and the average duration of each follow-up was 17.78 min. The olaparib starting dose for most patients (97.59%) was 600 mg/d. 36.14% of the patients had missed olaparib doses and 27.71% of the patients had dose adjustments due to ADRs. The most common ADRs (incidence≥10%) were: fatigue (40.96%), anemia (36.14%), leukopenia (36.14%), nausea (28.92%), thrombocytopenia (16.87%), anorexia (16.87%), dyspepsia (15.66%). The tolerability profiles were generally similar between patients treated for "first-line maintenance" and those treated for "recurrence maintenance" ($p > .05$). There were 42% of the patients who were concomitantly taking medications without exact chemical contents (such as formulated Chinese medicines and Chinese decoctions), and common types of concomitant medications with exact drug names were antihypertensive, anti-hyperglycemic, and anti-hyperlipidemic medications. The pharmacists identified 4 clinically significant drug-drug interactions (DDIs) in two

patients. Pharmacists made 196 suggestions mainly related to rational use of the medications and management of ADRs.

Conclusion: The study provides the first report about pharmacist-led follow-up service for olaparib. The types of ADRs were similar to those previously observed in clinical trials, and the profiles of ADRs in different types of patients (first-line maintenance vs. recurrence maintenance) were also similar. Pharmacists identified drug-related problems (such as adherence, DDIs and management of ADRs) and offer suggestions for the patients.

KEYWORDS

olaparib, ovarian cancer, pharmacist, follow-up, adverse drug reactions, drug adherence, drug-drug interaction

Introduction

Ovarian cancer is a common gynecological cancer worldwide. The majority of ovarian cancers are epithelial ovarian cancer (EOC), and most patients are diagnosed as FIGO (International Federation of Gynecology and Obstetrics) III/IV (Ni et al., 2019). The traditional standard treatment for EOC is maximal cytoreductive surgery and platinum-based chemotherapy. However, about 80% of the patients experienced relapse within 1–2 years (Kim et al., 2012).

In recent years, olaparib, a poly ADP-ribose polymerase (PARP) inhibitor, provides a new modality for treating ovarian cancer. Substantial clinical benefit has been shown in trials such as SOLO1 (Moore et al., 2018), SOLO 2 (Poveda et al., 2020), and Study 19 (Friedlander et al., 2018). Olaparib is the first-class inhibitor of PARP enzymes, including PARP1, PARP2 and PARP3. Olaparib has been approved by US Food and Drug Administration (FDA) for the following indications: 1) maintenance treatment of recurrent ovarian cancer (including epithelial ovarian, fallopian tube or primary peritoneal cancer) in adults who are in complete or partial response (CR or PR) to platinum-based chemotherapy (also called "recurrence maintenance"); 2) first-line maintenance treatment for deleterious or suspected deleterious somatic or germline BRCA-mutated (sBRCAm or gBRCAm) advanced ovarian cancer patients who are in CR or PR to first-line platinum-based chemotherapy (also called "first-line maintenance"); 3) first-line maintenance treatment for advanced ovarian cancer in combination with bevacizumab for adult patients who are in CR or PR to first-line platinum-based chemotherapy and with homologous recombination deficiency (HRD) positive status; and 4) treatment of adults with deleterious or suspected deleterious gBRCAm advanced ovarian cancer who have been treated with ≥3 prior lines of chemotherapy (US Food And Drug Administration, 2020). In China, olaparib is approved only for the first two indications.

Patients treated with oral antitumor agents are likely to have less frequent contact with healthcare professionals. As a result, patient safety, drug adherence, medication therapy monitoring, and timely follow-up might be compromised (Krikorian et al., 2019). As shown in SOLO-1 trial, SOLO-2 trial and Study 19, commonly seen olaparib-induced adverse drug reactions (ADR) were fatigue (67%, 66% and 63% respectively), anemia (38%, 44% and 23%), thrombocytopenia (11%, 14% and 4%), neutropenia (17%, 19% and 5%), nausea (77%, 76% and 71%), vomiting (40%, 37% and 35%), diarrhea (37%, 33% and 28%), and dysgeusia (26% and 27% respectively for Solo-1 and Solo-2 trials, not reported in Study 19). The consequences of severe adverse reactions are usually catastrophic, in particular, hematological ADRs are typically difficult to identify, especially in the absence of regular monitoring. Most of the patients receiving olaparib are middle-aged or elderly who commonly receive different medications for chronic conditions, such as anti-hypertensives, anti-hyperglycemics and anti-hyperlipidemia medications. Therefore, patients would benefit from regular professional evaluation and guidance on potential drug-drug interactions (DDIs) as well as other drug-related problems.

Oncology clinical pharmacists, as members of the healthcare team, are playing important roles in delivering care (such as drug selection, dose adjustment, ADR monitoring, identification and management of DDIs etc.) (Riu-Viladoms et al., 2019; Wang et al., 2020a; Wang et al., 2020b). Recently, oncology pharmacists have demonstrated their contributions in optimizing treatment outcomes and enhancing patient satisfaction in follow-up programs for oral antitumor drugs (Bertsch et al., 2016; Ribed et al., 2016; Riu-Viladoms et al., 2019; Collado-Borrell et al., 2020; Khrystolubova et al., 2020). They have also assumed active roles in developing clinical guidelines and expert consensuses on safe and rational medication use in oncology practice (Holle and Boehnke, 2014; Li et al., 2019a; Li et al., 2019b; Li et al., 2019c; Yang et al., 2020).

Olaparib was approved at the end of 2018 in China. So far, little has been reported about the services provided by oncology pharmacists during olaparib treatment. In order to address this challenge, an oncology pharmacist-driven follow-up program was established to provide pharmaceutical care for ambulatory ovarian cancer patients (including epithelial ovarian, fallopian tube or primary peritoneal cancer patients) receiving olaparib in a tertiary cancer-specialized hospital in China. The aim of this study led by

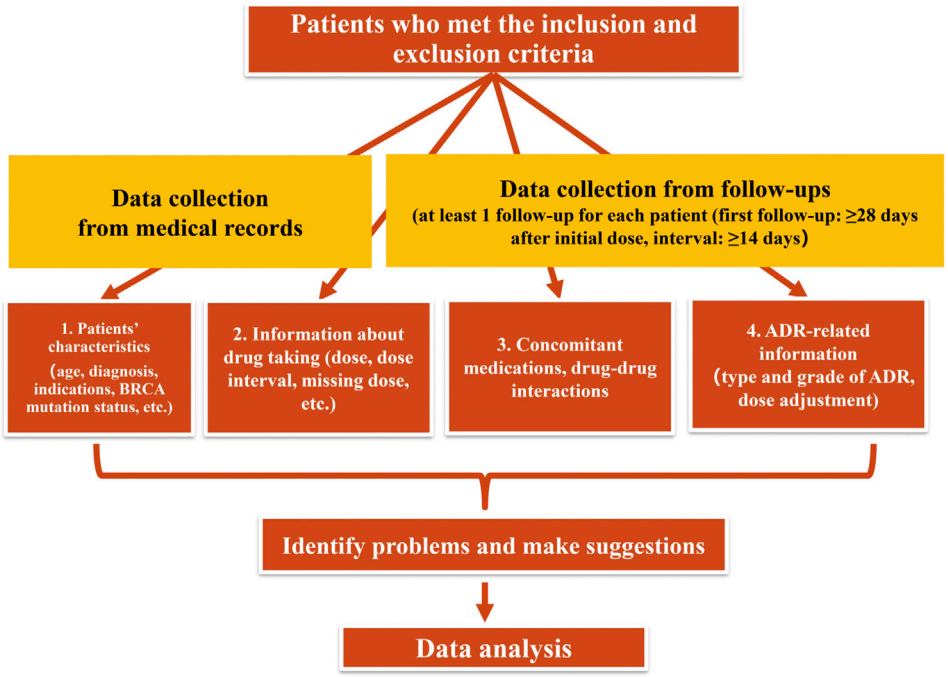

FIGURE 1
Flowchart of the study.

pharmacists was to establish a follow-up program for ovarian cancer patients receiving olaparib, provide patient education, get information on adverse drug reactions (ADRs), identify and manage drug-related problems.

Materials and methods

Inclusion criteria: Female ambulatory patients (≥18 years old) with ovarian, fallopian tube, or primary peritoneal cancers who were receiving olaparib.

Exclusion criteria: Patients who were not able to or unwilling to answer follow-up calls.

In this prospective study conducted from November 2019 to March 2021, the clinical pharmacists made at least one follow-up telephone call for each eligible patient during their treatment, the following data were obtained during the follow-up: 1) dosage and frequency of olaparib; 2) changes in olaparib dosing; 3) type and grade of olaparib-induced ADRs; 4) drug adherence (assessed by asking whether patients had any missing doses); 5) concomitant medications and clinically significant DDIs and drug-food interactions; 6) type and number of suggestions to the patients made by the clinical pharmacists; 7) duration of the follow-up; 8) number of follow-up calls for each patient. Additional medical information, such as age, diagnosis, BRCA mutation status, etc. were collected from electronic medical records. The flowchart of the follow-up was described in Figure 1.

TABLE 1 Patients' characteristics.

Item	N (%)
Total number of patients	83 (100%)
Age (years)	
<60	48 (57.83%)
≥60	35 (42.17%)
Median age (range)	58 (35–82)
Diagnosis	
Ovarian cancer	81 (97.59%)
Fallopian tube cancer	1 (1.20%)
Ovarian and fallopian tube cancer	1 (1.20%)
BRCA status	
BRCA1 mutation	24 (28.92%)
BRCA2 mutation	7 (8.43%)
BRCA1/2 mutation (not recorded exactly)	3 (3.61%)
No mutation	15 (18.07%)
Not known	34 (40.96%)
Indication for olaparib	
Maintenance treatment after first-line chemotherapy	23 (27.71%)
Maintenance treatment after recurrence	58 (69.88%)
Unknown	2 (2.41%)
The initial dose of olaparib	
600mg/d	81 (97.59%)
450mg/d	2 (2.41%)

TABLE 2 Incidence of olaparib-induced ADRs.

Adverse drug reactions	All grades	Incidence (%)	Grades 3/4	Incidence (%)
Fatigue	34	40.96	3	3.61
Anemia	30	36.14	6	7.23
Leukopenia	30	36.14	2	2.41
Nausea	24	28.92	0	0.00
Thrombocytopenia	14	16.87	2	2.41
Anorexia	14	16.87	0	0.00
Dyspepsia	13	15.66	0	0.00
Pain (excluding gastrointestinal pain and headache)	8	9.64	0	0.00
Oral mucositis	7	8.43	1	1.20
Vomiting	6	7.23	0	0.00
Dysgeusia	5	6.02	0	0.00
Rash maculo-papular	4	4.82	0	0.00
Constipation	3	3.61	0	0.00
Dizziness	3	3.61	0	0.00
Insomnia	3	3.61	0	0.00
Gastrointestinal pain	2	2.41	0	0.00
Headache	2	2.41	0	0.00
Hypersomnia	2	2.41	0	0.00
Hypotension	2	2.41	0	0.00
Aminotransferase increased	2	2.41	0	0.00
Diarrhea	1	1.20	0	0.00
Edema limbs	1	1.20	0	0.00
Alopecia	1	1.20	0	0.00
Creatinine increased	1	1.20	0	0.00
Tachycardia	1	1.20	0	0.00

Adverse drug reactions were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0.

Two well-trained independent pharmacists performed the causality assessment of ADRs using the World Health Organization-Uppsala Monitoring Centre causality scale (WHO-UMC causality scale). The DDIs were assessed by two independent pharmacists and the assessment was mainly based on databases "UpToDate" and "Drugs.com".

Statistical analysis

Data processing was performed using SPSS 22.0 statistical software (SPSS Inc., Chicago, USA). All data are expressed as numbers (n) or percentages (%). Categorical variables were analyzed with the χ test. A P value of <0.05 was defined as statistically significant.

Results

Patient's characteristics

Eighty three patients were enrolled in the study and included in the analysis. The total number of the follow-up phone calls were 109, and the total duration of all the follow-up calls were 1,440 min. There were 2 patients whose data for the duration of the follow-up were not recorded. On average, each patient

TABLE 3 The tolerability profile among patients receiving olaparib due to different lines of treatment.

	Number (%)	Indications of olaparib			F	*P* Value
		Maintenance after first-line chemotherapy	Maintenance after recurrence chemotherapy	Not known		
Blood and lymphatic system disorders	—	—	—	—	1.373	0.547
With	47 (56.63%)	12	33	2	—	—
Without	36 (43.37%)	11	25	0	—	—
Gastrointestinal disorders	—	—	—	—	3.011	0.177
With	43 (51.80%)	10	33	0	—	—
Without	40 (48.20%)	13	25	2	—	—
Metabolism and nutrition disorders	—	—	—	—	1.706	0.537
With	14 (16.87%)	2	12	0	—	—
Without	69 (83.17%)	21	46	2	—	—
General disorders	—	—	—	—	2.491	0.235
With	39 (46.99%)	12	25	2	—	—
Without	44 (53.01%)	11	33	0	—	—
Nervous system disorders	—	—	—	—	2.617	0.299
With	11 (13.25%)	3	7	1	—	—
Without	72 (86.75%)	20	51	1	—	—
Skin and subcutaneous tissue disorders	—	—	—	—	0.778	1.000
With	5 (6.02%)	1	4	0	—	—
Without	78 (93.98%)	22	54	2	—	—
Miscellaneous	—	—	—	—	5.500	0.066
With	8 (9.64%)	1	5	2	—	—
Without	75 (90.36%)	22	53	0	—	—

The classification of adverse drug reactions was based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0.

received 1.31 follow-up calls, and the average duration was 17.78 min. Other information such as age, diagnosis, BRCA mutation status, and the initial dose of olaparib is shown in Table 1.

Drug adherence

There were 36.15% of patients had missed one or more doses of olaparib. Most patients missed doses because they forgot to take the drug, while some patients missed doses intentionally because they had concerns about potential DDIs. For example, one patient who was receiving concurrent ibuprofen intentionally missed one olaparib dose every day because she was afraid of the potential DDI between ibuprofen and olaparib. For patients who had missed doses, we asked patients for the exact reasons for missing the doses, educated patients about the importance of adherence, and made the following suggestions: 1) use tools to aid adherence (such as pill boxes, alarms, calendars, daily routines); 2) ensure timely orders for refill; 3) confirm with physicians or pharmacists when they have to take additional medications and have concerns about DDIs.

Tolerability profiles of olaparib-induced adverse drug reactions

In this study, the most common ADRs (incidence≥10%) were: fatigue (40.96%), anemia (36.14%), leukopenia (36.14%), nausea (28.92%), thrombocytopenia (16.87%), anorexia

TABLE 4 Concomitant medications in patients receiving olaparib.

Concomitant medications	Types of medications (%)
Anti-tumor medications	5 (6.2%)
Altretamine	1
Letrozole	1
Thalidomide	1
Megestrol	1
Apatinib	1
Medications for chronic diseases	42 (51.9%)
Anti-hypertensive medications	17
Anti-hyperglycemic medications	6
Anti-hyperlipidemic medications	3
Anti-platelet medications	1
Neuropsychiatric medications	3
Others	12
Other medications with unknown potential for DDIs or without specific name (or without exact chemical contents)	34 (42.0%)
Health products (or food supplements)	2
Medications without exact name	6
Formulated Chinese medicines	16
Chinese decoction	10

TABLE 5 DDIs identified by the pharmacists.

Concomitant medications	Risk rating	Reason for the interaction	Suggestions made by the pharmacists
Acarbose and hydrochlorothiazide	C (monitor therapy)	Hydrochlorothiazide may diminish the therapeutic effect of acarbose	Closely monitor blood glucose by lab test
Metformin and hydrochlorothiazide	C (monitor therapy)	Hydrochlorothiazide may diminish the therapeutic effect of metformin	Closely monitor blood glucose by lab test
Glimepiride and acarbose	D (consider therapy modification)	Acarbose may enhance the hypoglycemic effect of glimepiride	Closely monitor blood glucose by lab test and to have an endocrinologist to assess the potential use of an alternative medication
Glimepiride and metformin	C (monitor therapy)	Metformin may enhance the hypoglycemic effect of glimepiride	Closely monitor blood glucose by lab test

(16.87%), dyspepsia (15.66%). The incidence of all the ADRs (all grades) and all the severe ADRs (grades 3–4) were tabulated in Table 2. There were 27.71% of the patients who had dose adjustments due to ADRs. In addition, we also compared the ADR profiles among different groups of patients, and the result showed that the tolerability in patients treated with olaparib for "first-line maintenance" was not different with those for "recurrence maintenance" (Table 3).

Concomitant medications and DDIs

The pharmacists recorded all the concomitant medications (including patent and generic medications, formulated Chinese medicine and Chinese decoctions, and food supplements) and evaluated potential DDIs for all the patients in the study. 57 patients were found to have 81 types of concomitant medications (Table 4). The pharmacists identified four

TABLE 6 Suggestions made by the pharmacists.

Item	Number of suggestions (%)
Recommendations on obtaining relevant lab test to monitor ADRs on a regular basis	51 (26.02%)
Recommendations on rational use and contacting physicians for dosage adjustment for olaparib	36 (18.37%)
Recommendations on seeking medical care	25 (12.76%)
Recommendations on drug-food interactions	23 (11.73%)
Recommendations on modification of eating habits for preventing specific ADRs	23 (11.73%)
Recommendations on DDIs	18 (9.18%)
Recommendations on management of ADRs	13 (6.63%)
Recommendations on life style modification for preventing specific ADRs	7 (3.57%)
Total number of suggestions	**196**

clinically significant DDIs, involving 4 types of medications in two patients, and provided suggestions for management (Table 5). It is important to note that some patients were taking concomitant Chinese decoction or formulated Chinese medicine, whose interactions with olaparib were unknown or difficult to evaluate (due to the complexity of their contents). The pharmacists therefore recommended patients to take olaparib and Chinese decoction (or formulated Chinese medicine) separately, with at least 2 h in-between to try to avoid potential DDIs.

Suggestions made by the pharmacists

During the follow-up, the pharmacists identified drug-related problems and made 196 suggestions to the patients. Some patients were not aware of the importance and the frequency of obtaining lab tests to monitor ADRs, and we suggested them that the frequency could be once every week at the beginning of olaparib treatment, and then once every 2–4 weeks when stable. Some patients had developed grade 2 or higher ADRs, and we suggested them to contact physicians for dose adjustments. Some patients were taking olaparib with a wrong frequency, and we suggested them to take it twice a day with the best frequency of 12 h. Some patients were not aware that limes and grapefruits should not be taken concomitantly with olaparib, and we suggested that it was best not to eat these fruits during the treatment and explained the underlying reasons. The nature/types of the suggestions as well as the number and percentage for each type are tabulated in Table 6.

Questions raised by patients during the follow-up phone calls

During the follow-up phone calls, aside from responding to questions raised by the pharmacists, some of the patients (36/83, 43.37%) positively raised some questions about the drug. For example, some patients were curious about the duration of the treatment, and we told them that this should be determined by physicians with both evaluations of the efficacy and the ADRs. Some patients were complaining that it was difficult to refill the prescriptions during the COVID-19 pandemic and asking for our advice, and we patiently told them the ways to make appointments online or by telephone. Some patients were curious about the nature and the purpose of the follow-up, and we explained that this work was conducted to identify drug-related problems and offer professional suggestions for the patients. A total of 54 questions were raised, which have been classified into 8 types. The pharmacists answered the questions and resolved the patients' confusion. The number and percentage of each type of the questions are tabulated in Table 7.

Discussion

The study provides the first report about pharmacist-led follow-up service for olaparib and portrayed several characteristics for these patients in the real world: 1) the types of ADRs were similar to those previously observed in clinical trials, and the profiles of ADRs in different types of patients (first-line maintenance vs. recurrence maintenance) were also similar; 2) there were 36.14% of the patients had missed olaparib doses, indicating drug adherence is not very good; 3) there were 42% of the patients who were concomitantly taking medications without exact chemical contents (such as formulated Chinese medicines and Chinese decoctions), and common types of concomitant medications with exact drug names were antihypertensive, anti-hyperglycemic, and anti-hyperlipidemic medications; 4) the pharmacists identified 4 clinically significant Drug-drug interactions (DDIs) in two patients; 5) pharmacists made 196 suggestions mainly related to rational use of the medications and management of ADRs.

TABLE 7 Questions from patients during the follow-up sessions.

Types of the questions	Number of questions (%)
Drug information (such as ADRs, dosage, half-life, etc.)	12 (22.22%)
DDIs	3 (5.56%)
Drug-food interactions	9 (16.67%)
The nature of the follow-up performed by pharmacists	9 (16.67%)
Seeking medical care and filling prescriptions	6 (11.11%)
Treatment efficacy	4 (7.41%)
Course of the treatment	6 (11.11%)
Treatment costs (including medical insurance coverage)	5 (9.26%)
Total number of questions	**54**

In this study, we found that the most common ADRs (incidence≥10%) were: fatigue, anemia, leukopenia, nausea, thrombocytopenia, anorexia, dyspepsia. Most of the patients experienced grades 1–2 ADRs. 16.87% (14/83) of the patients developed grades 3–4 ADRs, including severe fatigue, anemia, leukopenia, thrombocytopenia and oral mucositis. In general, these ADRs were manageable, as indicated by the relatively low proportion of patients who required olaparib dosage adjustment due to the ADRs (23/83, 27.71%). Previously, in a pooled safety analysis with data from 2,351 patients (1,585 patients among them were exposed to 300 mg olaparib tablet, twice a day, and 766 patients were exposed to 400 mg olaparib capsule, twice a day), the types of the most common adverse reactions in ≥10% of the patients were similar to those reported in our study (US Food And Drug Administration, 2020). Additionally, we have been the first to report that there was no significant difference of the incidence of ADRs between patients who used olaparib as "first-line maintenance" and those used it as "recurrence maintenance", indicating that the methods of ADR management in these groups of patients could be generally the same.

Adherence is defined as the degree to which one conforms to provider's instructions on day-to-day treatment with respect to the timing, dosage, and frequency (Cramer et al., 2008). Adherence is important in improving outcomes of chronic diseases and has been shown to be associated with reduction in healthcare costs (Sokol et al., 2005). There are several ways (direct, indirect, indirect and subjective ways) to measure adherence, but none of them has been considered a "gold standard". The direct ways are either direct observation or measurement of serum drug levels. The indirect ways include 1) pill counts; 2) microelectronic event monitoring system; 3) refill records; 4) biomarkers; and 5) outcomes. The indirect and subjective ways are 1) self-report; 2) others' assessment; and 3) diaries (Geynisman and Wickersham, 2013). In our study, we used "self-report" as the single indicator for adherence. Our results show that 36.15% of patients had missed one or more doses of olaparib, indicating that patient education about the importance of adherence is very necessary. Besides, it is worth noting that it could be more objective to evaluate adherence with combined ways in further studies.

Olaparib is primarily metabolized by CYP 3A4/5. Potent CYP3A inhibitors (such as itraconazole, clarithromycin, voriconazole, lopinavir/ritonavir) and potent CYP3A inducers (such as phenytoin, rifampicin, carbamazepine) should not be used concomitantly with olaparib. Additionally, food containing CYP3A inhibitors should also be avoided, such as grapefruit (or grapefruit juice) and lime (or lime juice). In this study, there was no patient concomitantly using potent CYP3A inhibitors or inducers, and we only identified four clinically significant DDIs. However, it is worth noting that many patients were taking concomitant Chinese decoction or formulated Chinese medicine, whose interactions with olaparib were unknown or difficult to evaluate (due to the complexity of their contents). This is a very common and important phenomena in Chinese patients. Further study could be focused on looking for ways to get to know the full formula of the Chinese decoctions and develop databases for analyzing DDIs among Chinese decoctions and western medicines.

In addition to evaluating potential DDIs and making related recommendations, the pharmacists also initiated other suggestions that were important to optimize treatment, such as: 1) reminding patients the need to regularly monitor ADRs with relevant lab tests at a clinic; 2) making recommendations to patients on rational drug usage and contacting physicians for dosage adjustment; 3) giving advice on avoiding potential drug-food interactions; 4) making recommendations to patients on management of ADRs. It is worth noting that all the recommendations were provided directly to the patients. The reasons for this are that, 1) in China, pharmacists have no prescription rights; 2) the number of outpatients is very big in large hospitals; 3) outpatients in the same department are from

many different physicians. For these reasons, when pharmacists identify that there is a need for patients, especially outpatients, to change the prescription, they usually suggest them to directly contact the physicians, rather than making suggestions to the physicians. The shortcoming of this is that it is not convenient to evaluate the roles of pharmacists (e.g., the acceptance rate of the suggestions made by the pharmacists to physicians). However, in some countries, pharmacists work with physicians in many kinds of collaborative programs under specific agreements, in this case the impact of services provided by pharmacists could be better demonstrated. For example, Conliffe and colleagues reported a pharmacist-run oral antineoplastic monitoring program and its impact on improving therapy adherence. In this program, pharmacists made clinically significant interventions and received high patient satisfaction, providing justification for service expansion into other disease states (Conliffe et al., 2019). Khrystolubova and colleagues reported a pharmacist-led, multi-center, collaborative patient education and proactive ADR management program in a community-based oncology setting. They showed that ADRs in patients with EGFRm+ non-small cell lung cancer receiving afatinib were well managed by this pharmacist-led service (Khrystolubova et al., 2020). Suzuki and colleagues collaborated with medical oncologists to establish an integrated support program aimed at preventing unnecessary treatment interruption or dose reduction during oral lenvatinib targeted therapy. They showed that the interventions provided by pharmacists and medical oncologist improved lenvatinib therapy, by adding supportive medications for management of ADRs and correcting mistakes in taking medications (Suzuki et al., 2020). Hansen and colleagues reported a Collaborative Drug Therapy Management (CDTM) program in the gynecologic oncology clinic, and they demonstrated that pharmacists (with authorities to order lab tests and prescribe certain medications in accordance with CDTM program agreements) managed chemotherapy-related adverse reactions and provided therapeutic interventions. Additionally, both patients and physicians reported that such collaborative services were valuable (Hansen et al., 2016). To improve our service, we are now planning to establish a physician-pharmacist collaborative program for ambulatory patients, in which pharmacists and physicians would work closer to provide services to patients in a real-time fashion, and share professional opinions with each other in a more convenient way.

Limitations

First, the sample size of the study is relatively small. Second, only one indicator was used to evaluate patients' adherence. Third, the direct impact and the roles of pharmacists could be better demonstrated by having a comparison group of patients without follow-up service conducted by pharmacists.

Conclusion

The study provides the first report about pharmacist-led follow-up for olaparib. The types of ADRs were similar to those previously observed in clinical trials, and the profiles of ADRs in different types of patients (first-line maintenance vs. recurrence maintenance) were also similar. Pharmacists identified drug-related problems (such as adherence, DDIs and management of ADRs) and offer suggestions for the patients.

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 human participants were reviewed and approved by Independent Ethics Committee, National Cancer Center/Cancer Hospital Chinese Academy of Medical Sciences and Peking Union Medical College. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YW designed the study, conducted the majority of the follow-up and prepared the manuscript. DD was responsible for a part of the follow-up, the data analysis and revised the manuscript. JY, AL, YD, and WQ contributed to the development and revision of the manuscript. NL and GL were responsible for the design and conduct of the study as well as the revision of the manuscript. All authors read and approved the final manuscript.

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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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Perceptions of healthcare professionals and patients on the role of the pharmacist in TB management in Pakistan: A qualitative study

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Background: Globally, tuberculosis (TB) is the second major cause of death from infectious diseases, particularly in developing countries. A multidisciplinary approach to the management of TB may help to curb the disease burden.

Objective: The objective of this study was to outline the perceptions of healthcare professionals and patients regarding the potential role of pharmacists in TB management in Pakistan.

Method: This was a large-scale qualitative study conducted at the Chest Disease Unit (CDU) of the Bahawal Victoria Hospital (BVH), Punjab, Pakistan. Data were collected through semi-structured interviews with physicians, pharmacists, and patients recruited using a mix of convenient and snowball sampling. The sample size was decided through standard saturation point criteria. All interviews were audio recorded and transcribed verbatim. The data were analyzed to draw conclusions using a thematic analysis approach.

Results: Analysis of the data yielded 19 categories and seven themes. Physicians considered pharmacists qualified healthcare professionals, whereas patients considered them merely dispensers. Inventory management and dispensing of medicines were considered as major responsibilities of pharmacists. Physicians were extremely overburdened and wanted to delegate certain duties to pharmacists, subject to their prior extensive trainings. However, most of the physicians were unaware of the legal scope of pharmacy practice in Pakistan. With regard to the potential duties of pharmacists, physicians, pharmacists, and patients (patients—upon explaining the potential roles during the interview) endorsed monitoring, counseling, medicine brand selection, dose adjustment, inventory management, dispensing, and polypharmacy assessment as their potential roles. In view of all stakeholders, the rationale for integrating pharmacists in TB management included overburdened physicians, sub-standard patient care, medication safety issues, and patient dissatisfaction.

The healthcare professionals highlighted that the major barriers to integrating pharmacists within the TB management system were limited interest of regulatory authorities and policy makers, followed by inadequate training and experience-driven questionable competency of pharmacists.

Conclusion: The study participants acknowledged the potential role of pharmacists in TB management. However, it was emphasized that healthcare policy makers should devise strategies to overcome the underlying barriers before assigning medicine-related clinical roles to pharmacists.

KEYWORDS

pharmacist, tuberculosis management, multidisciplinary approach, patient centered care, National Tuberculosis Control Program of Pakistan, Pakistan, FIP

Background

The global burden of tuberculosis (TB) is significant and will remain a major public health issue worldwide unless addressed with some vigor (World Health Organization, 2010). According to a recent report, two-thirds of the total disease burden is borne primarily by eight countries: India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa (in descending order) (World Health Organization, 2017). Despite the fact that effective TB therapy has been available for more than half a century and the overall TB mortality rate has fallen by 9.2% (2015–2020), TB killed approximately 1.3 million people globally in 2020 (World Health Organization, 2017).

In the developing countries, insufficient access to diagnosis and treatment, co-existence of TB with other diseases such as diabetes and human immunodeficiency virus (HIV), and an increase in the incidence of multidrug-resistant TB (MDR-TB) are considerable challenges that need to be addressed for its effective management (Sia and Wieland, 2011; Atif et al., 2014). Moreover, the necessary education of TB patients about the disease and its treatment is important for the achievement of desirable outcomes (Kulkarni et al., 2013). In the traditional context, physicians prescribe medicines, and pharmacists compound and dispense these medicines (Richardson and Pollock, 2010; Gokcekus et al., 2012). However, there is evidence that a patient-centered approach based on the involvement of a multi-disciplinary team (including a pharmacist) is helpful for the effective management of a disease as calamitous as TB (Cipolle et al., 2012; Armor et al., 2014). Pharmacists can play a significant role in direct patient care. For example, counseling by pharmacists can minimize missing dose scenarios and aid in promoting adherence to anti-TB treatment, which are main barriers to favorable treatment outcomes in Pakistan (Atif et al., 2016a; Atif et al., 2018; Khan et al., 2019; Atif et al., 2020a; Atif et al., 2020b; Atif et al., 2021). Besides, appropriate medicine use and self-care practices can be improved through patient/caregiver education on medication use and disease control and prevention. Likewise, pharmacists can assist physicians in evidence based clinical practice by assessing patients for drug resistance and analyzing therapeutic problems and patients' pharmaceutical care needs, such as pain control, nutrient replacement, rationale prescribing, and managing comorbidities. Similarly, pharmacists hold well-proven expertise in monitoring therapy for effectiveness, adverse drug reactions (ADRs) and drug interactions, posology, and post-discharge counseling, thereby ensuring medication safety (Mitrzyk, 2008; Mkele, 2010).

Pakistan ranks fifth among TB high burden countries (HBCs), which should be a point of concern for policymakers (National Tuberculosis Control Programme Pakistan, 2016; World Health Organization, 2021). This partially might be attributed to a shortage of TB management staff, lengthy treatment courses, side effects associated with anti-TB drugs, resistance to first-line anti-TB drugs, and the disappearance of signs and symptoms of TB after partial anti-tuberculosis treatment (ATT) (Atif et al., 2014; Atif et al., 2017a). Alongside poor health literacy, stigma associated with the disease, and poor financial status of TB patients and their families, these factors further complicate the TB treatment cascade (Khan et al., 2022a). In addition, inequality in healthcare services and/or limited access to alternative treatment, for example, for patients residing in rural areas or distant areas, halts the achievement of national TB-related targets (Khan et al., 2022a). With regard to healthcare professionals, Pakistan's Ministry of Finance in Economic Survey 2020–2021 indicated that a single physician caters to the needs of hundreds of patients requiring treatment (Ministry of Finance, 2021). It was also reported that the mean consultation time (1.2 min–2.2 min) and the dispensing time (8.7 s–38 s) in the public sector facilities of Pakistan were suboptimal (Atif et al., 2016b; Atif et al., 2016c). Most of the pharmacists (20 per tertiary care hospital and 1–2 per secondary care hospital) performed their role in medicine management but did not provide any direct patient care.

TABLE 1 Inclusion criteria.

Inclusion criteria
Physicians working in the chest disease unit for at least three months
Pharmacists currently working in the chest disease unit for at least three months or who had worked in the chest disease unit for at least one year
Patients aged ≥ 18 years of age suffering from pulmonary tuberculosis for at least three months

Given the aforementioned facts, including increase in TB burden (World Health Organization, 2021), shortage of TB management staff and poor patient adherence, integration of pharmacists in TB management seems very much value-added (Kulkarni et al., 2013; Atif et al., 2016d; Khan et al., 2022a). Unfortunately, the importance of pharmacists in direct patient care is not recognized as an important and integral part of the Pakistani healthcare system (Atif et al., 2017a), regardless of the fact that the Drug Regulatory Authority of Pakistan (DRAP) Act 2012 acknowledges the advanced patient-oriented roles of pharmacists. Given that, research on this aspect was required to guide policy and practice reforms. Since physicians are key players in Pakistan's healthcare system, their perspective on the patient-oriented roles of pharmacists was important. Moreover, it was equally important to know whether pharmacists were ready to take on these advanced roles. Being the ultimate beneficiary of any healthcare system, the perspective of patients was also required in this regard. Therefore, this study was conducted to gain insight into the perceptions of physicians, pharmacists, and patients about the role of pharmacists in TB management in Pakistan.

Methods

Study setting

The study was conducted at the Chest Disease Unit (CDU) of the Bahawal Victoria Hospital (BVH), Punjab, Pakistan. This tertiary care hospital has more than 1,600 beds and delivers services throughout all medical and surgical specialties. A monthly average of 90,000 patients is served by about 350 physicians, 20 pharmacists, 400 nurses, and 3,000 paramedics (Atif et al., 2017b). The CDU (60 bedded facility) is one of the major departments of BVH. 6–8 TB medical consultants, 3–5 medical officers, 6–8 postgraduate residents (serving inpatients), 6–8 house officers, one pharmacist, and 57 nurses serve TB patients and other patients with chest-related diseases. Currently, along with a permanent hospital-based pharmacist, a specialist pharmacist is appointed by the provincial TB control program, essentially supervising MDR-TB cases. The Global Fund and the National Tuberculosis Control Program of Pakistan (NTP) fund the TB sub-division of the CDU (Atif et al., 2016d).

Study design

A qualitative study design was employed, where face-to-face interviews were conducted with healthcare professionals (i.e., physicians and pharmacists) and patients using a semi-structured interview schema. The inclusion criteria for the respondents are provided in Table 1. Sample size was determined by applying the saturation point criteria (Morse, 2000).

Interview schema development

The interview schema was developed through formulating questions that answer the research problem and address gaps in the literature (Atif et al., 2016a; Atif et al., 2018; Khan et al., 2019; Atif et al., 2020a; Atif et al., 2020b; Atif et al., 2021). The patient and health professional interview schemas had six and seven questions (with additional sub-questions), respectively. The interview schema included questions about the importance of pharmacists in TB management, the roles that pharmacists currently play, and what roles are expected of them in the future. In addition, the barriers to and facilitators of integrating pharmacists into the TB management system and the perceived benefits of doing so were also inquired about. Before conducting the interviews, schema was administered to one participant from each cohort to ensure its uniformity and face validity. These pilot interviews were not included in the final analysis. To clarify the role of the pharmacist with the patients, Box 1 was used in the interview process (see Box 1).

Data collection

The study was conducted in three stages. In the first stage, physicians (registered with the Pakistan Medical and Dental Council) were interviewed to explore their perspectives regarding the roles of pharmacists in the TB management process. In stages 2 and 3, patients and pharmacists (registered with the Pakistan Pharmacy Council) were interviewed, respectively. Data were collected between 1st February and 31st May 2017. A mix of convenient and snowball sampling was used to engage healthcare

BOX 1 Role of the pharmacist explained to the patients

- Provide medicine-related information
- Counsel the patient about medicine use
- Answer the queries of patients related to their medicines
- Assess the patient's medication for appropriateness and safety
- Observe the effects of medicines in patients
- Early detection and resolution of adverse drug events in patients
- Design a therapeutic regimen tailored to an individual patient's particular needs
- Promote adherence to medication

professionals. Most of the healthcare professionals working in the CDU were difficult to reach because they were preoccupied with their routine clinical duties. Therefore, a convenient sampling method was deemed most appropriate, and interviews were conducted with individuals who were easiest to find and who consented to participate. After the initial stage of the convenient sampling method, a snowball sampling strategy was adopted, in which existing study subjects made recommendations and helped in the recruitment of future study subjects from among their colleagues and acquaintances. Patients were recruited using a convenient sampling method because they were reluctant to participate in the study and were exhausted due to long waiting hours.

Data analysis

The data were analyzed using an inductive thematic analysis approach (Boyatzis, 1998). A verbatim translation of all the interviews was undertaken. The audio recordings of the interviews were listened to several times, and the written transcripts were also read several times inorder to immerse oneself in the data and develop a rich and deep understanding of it. After considerable discussion, meaningful data were extracted from each case, and particular codes were assigned to them. The coded data were read again and again and carefully analyzed to reduce and organize the same information and subsequently draw categories and themes (Starks and Brown Trinidad, 2007) Cross-checking was undertaken at each step of the analysis to ensure credibility and enhance the trustworthiness of the data (Lincoln and Guba, 1985).

Ethics approval and consent to participate

Ethical approval was obtained from the Pharmacy Research Ethics Committee (PREC) at the Islamia University Bahawalpur (Reference: 42–2016/PREC). Prior to conducting interviews, the purpose of the study was explained to all participants (patients and healthcare professionals). Signed, written, informed consent was obtained from all study participants. The identity of the respondents (names and personal identifiers) was protected by assigning them a participant number.

Results

A total of 30 healthcare professionals and 17 patients were initially approached, while 27 (90% response rate) healthcare professionals and 15 (88% response rate) patients consented to participate. Three healthcare professionals declined to participate in the study due to their busy work schedules (two) and lack of interest in the study (one). After reaching saturation point (14th interview for physicians, the 8th interview for pharmacists, and 11th interview for patients), one additional interview with each cohort of participants was conducted to confirm saturation in the emerged data. Among physicians, 10 were males and 5 were females, and among pharmacists, 4 were males and 5 were females. There were 10 male patients and 2 female patients. The average interview duration of physicians, pharmacists, and patients was 29.9 min (SD = 5.1), 28.4 min (SD = 5.3), and 22.2 min (SD = 2.7), respectively. The age range of the respondents was 2152 years. The characteristics of the respondents are provided in Table 2.

Thematic analysis

The data analysis process yielded seven themes and 19 categories representing the perspectives of study participants about pharmacists and their potential roles, rationale for integrating pharmacists in TB management, together with barriers and facilitators to efficient integration. For clarification, it is stated that patient-related findings under themes 1 and 3 depict their views before providing the information mentioned in Box 1 (potential role of pharmacists in TB management), while their views enclosed in themes 4 and 5 belong to a post-information inquiry. The emergent themes, categories, and supporting quotations are outlined in Table 3.

Theme 1: Pharmacists: Who are they?

Most of the physicians (13 out of 15) described pharmacists as experts in medicines, having sound knowledge of the pharmacokinetics and pharmacodynamics of drugs. However, very few patients (3 out of 12) were aware of pharmacists and their duties. Most of the patients (9 out of 12) were completely unaware of the pharmacist and their role and believed that the pharmacist was merely a medication dispenser who was employed in medical stores and provided

TABLE 2 Characteristics of the respondents.

Healthcare professionals				Patients			
Respondent	**Gender**	**Specialization/ qualification**	**Interview duration*(minutes)**	**Respondent**	**Gender**	**Qualification**	**Interview duration*(minutes)**
Physician 1	Male	Pulmonologist	31	Patient 1	Male	¶Secondary	22
Physician 2	Female	Pulmonologist	29	Patient 2	Male	Secondary	18
Physician 3	Male	Pulmonologist	44	Patient 3	Male	Secondary	24
Physician 4	Female	Pulmonologist	32	Patient 4	Male	Secondary	25
Physician 5	Male	Pulmonologist	35	Patient 5	Male	Secondary	22
Physician 6	Male	Pulmonologist	32	Patient 6	Male	Secondary	25
Physician 7	Male	Pulmonologist	27	Patient 7	Male	Secondary	19
Physician 8	Female	Pulmonologist	29	Patient 8	Male	Secondary	20
Physician 9	Female	Pulmonologist	26	Patient 9	Female	§Primary	19
Physician 10	Male	Pulmonologist	32	Patient 10	Male	Secondary	22
Physician 11	Male	Graduate	24	Patient 11	Female	Primary	24
Physician 12	Male	Pulmonologist	23	Patient 12	Male	Secondary	26
Physician 13	Male	Pulmonologist	29				
Physician 14	Male	Pulmonologist	27				
Physician 15	Female	Pulmonologist	29				
Pharmacist 1	Male	Graduate	24				
Pharmacist 2	Female	Post graduate	26				
Pharmacist 3	Male	Post graduate	35				
Pharmacist 4	Male	Graduate	23				
Pharmacist 5	Female	Post graduate	28				
Pharmacist 6	Female	Post graduate	38				
Pharmacist 7	Female	Graduate	23				
Pharmacist 8	Female	Graduate	31				
Pharmacist 9	Male	Graduate	28				

*Rounded, §primary (≤ 5 years of education), ¶secondary (6–13 years of education), tertiary (≥ 14 years of education).

medicines to patients according to the physician's prescription (Table 3).

Theme 2: General responsibilities

Most of the physicians (12 out of 15) and pharmacists (8 out of 9) stated that pharmacists were responsible for keeping an up-to-date record of the inventory items, ensuring the availability of medicines, maintaining inventory, and dispensing medicines (Table 3).

Theme 3: Knowledge about the scope of practice of pharmacists in Pakistan

Almost all physicians (13 out of 15) were unaware of the legal scope of pharmacy practice in Pakistan and whether responsibilities such as dose selection, clinical monitoring of the patients, patient counseling, etc., could be performed by pharmacists. However, they believed that these should come under their legal scope. On the other hand, pharmacists (9 out of 9) were quite certain that clinical activities, such as those outlined previously, were legislated for and expected to be undertaken by pharmacists (Table 3).

Theme 4: Potential duties of pharmacists in the TB management

When asked about the potential duties of pharmacists (after explaining the role of pharmacists to patients as described in Box 1), a number of physicians (13 out of 15), pharmacists (9 out of 9), and patients (7 out of 12) endorsed monitoring, counseling, brand selection, dose adjustment, inventory management, dispensing, and polypharmacy assessment as their potential duties in TB management. Almost all participants [physicians (14 out of 15), pharmacists (7 out of 9), and patients (11 out of 12)] agreed that pharmacists should not be involved in partial or differential diagnosis as it was not their field of work (Table 3).

Theme 5: Rationale for integrating pharmacists in the TB care cascade

The physicians (13 out of 15) said that they were overburdened and wanted to share their duties with pharmacists and nurses, preferably pharmacists. They elaborated that sharing responsibilities with pharmacists will

TABLE 3 Themes, categories, and supporting quotations from healthcare professionals and patients about the role of the pharmacist in TB management.

Categories	Supporting quotations
Theme 1: pharmacists: who are they?	
A qualified medicine expert	Physician 4: "A qualified person having a 5 years degree of Doctor of Pharmacy, who is an expert in medicines, who has a sound knowledge of the pharmacokinetics and pharmacodynamics of drugs, who is an expert in detecting and managing drug interactions and side effects, and who makes dose calculations according to the patient's particulars. This is a pharmacist"
	Physician 14: "Someone who basically deals with drugs, their doses, their side effects, and their expiries. And who deals with a particular patient alongside with us. A person who has been dealing with drugs, their effects, side effects, and their dose, which will be selected according to the patient's weight, is a pharmacist"
	Patient 6: "He is the one who gives the medicine, so I meet him every time I come. He counsels me on medicines, how to take it, when to take it. He assures me of the quantity being given to me for one month's course. Then he allows me to leave the room"
Merely an unqualified dispenser	Patient 5: "We have heard and listened about doctor since we opened our eyes. We do not know about pharmacists. I have heard about people working in the medical store. They are not qualified enough. A doctor is well qualified and well educated"
	Patient 4: "No. What I know is that the person at the medical store who tells us about medicines and how much to take and how often. . ."
Theme 2: general responsibilities	
Inventory management	Physician 6: "A pharmacist is concerned with the availability of medicines in the department. He/she manages the stock, i.e., what medicines are being purchased, how to store those..."
	Pharmacist 9: "I am working as a hospital pharmacist in BVH. I am supervising the inventory of medicines and surgical items. I am supervising the dispensers; dispensing medicines to staff and to patients"
Dispensing of medicines	Physician 6: "A pharmacist is concerned with . . . dispensing of drugs, checking the expiry of the drugs"
	Pharmacist 9: ". . .I am supervising the dispensers, dispensing medicines to staff and to patients"
Theme 3: knowledge about the scope of practice of pharmacists in Pakistan	
Physicians' perspective	Physician 8: "I do not know about laws. There were some amendments to the law. So we are not sure. According to my knowledge, this is a team work. Every job is not for the doctors and pharmacist is there to share our work. Together we can treat the patient in a better way, so it should be legal"
Pharmacists' perspective	Pharmacist 4: "Legal is when you are permitted to do. A patient is coming to the hospital, and the most educated and qualified persons here are either doctors or us, the pharmacists. These duties are legal for us to perform. Whether we are permitted or not, it is a separate issue"
	Pharmacist 2: "This is our job, and by practicing all of these, the health system will get better. The patient's care will improve. There will be fewer flaws and mistakes"
Theme 4: potential duties of pharmacists in the TB management	
Clinical duties	Physician 12: "Their basic work is inventory management . . . dose selection/adjustments, and inventory management . . . can be hired as treatment supporter . . . proper counseling . . . medication adherence assessment. . ."
	Pharmacist 9: "There should be a full-time, fully functional TB pharmacist whose responsibility should be to educate patients and their attendants about disease and therapy, to monitor the patients, to promote adherence to the treatment course, and to minimize the harms of therapy"
	Patient 12: "I want them to guide me. I shall take the medicine in a proper way and shall be cured soon with their guidance" (patient no. 12)
Prescribing	Pharmacist 8: "We are educated, we are experts in medicines, we have an authorized degree, we are supposed to assist doctors in finding better therapeutic alternatives, we are supposed to verify the doses, and then why should we not write a prescription. Diagnosis is not our field, it can never be, but once diagnosed by the doctors, we should be allowed to write a prescription while we are supposed to do all the other work"
Partial or differential diagnosis	Physician 4: "If a person comes to you with the complaint of pain in the epigastric region, there are numerous reasons for it. It can be simple heart burn or it can be angina or muscular pain and further sub categories of that. Now an untrained person cannot recognize it"

(Continued on following page)

TABLE 3 (*Continued*) Themes, categories, and supporting quotations from healthcare professionals and patients about the role of the pharmacist in TB management.

Categories	Supporting quotations
	Physician 5: "They do not need to do it. Diagnosis is not their job"
	Pharmacist 8: "Diagnosis is not our field, it can never be but once diagnosed by the doctors, we should be allowed to write a prescription when we are supposed to do all the other work"
	Patient 7: "Pharmacist's job is confined to medicines and related aspects, not the diagnosis. Diagnosis is a specific work of the doctor"
Theme 5: rationale for integrating pharmacists into the TB care cascade	
Overburdened physicians	Physician 15: "We would like someone to share our burden or to help us. You know that diagnosis is our main task. So, sometimes the dosage and whether the drug is to be given through an IV route or an oral route, these things are confusing, and we have to search the internet, so, it will be a lot better when we have pharmacists, and they will just tell us"
	Physician 5: "Primarily, our burden will be shared. We will have more time for patients. We will be able to the study case thoroughly, diagnosis will be better"
Medication safety issues	Physician 14: ". . .if they will explain how to use the medicine and when to use, the side effects to the patients, compliance will be good. . .. Resistance will be overcome. Overall patient management will be better"
	Physician 14: "Pharmacists have a good command over pharmacology, if they will explain how to use the medicine and when to use, the side effects, to the patients, compliance will be good"
	Pharmacist 7: "We are unable to provide patient-centered TB care according to guidelines because we don't have enough pharmacy workforce. Tackling medication safety issues is the responsibility of pharmacists in other countries. A single pharmacist cannot do this. . .I am overburdened. I have to look after two wards simultaneously, so the work is difficult to manage here . . . I will love to extend my duties if more staff is hired"
	Patient 12: "We do not know the appropriate way of taking medicine. That is why we often face the perilous effects of drugs, and the most dangerous is that the disease is not cured. If there will be a person to guide us, counsel us on the proper use of medicine and foods to take, we will get cured soon"
Poor patient-healthcare professional interaction and patient dissatisfaction	Patient 12: "Doctor did not attend me properly. He just saw the reports and went off. He did not discuss anything. I tried to talk to him about medicine, but he seemed angry. So I sat back. He wrote the prescription, and that's all. He did not say a word or listen to me . . . there should be someone who can respond to us . . . like when I visit a medical store, the dispenser guides me about medicine and answers my questions, but here no one listens"
Theme 6: barriers to integrating pharmacists in the TB management	
Limited interest of regulatory authorities and policy-makers	Physician 15: "I think that is the government policies that matter here. I think the government is not creating the jobs because if vacancies are available obviously they will fill them. Other than that, hospital management does not realize their need and importance in the system, but I think it is policy related because there is a need of pharmacist"
	Pharmacist 2: "Main problem. Major issue. There are no proper policies for pharmacists. The rules are not being followed. The place, the seats we deserve are not being created. There is a need, there is demand for pharmacists, but it is not being fulfilled"
Lack of training	Physician 14: "Training can be an issue. Basically training at clinical side. The pharmacist who is working here, she is not having any clinical training. The duties that you have discussed earlier require clinical training"
	Pharmacist 4: "We are given training of only 6 weeks (internship) after studies, and that too does not involve any clinical training. So yes! We lack training"
Questionable competency	Physician 2: "I am not sure when to refer a patient to the pharmacist. Pharmacists themselves do not know what they are here for! This is a policy-related problem. Standard operating procedures for pharmacists are not clearly defined. They do not know whether they are here as hospital pharmacists or clinical pharmacists"
	Physician 1: "Honestly speaking, Yes! I do not consider them competent enough"
Lack of acceptability and awareness among community =	Physician 6: "It can be a problem. Our patients are not well educated. They are unaware of the importance of the pharmacist. From their view point, only the person who is diagnosing and prescribing is a doctor. Everyone else is just a supporter"
	Pharmacist 8: "Our community is mostly illiterate, they do not know who is a doctor and who is a pharmacist. Anyone giving them medicines is a doctor to them. They do not go and ask for your degree. They are concerned with the therapy and being cured"

(Continued on following page)

TABLE 3 (*Continued*) Themes, categories, and supporting quotations from healthcare professionals and patients about the role of the pharmacist in TB management.

Categories	Supporting quotations
Theme 7: facilitators to the integration of pharmacists in the TB management	
Appropriate training	Physician 8: "Yes, there should be some training and workshops for them. This is very important. The world is totally different in books and wards. In wards, there must be a supervisor for the pharmacist who can tell them how they can manage the disease"
	Pharmacist 9: "We have good knowledge of pharmacology; we also study diseases so we can better guide doctors on drugs and their actions and reactions on the patients. As far as training is concerned, our training should begin at undergraduate level and it should be a compulsory part of our course work. Training is required on the clinical side with proper supervision"
Improved awareness among community	Physician 15: "First of all create awareness among people. If the community do not know the basic infrastructure of the healthcare system like they does not know that what are the duties of nurses, doctors, and pharmacists"
Active participation of pharmacists in ward rounds	Pharmacist 1: "Pharmacists should work in wards, perform patient counseling, check drug interactions, and help counter medication/prescription errors. The patient will benefit from getting optimal treatment, and we shall gain experience"

help them have more time for other core clinical responsibilities. They also opined that patient counseling by pharmacists will facilitate improved treatment adherence and subsequently improve patient outcomes. Besides, pharmacists (8 out of 9) advocated that medication safety issues, for example, inappropriate use, medication errors, adverse drug events, etc., demand integration of the pharmacy workforce. However, they lamented that there was a shortage of pharmacist in TB management and a single pharmacists was unable to extend his/her duties due to excessive workloads. Harmoniously, patients (9 out of 12) accepted that pharmacists can better guide them about the proper use of medicines, thus reducing medication errors and improving their health status. In addition, patient satisfaction and effective consultation called for pharmacist integration into TB management, as patients (7 out of 12) were found complaining about the physicians' behavior, lack of attention, and poor consultation style (Table 3).

Theme 6: Barriers to integrating pharmacists in the TB management

The major barrier to integrating pharmacists in the TB management system was the lack of interest of regulatory authorities and policymakers. Both the cohorts, i.e., physicians (15 out of 15) and pharmacists (8 out of 9), shared the same views on this matter. Physicians (14 out of 15) and pharmacists (8 out of 9) further expressed that though pharmacists hold relevant academic degrees (Doctor of Pharmacy), they still lack basic clinical training and experience, which influence their competency. Physicians (12 out of 15) were unclear about the competency and scope of pharmacy practice activities and did not know when it was appropriate to refer the patient to a pharmacist. One of the major barriers indicated by physicians (10 out of 15) was negative feedback from the community about the involvement of pharmacists in medicine-related decisions. A few pharmacists (3 out of 9) agreed with the physicians that patients were not familiar with their professional role or their services (Table 3).

Theme 7: Facilitators to the integration of pharmacists in the TB management

Nearly all physicians (14 out of 15) and pharmacists (9 out of 9) recommended that there should be arrangements for the clinical training of pharmacists, preferably at the undergraduate level. Most of the physicians (13 out of 15) and pharmacists (7 out of 9) were of the view that the community should be made aware of the role of pharmacists in TB management and the importance of engaging them in clinical activities. In addition to this, pharmacists (8 out of 9) suggested that they should join physicians on ward rounds to evaluate patients' medication charts and assist them in therapeutic decision-making processes (Table 3).

Figure 1 summarizes the need, barriers, facilitators, and benefits of integrating pharmacists in TB management.

Discussion

It is widely acknowledged that integrating pharmacists in TB management improves therapeutic outcomes and patient safety and lessens the workload on infectious disease specialists (Atif et al., 2016b; Atif et al., 2016c). However, in Pakistan, the role of the pharmacist in the management of TB is restricted to the dispensing of medications only. Given the status quo, this study was conducted to understand the views of physicians, pharmacists, and patients with regard to integrating pharmacist roles in TB management, the

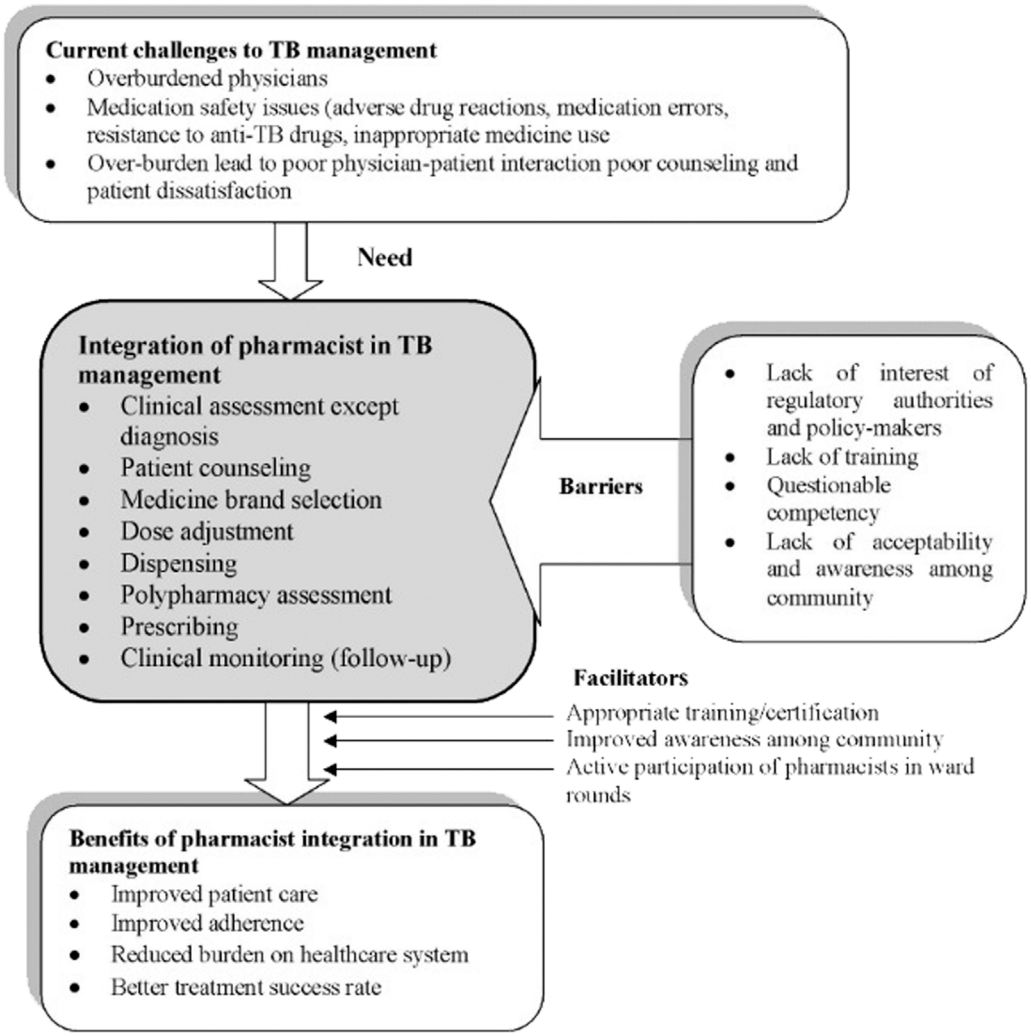

FIGURE 1
Summary of findings.

potential duties pharmacists can perform, and the barriers linked to the integration of pharmacists in TB management. Analysis of the data yielded eight themes and 22 categories. The first six themes represented what is happening in the current scenario, whereas the latter two were related to future perspectives.

Implications for the literature

In this study, physicians considered pharmacists to be "medicines expert" with the professional holding a responsibility of maintaining medicine inventories. Multiple studies (Azhar et al., 2010; Li et al., 2014; Sabry and Farid, 2014) demonstrated that, though physicians considered pharmacists as medicine experts, they were uncomfortable with their involvement in direct patient care. In the context of a developing country, this may be due to the fact that pharmacists were mostly restricted to medicine supply and distribution and were not involved in direct patient care (Adnan et al., 2014). Moreover, the current study revealed that most of the patients (when asked prior to explaining the potential role of pharmacists) were not aware of the existence of pharmacists and their potential role in TB management. The ignorant perception of patients may be attributed to a lack of education, poor health literacy, and limited access to pharmacy services. It is important to note that most of the TB patients in Pakistan have a low educational background and belong to rural areas (Atif et al., 2016a; Atif et al., 2018; Khan et al., 2019; Atif et al., 2020a; Atif et al., 2020b; Atif et al., 2021; Khan et al., 2022a). The same was reported in other studies (Ried

et al., 1999; Wilbur et al., 2010; Adnan et al., 2014), where patients did not know the role of pharmacists, particularly in the provision of pharmaceutical care.

The healthcare professionals in the current study suggested that a pharmacist may provide patient-specific services such as assessing and promoting patients' medication adherence and counseling the patients about the appropriate use of medicines and the importance of completing therapy. In addition, they also advocated that pharmacists could help physicians in monitoring the patients assessing the prescriptions for appropriateness and polypharmacy. Likewise, several studies (Clark et al., 2007; Mkele, 2010; Khan et al., 2022b) highlighted these roles of pharmacists in controlling and managing TB disease. Interestingly, in the current study, most of the pharmacists agreed that they were able to prescribe TB medicines to the patients. However, the legislations of pharmacy practice in Pakistan did not allow pharmacists to prescribe medicine for any disease. To date, Pharm-D graduates in Pakistan are not offered advanced training in pharmacotherapy and residency training to become independent prescribers. Nevertheless, in developed countries such as the United Kingdom, the United States, and Canada, where clinical pharmacy specialty courses are offered, pharmacists are allowed to prescribe (Tonna et al., 2007; Cooper et al., 2008; Stewart et al., 2009) after certification and necessary training, and patients consider pharmacists as competent and easily accessible healthcare professionals (Cooper et al., 2008).

The involvement of pharmacists in TB diagnosis was negatively viewed by almost all respondents to the current study. Though pharmacists in our study were not entrusted with the responsibility of diagnosis, a study (Glaze and Rowe, 2015) showed that involvement of pharmacists in this domain could help in the early detection of TB, thus preventing delays in treatment. A study conducted in New Mexico (Jakeman et al., 2015) found that the initial detection of presumptive TB patients by pharmacists resulted in valuable public health benefits. In countries with a high TB burden where healthcare professionals (especially physicians) are extremely overburdened, pharmacists can triage presumptive TB patients and refer them to physicians or the TB laboratory based on their needs. The same activities could also be performed by pharmacists at community pharmacies, which are often the first point of contact and consultation for presumptive cases with early symptoms of TB (i.e., cough, low grade fever, loss of weight, night sweats, etc.).

Nearly all respondents in this study demonstrated a positive response towards pharmacists' authority to select any brand of prescribed medicines, and studies conducted in other countries showed almost similar findings (Hassali et al., 2009; Chong et al., 2010). Contrary to this, a study conducted in Jamaica (Gossell-Williams, 2007) found the opposite opinion of physicians in this regard. Jamaican physicians were not in favor of pharmacists undertaking substitution due to assorted reasons such as therapeutic failures, the occurrence of adverse drug reactions, etc. In the developing countries, for example Pakistan, pharmaceutical companies invest a lot on physicians to convince them to prescribe their brand. Understandably, in this case, physicians would not allow other health professionals to select a specific brand (Atif et al., 2019; Atif et al., 2020c). Interestingly, physicians in our study agreed to offer brand selection (for TB medicines) responsibility to pharmacists. This might be due to the fact that anti-TB medicines were available free of cost to the patient at public sector hospitals in Pakistan. Also, the physicians had to prescribe what was available in stock and they were not at the liberty to undertake selection of alternate brands available in market. The current study also revealed that the physicians did not agree that pharmacists could perform therapeutic substitution. This might be due to either the physician's lack of trust in the pharmacist's ability to select the appropriate medicine or they did not want pharmacists to interfere with their prescription-writing processes.

The majority of the stakeholders in this study were of the opinion that integration of pharmacists in TB management was direly needed in view of overburdened physicians, as excessive workload leads to sub-standard patient care. They raised concerns that poor counseling results in medication safety issues, such occurrence of ADEs associated with anti-TB drugs, medication errors, and the development of antibiotic resistance due to poor adherence to treatment, etc. Besides, the integration of pharmacists in TB management was also considered important in light of the meager patient-physician interaction and consequential patient dissatisfaction. Similar findings were also reported in previous studies (Clark et al., 2007; Mitrzyk, 2008; Mkele, 2010). Evidently, pharmacists are in an ideal position to educate TB patients about the disease and its management and subsequently help in reducing the occurrence of ADE associated with anti-TB drugs and improving compliance to TB treatment (Clark et al., 2007; Mitrzyk, 2008; Mkele, 2010; Atif et al., 2016d). Moreover, pharmacists in Pakistan could offer extended pharmacy services (Abrogoua et al., 2016; Atif and Malik, 2020; Atif et al., 2020d) at TB clinics, which may include pharmaceutical care, counseling, optimal use, pharmacoeconomics, and drug use evaluation. These roles are in line with the Drug Regulatory Authority of Pakistan (DRAP) Act no. XXI of 2012 (51).

With regard to barriers associated with the integration of pharmacists in TB management, physicians and pharmacists highlighted lack of interest by regulatory authorities, inadequate training, lack of acceptance, and questionable competency as major obstacles that hindered the integration of pharmacists in TB management. In addition, pharmacists also reckoned that a limited recruitment-driven shortage of pharmacists in the TB management unit imposed a burden on employed pharmacists, thereby making them unable to perform their duties efficiently. Similar barriers were reported in another study, which described how the limited availability of pharmacists makes it difficult for pharmacists to perform clinical roles in collaboration with physicians (Doucette et al., 2005).

Implications for policy and practice

As with most exploratory studies, there are implications for policy and practice that come out of this work. First, Pakistani health policymakers need to be aware that physicians are significantly overburdened. Second, physicians see pharmacists as the "medicine experts," yet are unaware of the legislation surrounding what is within the scope of a practicing pharmacist. There is a need for campaigns that aware physicians about the potential clinical roles of pharmacists. Third, various certification and residency programs should be available for pharmacists who want to improve their clinical skills. Finally, patients are unaware of the potential role of the pharmacist in their disease management. This requires education campaigns to change their perception.

Limitations

There are some limitations to this study. First, the majority of the study patients were illiterate and from poor socioeconomic backgrounds. The perception of educated patients could have been different. Second, the study participants were only recruited from the Bahawalpur region; therefore, the results could not be generalized for the whole country. However, all TB management units in the country work under the National Tuberculosis Program and follow the same TB care cascade, in terms of staff availability, patient care services, medication, etc. Therefore, we believe that our findings can be generalized throughout the country. Third, the perspectives of nurses, policymakers, and NTP managers were not explored, which is recommended for future studies.

Conclusion

Physicians considered pharmacists qualified healthcare professionals; whereas patients (pre-information inquiry) considered them merely dispensers. With regard to the potential duties of pharmacists, physicians, pharmacists, and patients [upon post-role-explanation (Box 1) inquiry] they endorsed monitoring, counseling, medicine brand selection, dose adjustment, inventory management, dispensing, and polypharmacy assessment as their potential roles. In view of all stakeholders, the rationale for integrating pharmacists in TB management included overburdened physicians, sub-standard patient care, medication safety issues, and patient dissatisfaction. The healthcare professionals highlighted that the major barriers to integrating pharmacists within the TB management system were limited interest of regulatory authorities and policymakers, followed by inadequate training and experience driven questionable competency of pharmacists. Moreover, awareness campaigns to sensitize healthcare professionals and the community about the legal role of pharmacists in patient-oriented services were deemed mandatory by the study participants.

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

Conceptualization: MA, KM, IMa, IMu, and NA; data curation: KM; formal analysis: MA, KM, IMa, IMu, and NA; investigation: MA, KM, IMa, YA-W, IMu, and NA; methodology: MA, KM, IMa, YA-W, and IMu; supervision: MA; validation: MA; visualization: KM; roles/writing—original draft: MA, KM, IMa, YA-W, and NA; and writing—review and editing: MA, KM, IMa, and IMu.

Ethic statement

Ethical approval was obtained from the Pharmacy Research Ethics Committee (PREC) at the Islamia University Bahawalpur (Reference: 42-2016/PREC, dated 20-12-2016). Signed, written, informed consent was obtained from all study participants.

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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A pharmacist-led medication review service with a deprescribing focus guided by implementation science

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Background: Little research addressed deprescribing-focused medication optimization interventions while utilizing implementation science. This study aimed to develop a pharmacist-led medication review service with a deprescribing focus in a care facility serving patients of low income receiving medications for free in Lebanon followed by an assessment of the recommendations' acceptance by prescribing physicians. As a secondary aim, the study evaluates the impact of this intervention on satisfaction compared to satisfaction associated with receiving routine care.

Methods: The Consolidated Framework for Implementation Research (CFIR) was used to address implementation barriers and facilitators by mapping its constructs to the intervention implementation determinants at the study site. After filling medications and receiving routine pharmacy service at the facility, patients 65 years or older and taking 5 or more medications, were assigned into two groups. Both groups of patients received the intervention. Patient satisfaction was assessed right after receiving the intervention (intervention group) or just before the intervention (control group). The intervention consisted of an assessment of patient medication profiles before addressing recommendations with attending physicians at the facility. Patient satisfaction with the service was assessed using a validated translated version of the Medication Management Patient Satisfaction Survey (MMPSS). Descriptive statistics provided data on drug-related problems, the nature and the number of recommendations as well as physicians' responses to recommendations. Independent sample t-tests were used to assess the intervention's impact on patient satisfaction.

Results: Of 157 patients meeting the inclusion criteria, 143 patients were enrolled: 72 in the control group and 71 in the experimental group. Of 143 patients, 83% presented drug-related problems (DRPs). Further, 66% of the screened DRPs met the STOPP/START criteria (77%, and 23% respectively). The intervention pharmacist provided 221 recommendations to physicians, of which 52% were to discontinue one or more medications. Patients in the intervention group showed significantly higher satisfaction compared to the ones in the control group ($p < 0.001$, effect size = 1.75). Of those recommendations, 30% were accepted by the physicians.

Conclusion: Patients showed significantly higher satisfaction with the intervention they received compared to routine care. Future work should assess how specific CFIR constructs contribute to the outcomes of deprescribing-focused interventions.

KEYWORDS

implementation science (MeSH), pharmacy, deprescribing, polypharmacy (MeSH), patient satisfaction (MeSH), older adult patients, Lebanon, free medication

1 Introduction

Polypharmacy, commonly known as the concomitant daily uptake of five or more medications (Sloane and Zimmerman, 2018; Zechmann et al., 2020), is prevalent among older adults (Khera et al., 2019; Vasilevskis et al., 2019). With some chronic conditions, the use of multiple medications is essential for the improvement of a patient's health, making polypharmacy appropriate (Duncan et al., 2017; Mair and Fernandez-Llimos, 2017; Halli-Tierny A et al., 2019). In other circumstances, drug-related problems (DRPs) may occur. According to the Pharmaceutical Care Network Europe (PCNE), a DRP is "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes" (Pharmaceutical Care Network Europe, 2003). When DRPs occur while a patient is using multiple medications, the potential detriment of medications may exceed their projected benefit, deeming polypharmacy inappropriate (Chau et al., 2016; Duncan et al., 2017; Martin et al., 2018). Such DRPs are more likely to occur with Potentially Inappropriate Medications (PIMs). The American Geriatrics Society (AGS) Beers Criteria for Potentially Inappropriate Medication (PIM) use in older adults is an explicit list of PIMs that should be avoided among older adults and patients with certain diseases, prescribed at a lower dose or with caution (Samuel, 2015). When a decision is made to prescribe them, they should be carefully monitored. Beers Criteria PIMs have been found to be associated with poor health outcomes, including confusion, falls, and mortality (Fick et al., 2006; Stockl et al., 2010).

Medication review is often recommended to optimize medication use. Medication review, as an overarching term, is used to describe a review of medicines carried out when a health professional meets a patient and there is a decision to prescribe or stop a medicine following a comprehensive and structured process supported by the patient's records (National Institute for Health and Care Excellence, 2015). Medication optimization builds on the medication review process and occurs when a patient's medications have been "optimized" by the health professional care team and, consequently, the patient uses the regimen in an ideal manner to improve health outcomes (McFarland et al., 2021). Thus, a medication review is considered part of the plan for inappropriate therapy resolution aiming for medication optimization (de Oliveira Santos Silva et al., 2019).

One medication optimization strategy that has been gaining momentum in the past few years to address medication safety issues is deprescribing (Bleidt, 2019; Clark et al., 2020; Korenvain et al., 2020). Deprescribing is taken to mean more than simply stopping medicines and is considered to be "a planned, stepwise process, specifying the type of medication in question, detailing explicit goals, and including dose reduction and substitution" (Duncan et al., 2017). Deprescribing is the tapering of medications and has to take place to minimize medication-caused harm and improve outcomes (Bleidt, 2019; Tandun et al., 2019; Farrell et al., 2020). To that end, deprescribing has the potential not only to solve DRPs but also to minimize health costs and improve quality of life, while maintaining or even improving clinical outcomes. Studies addressing deprescribing showed a significant potential for reducing the use of potentially inappropriate medications and subsequent adverse outcomes reduction in various settings (Kojima et al., 2012; Mckean et al., 2016; Cossette et al., 2017; Kimura et al., 2017; Wouters et al., 2017; Vasilevskis et al., 2019; Balsom et al., 2020; Dharmarajan et al., 2020; Kua et al., 2020; Schapira et al., 2020; McCarthy et al., 2022). Deprescribing-focused interventions showed promising results in the available literature. Studies addressing deprescribing in the hospital setting showed a significant decrease in PIMs use among older adults (Mckean et al., 2016; Cossette et al., 2017; Kimura et al., 2017; Vasilevskis et al., 2019; Schapira et al., 2020). Similarly, with five studies conducted in nursing homes, physicians' or pharmacists-directed reviews led to PIMs and subsequent adverse outcomes reduction (Kojima et al., 2012; Wouters et al., 2017; Balsom et al., 2020; Dharmarajan et al., 2020; Kua et al., 2020). A recent intervention focusing on general practitioners in primary care showed a significant decrease in medications they originally prescribed to patients reducing unnecessary medication use by patients (McCarthy et al., 2022). Deprescribing of specific medications has been investigated in earlier interventions. Many of those showed positive outcomes as those targeting benzodiazepines, antidepressants, antidiabetics, anticholinergics, proton pump inhibitors, and non-steroidal anti-inflammatory medications (Reeve et al., 2017; Maund et al., 2019; Tandun et al., 2019; Martinez et al., 2020; Rashid et al., 2020); while deprescribing of other medications continues to be challenging. For example, the withdrawal of urate-lowering drugs was associated with the recurrence of gout episodes (Beslon et al., 2018). The discontinuation of some preventative medicines, such as warfarin, was found to cause harm (Narayan and Nishtala, 2017). Further, little evidence is known about statins' maximum duration of use, hence a physician's clinical judgment is needed to decide whether a patient needs to continue taking a statin (van der Ploeg et al., 2020).

To be successfully implemented in practice, and for this success to be sustainable, some issues should be addressed. Medication reviews successful in achieving medication optimization through deprescribing would involve health professionals of multiple backgrounds. Strategies and interventions that would facilitate this collaboration would include factors such as mutual acceptance and readiness of team members towards collaboration, performing as a team rather than an individual; communication strategies among clinicians and shared decision-making, and care coordination (Mustafa Sirimsi et al., 2022). Further, pharmacist-led deprescribing strategies would need to be conceptualized and guided by implementation science (IS) (Pereira et al., 2021; Ailabouni et al., 2022)—the study of the incorporation of evidence-based findings into practice, to improve healthcare—(Bauer et al., 2015; Ronquillo et al., 2018). One framework that has shown promise in implementing

medication regimen optimization services in practice is the Consolidated Framework for Implementation Research (CFIR) (Shoemaker et al., 2017; Baumgartner et al., 2020). The prospect of utilizing CFIR in implementing health services in low- and middle-income countries is promising (Ojo et al., 2021). A recent study applied the CFIR in medication reconciliation implementation in a Brazilian hospital indicating that available resources and communication are key constructs of influence in the implementation process (Fernandes et al., 2022). Further, Shoemaker et.al highlighted the importance of using CFIR in implementing professional services at the community pharmacy level (Shoemaker et al., 2017).

Patients' attitude toward deprescribing was assessed in multiple studies and a positive attitude was observed in most of these studies (Tegegn et al., 2018; Kua et al., 2019; 2020; Shrestha et al., 2021). For instance, in a study performed in a resource-limited setting in Ethiopia, 82% of patients were willing to have one of their medications stopped if the physician suggested it. Assessing patient satisfaction with pharmacist-led services including medication reviews and medication optimization is increasingly investigated in research (Moczygemba et al., 2010; Kim et al., 2016; Cardosi et al., 2018; Nigussie and Edessa, 2018; Basheti et al., 2019; Jordan et al., 2021; Kabba et al., 2021; Kebede et al., 2021). A recent systematic review showed high patient satisfaction toward pharmacist-led medication review interventions (Bou Malham et al., 2021). In addition, patients showed a positive attitude toward pharmacists' competencies and involvement in deprescribing, especially the elderly (Bužančić et al., 2021). Further, a study reported that patient satisfaction could be enhanced by deprescribing as patients felt uncomfortable with the use of multiple medications (Reeve et al., 2014). For example, review tackling patient satisfaction with the use of proton-pump inhibitors indicated that patients were more satisfied when taking PPI on-demand rather than chronically, meaning that they showed satisfaction with PPI deprescribing (Boghossian et al., 2017). To that end, assessing patient satisfaction with a pharmacy service after being introduced to a medication review service focusing on deprescribing would be helpful when disseminating and implementing such a service.

This study addresses several literature gaps. First, little research has addressed interventions focusing on deprescribing in facilities serving patients of low socioeconomic status, especially in the primary care setting (Milos et al., 2013; Cheong et al., 2018; Hailu et al., 2020). Patients of low income, a class representing a significant proportion of the global patient population, are most likely to benefit from deprescribing in multiple ways. Those include therapeutic as well as economic benefits resulting from the reduced burden of money spent on medications by institutions that subsidize those medications ensuring the sustainability of service provision to those patients. This is particularly relevant in the Lebanese healthcare system where a significant percentage of medication expenses are not covered. Second, few studies have utilized an implementation science conceptual framework to guide the implementation of interventions with a focus on deprescribing. This approach would ensure that different factors influencing implementation are being considered and incorporated as needed. Third, little work has assessed patient satisfaction related to deprescribing, a key desired outcome of deprescribing interventions that would enhance the incorporation of patient' preferences in the care process. Finally, few studies addressed deprescribing in the Arab region and in developing countries where polypharmacy is suspected to be as high as it is in developed countries (Alsuwaidan et al., 2019; Al-Dahshan et al., 2020; Badawy et al., 2020; Abu Farha et al., 2021).

This study is guided by the Consolidated Framework for Implementation Research (CFIR), a conceptual framework developed to guide the systematic assessment of implementation contexts while addressing factors that might influence intervention implementation and effectiveness (Shoemaker et al., 2017). The CFIR includes five major domains (intervention characteristics, outer setting, inner setting, characteristics of individuals, and process) with underlying constructs that can potentially influence the implementation of interventions. Using tools such as STOPP/START criteria, this study aimed to develop a pharmacist-led medication review service with a deprescribing focus in a healthcare facility serving patients of low-income receiving medications for free in Beirut, Lebanon followed by an assessment of the recommendations' acceptance by prescribing physicians. As a secondary aim, the study evaluates the impact of this medication review service on the satisfaction of the study participants compared to the routine care they receive.

2 Methods

2.1 Ethical consideration

This research project followed a prospective experimental study design. Ethical approval for the study was obtained from the Institutional Review Board (IRB) at Beirut Arab University (protocol number 2022-H-0076-P-M-0465). Written informed consent was obtained from all participants assuring that any information provided by the patients is confidential.

2.2 Research setting and study population

The research team searched for a site serving patients of low income at subsidized rates or for free in Beirut, Lebanon. This was intended to provide a dual benefit so that in addition to patient benefit from improved health outcomes, which would apply to patients on polypharmacy in different settings, the site might benefit from decreasing the economic burden of unnecessary medication use. Accordingly, a non-governmental charitable association located in Beirut, Lebanon was selected as the intervention site. The healthcare facility provides low-charge consultations and free medications to 1,000 registered patients of low income. The healthcare team consists of 28 physicians, one full-time nurse, and three assistants in addition to a pharmacist, a volunteer nurse, and assistant staffing the pharmacy. In this facility, GPs prescribe medications, but their role is mostly centered around referral to specialty physicians for patients with chronic conditions.

Following two visits by the intervention pharmacist that were intended to introduce the project to the leadership team of the healthcare facility and study the pharmacy setting, a letter was obtained from the facility manager, who is also a general practitioner at the facility, approving the study execution at the

TABLE 1 The deprescribing intervention setup mapped to the adapted Consolidated Framework for Implementation Research.

Construct	Subconstruct	Description	
Pharmacy Service Characteristics	Relative advantage	**Perception of staff, providers, and patients of the benefits of deprescribing services.**	
		The intervention pharmacist met with the facility manager and explained the benefits of providing deprescribing services for patients at the facility. The perception of the facility staff towards the intervention was favorable. To address staff perceptions of the project, the intervention pharmacist drafted a letter to the facility physicians explaining the rationale for the project and provided them with a description of the materials to be used including a copy of the STOPP/START criteria, after getting the acceptance of those physicians to be involved in the study.	
	Adaptability	**The degree to which deprescribing service can be tailored to meet local needs at the organization.**	
		The deprescribing service meets the local needs of the organization by 1) improving patient outcomes, and 2) reducing the cost of inappropriate medications that burden the budget of the facility at a time of an economic crisis.	
	Complexity	**The difficulty of implementing deprescribing service (scope, incorporation into workflow, staff needed, number of steps required).**	
		The intervention pharmacist shadowed the pharmacy staff before proposing the intervention, which was piloted to ensure smooth integration into the workflow, without being staff intensive and to improve the feasibility and patient safety.	
	Cost	**Cost of providing deprescribing service.**	
		The deprescribing intervention was provided by the intervention pharmacist for no charge and was not sponsored by extramural funds.	
Outer Setting	Patient needs and resources	**A patient's needs for deprescribing; barriers and facilitators to meet these needs.**	
		A significant proportion of patients getting their services from the facility are on polypharmacy. This puts the patients in need of intervention.	
		The pharmacy staff members do not have the time to perform additional cognitive services. Therefore, the deprescribing service provided by a pharmacist from the outside would complement the routine counseling that is currently provided to patients. The intervention pharmacist was supported by two data collectors who were members of the research team.	
	Cosmopolitanism	**The degree to which a pharmacy is networked with other pharmacies and providers.**	
		There is only one pharmacy at the facility and it was not networked with external pharmacies. Still, a connection was made between the intervention pharmacist and the providers at the facility as described in the intervention flow and description part.	
	Peer Pressure	**Competitive pressure to provide a deprescribing service.**	
		Since this is a charity organization, there is little competitive pressure to introduce a new service.	
	External policy and incentives	**Strategies to spread deprescribing services, including policy and regulations, external mandates, recommendations and guidelines, pay-for-performance, collaboratives, and public and benchmark reporting.**	
		The facility management had a dual incentive in the deprescribing intervention: 1) improved patient outcomes, 2) reduced cost of unhelpful medications that burden the budget of the facility at a time of economic crisis.	
Inner Setting	Structural characteristics	**Type of the pharmacy, size, physical space, staffing**.	
		A small-sized (420 cm*600 cm) pharmacy, located inside the organization, is managed by a pharmacist, a nurse, and an assistant. The pharmacy does not have a designated counseling area due to its relatively small size. However, a space at the facility next to the pharmacy was offered for the intervention pharmacist to interview patients.	
	Culture	**Norms, values, and basic assumptions of the pharmacy.**	
		The intervention fits within the values assessed in the facility, which emphasized providing high-quality services for vulnerable patients at little to no cost.	
	Implementation climate	Tension for change	**The degree to which the facility manager and staff perceived the situation as needing change and that a deprescribing service should be provided.**
			The manager of the facility and the site pharmacist agreed that their patients need the proposed intervention.
		Compatibility	**Degree of tangible fit between meaning and values attached to deprescribing service by pharmacy staff.**
			The mission of the institution as a charitable organization increased the enthusiasm of the facility manager and staff members to adopt the intervention.
		Organizational incentives and rewards	**Awards, performance reviews, promotions, raise in salary, increased stature, or respect.**
			The facility has not adopted such policies at the time of the intervention.

(Continued on following page)

TABLE 1 (*Continued*) The deprescribing intervention setup mapped to the adapted Consolidated Framework for Implementation Research.

Construct	Subconstruct	Description	
	Readiness for implementation	Leadership engagement	**Commitment, involvement, and accountability of leaders and pharmacy managers in implementing and providing a deprescribing service.**
			The facility manager, the executive health officer, and the pharmacy staff manager were committed to the intervention's success. The manager of the facility fully approved the study plan and participated in the study as one of the study physicians. A support letter was provided to the intervention pharmacist.
		Available resources	**Money, training, education, physical space, and time dedicated to providing deprescribing.**
			A private place adjacent to the pharmacy was provided to the intervention pharmacist for patient interviewing. The intervention pharmacist has provided enough time for completing the deprescribing service.
		Access to knowledge and information	**Ease of access to digestible information and knowledge about deprescribing services.**
			The updated guidelines for each medical condition, the last version of the STOPP/START criteria, and the Medscape drug interaction checker were available and utilized by the intervention pharmacists when needed. Recommendations from the intervention pharmacist were double-checked by a licensed pharmacist who is also a professor of pharmacotherapeutics before presenting these recommendations to physicians.
Pharmacy staff Characteristics	Knowledge and beliefs about the intervention	**Pharmacy staffs' attitudes, values, and familiarity with deprescribing components, steps, documentation, and care process.**	
		The pharmacy staff was introduced to the deprescribing service plan before the intervention commencement by the intervention pharmacist. A documentation form for each patient was provided to the facility manager at the end of the project.	
	Self-efficacy	**Pharmacy staff's belief in their capabilities to provide deprescribing.**	
		The intervention pharmacist was the one providing the intervention, and the pharmacy staff was not a part of the study.	
	Other personal attributes	**Tolerance of ambiguity, intellectual ability, motivation, values, competence, capacity, and learning style.**	
		Those personal attributes were not examined.	
Process	Planning	**The degree to which a scheme or a method for implementing a deprescribing service is developed and the quality of this scheme**.	
		The intervention was tested and piloted in an extensive process.	
	Engaging	Formally appointed internal leaders	**Individuals from within the pharmacy who have been formally appointed with responsibility for implementing and overseeing deprescribing.**
			The intervention pharmacist was responsible for implementing the intervention at the highest possible standard as part of an agreement with the facility director.
		Champions	**Individuals who dedicated themselves to supporting and driving through the provision of deprescribing.**
			The manager of the facility was the champion of the intervention as he discussed with the prescribing physicians the importance of implementing deprescribing at the facility.
		External change agents	**Individuals who are affiliated with an outside entity formally influence decisions in a desirable direction to provide deprescribing.**
			No external change agents contributed to the intervention implementation.
	Executing	**Carrying out implementation according to plan.**	
		The intervention pharmacist strictly followed the research plan as part of her Master's research.	
	Reflecting and evaluating	**Feedback about the progress and quality of deprescribing service, with a regular reflection on progress and experience.**	
		The intervention pharmacist regularly debriefed the thesis advisor and the manager of the facility about the progress of the study. A licensed pharmacist was debriefed about each recommendation before being presented to physicians.	

facility. The study was then introduced to all specialty physicians and general practitioners who might interact with eligible patients (a total of 17 physicians and general practitioners) to facilitate the endorsement of the project. Those physicians were candidates for following patients in our sample. The rest of the 28 physicians in the facility were of specialties not related to our study focus such as paediatricians for example. The 17 physicians were then provided with a formal letter describing the project plan. Physicians and pharmacy staff were provided with a copy of the STOPP/START criteria that were used as a key tool in the study (Cowan and Riley, 2015; O'mahony et al., 2015).

The study population consisted of patients registered within the facility. Patients were included in the study if they were 65 years or older, met the World Health Organization's polypharmacy definition of taking five or more medications (World Health Organization, 2019), picked up their medications themselves, and were cognitively capable of participating in the study. A class of patients collects their medications at the facility while being seen by a physician practicing outside the facility. Those patients were not targeted by this work. The intervention focused on patients seen by physicians in the facility so that the clinical pharmacist researcher can follow up on medication review results with physicians practicing at the facility that the clinical pharmacist researcher can access.

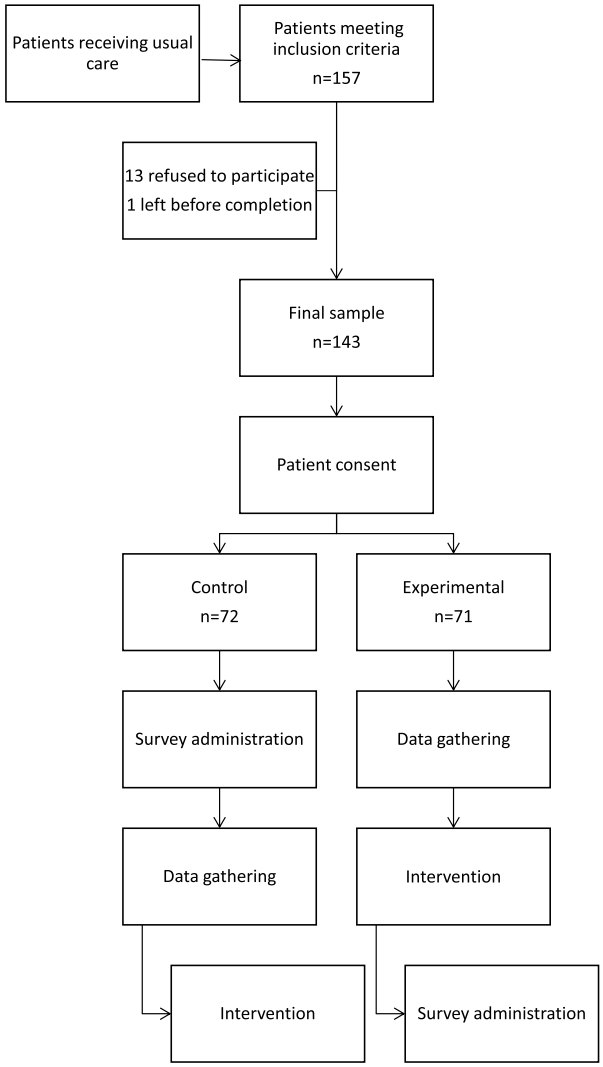

FIGURE 1
Medication optimization intervention flow diagram.

2.3 Intervention description

The intervention was guided by the adapted CFIR (Shoemaker et al., 2017). The CFIR comprised constructs that were operationalized and adapted into those five domains as follows: 1) *Proposed pharmacy service characteristics*-This domain addresses relative advantage, adaptability, complexity, and cost of the medication review service; 2) *Outer setting*-This domain addresses external influences on the intervention's implementation including patient needs and resources, cosmopolitanism or the level at which the pharmacy is networked with other pharmacies, peer pressure, and external policies and incentives; 3) *Inner setting*- This domain addresses different characteristics of the implementing facility such as structural characteristics, pharmacy culture, readiness for implementation including leadership engagement, available resources and access to knowledge and information, and the implementation climate including tension for change, compatibility, organization incentives and rewards; 4) *Pharmacy staff characteristics*- This domain addresses pharmacist's and pharmacy staff's beliefs about the intervention, self-efficacy, and other personal attributes that may affect implementation; 5) *Process of implementation*- This domain addresses stages of implementation for the proposed pharmacy service such as planning, engaging formally appointed internal leaders, champions and external change agents executing, reflecting and evaluating the intervention. A detailed mapping of the intervention setup to the CFIR is described in Table 1. The intervention was first tested on a convenience sample of eight patients at the facility using less than five medications. This was followed by a pilot study of 46 participants meeting inclusion criteria including the use of five or more medications. Findings from pilot study participants meeting the inclusion criteria were included in the final calculations since no changes were made to the employed methods following this step. Data collection for the pilot and the full study took place between June and September 2021.

Participants were approached by a trained data collector with a clinical pharmacy background after picking up their medications from the pharmacy at the facility, which included their routine interaction with the facility site pharmacist, who provides routine medication dispensing at the pharmacy. Informed patient consent was made by the intervention pharmacist or a trained data collector with a clinical pharmacy background at this point while explaining to patients that the care they receive at the facility would not be impacted in any way if they choose not to participate. Participants were divided into two groups in order of their exit from the pharmacy. The intervention group was first introduced to the study purpose of deprescribing PIMs, received disease and medication counseling, and was then administered the translated Medication Management Patient Satisfaction Survey (MMPSS) (Moon et al., 2016). The MMPSS was developed with the aim of providing a reliable and brief patient satisfaction survey specific to pharmacists providing comprehensive medication management services. It consists of ten questions, nine of which used a

scale from 1 to 4 (strongly agree, agree, disagree, strongly disagree) and asks patients to evaluate their experiences with the clinical pharmacist. The final question asks patients to rate their overall quality of care and services on a Likert-scale from 1 to 5 (excellent to poor). An aggregate scale score for MMPSS is calculated by summing the score for each item in the scale. See Supplementary Appendix SA1.

On the other hand, the control group was administered the MMPSS satisfaction survey before taking the intervention. For ethical reasons, control group patients were provided with the same intervention by the same intervention pharmacist following filling out the MMPSS survey. The satisfaction survey was administered verbally by two trained data collectors.

The patient interview lasted for 15–20 min and consisted of gathering data by the intervention pharmacist addressing demographic and full medical profile information with patients. These data included underlying medical conditions, chronic and acute medication lists including non-prescription and herbal products, any problem with medication, previous medical and surgical history, and family history. Those data were used along with data from the patient's health file at the facility to determine the current medications the patient is taking without reconciliation. Afterward, each patient's condition, from both groups, was assessed to screen for DRPs including PIMs and potential prescribing omissions (PPOs) using the most updated version of the STOPP/START criteria as well as the newly updated clinical guidelines of relevance to each case. The STOPP/START criteria are organized according to specific physiological body systems, thereby enhancing their useability. STOPP criteria, in particular, were selected for their comprehensiveness and sensitivity in assessing PIMs compared to alternative explicit criteria (e.g., Beers criteria) (Aguiar et al., 2021). The Medscape interaction checker was utilized in the initial assessment for the compatibility of drugs while checking related guidelines as needed including those by the American College of Cardiology/American Heart Association, the European Society of Cardiology, the Global Initiative for Chronic Obstructive Lung Disease, and the American Diabetes Association (O'Gara et al., 2013; Amsterdam et al., 2014; Yancy et al., 2017; Valgimigli et al., 2018; Whelton et al., 2018; Arnett et al., 2019; Grundy et al., 2019; Vogelmeir et al., 2020; American Diabetes Association, 2021; Medscape, 2021). The clinical pharmacist researcher assigned DRPs to one of eleven categories: no or unclear indication, better alternative available, regimen needs simplification, overdosage, overuse of therapy, drug-drug interaction, presence of an adverse drug reaction or drug allergy, unsafe medication, duplication therapy, omission, regimen needs intensification (Pharmaceutical Care Network Europe, 2003; Lim et al., 2018). Later, therapeutic recommendations which include drug discontinuation, dosage or regimen adjustment, drug substitution, or new drug prescription, were double-checked with a licensed pharmacist who is also a professor of pharmacotherapeutics. Final recommendations were then presented and discussed with prescribing physicians at the intervention site. In some instances, multiple DRPs for a patient would have been solved by one proposed recommendation, so the number of DRPs and the number of recommendations were not expected to match. These recommendations were either accepted, deferred (postponed to monitor the current patient's condition or to order laboratory testing), or rejected. The acceptance rate of DRPs was analyzed and presented according to physician specialty.

At the end of the project, a discussion was conducted with the manager of the facility to highlight all the recommendations and subsequent physicians' responses, together with the researcher's suggestions aimed at optimizing patient care. A copy of each patient documentation form was provided to the facility manager for the sustainability of patient care at the facility.

2.4 Study outcomes

The primary outcome of this study was the impact of the medication optimization deprescribing focused intervention on patient satisfaction. The process of translating, adapting, and validating the Medication Management Patient Satisfaction Survey (MMPSS) into Lebanese Arabic is described in the thesis of the first author (Alaa Eddine N, 2022). A manuscript describing the process is currently under review in this journal. Secondary outcome measures were the number of changes and subcategories of changes proposed by the pharmacist including drug discontinuation, substitution, initiation, or dosage adjustment, and the proportion of changes accepted by the prescribing physicians measured as a percentage of accepted, deferred, or rejected recommendations for each physician.

2.5 Statistical analyses

Descriptive statistics were used to describe the characteristics of the sample. They also provided data on drug-related problems, the nature and the number of recommendations as well as physicians' responses to recommendations. Descriptive analyses were done using IBM SPSS 24® generating frequencies, as well as means and ranges as relevant.

Descriptive statistics of the summary score (items 1–9) of MMPSS were computed for each experimental group to assess patient satisfaction with the service. Independent sample t-tests were used to check for the difference between control and intervention groups for the summary score of items one to nine and for item ten alone. Responses for items one to nine were coded from 0 to 3 with "strongly disagree" given a code of 0 and "strongly agree" given a code of 3. For item 10, a similar coding was followed with "poor" given a code of 0 and "excellent" given a code of 4.

A pilot study was carried out on 46 patients (23 per group) to calculate the required sample size needed that would ensure that the study is adequately powered. *A priori* power analysis was done and accordingly, a sample size of 57 patients per group was needed to detect an intervention effect size on patient satisfaction of 0.5 as measured by MMPSS, with a power of 80%. Power analysis and the analysis of the intervention's impact on patient satisfaction and on were done using the online software Jamovi®.

3 Results

3.1 Participants' characteristics

In total, 157 patients met the inclusion criteria for the study. Of those, 143 patients were enrolled in the study: 72 patients in the control group and 71 patients in the experimental group. See Figure 1. The mean age of the patients was 72 years in both groups. The majority of the patients were female (67% in the control group and 70% in the experimental group).

TABLE 2 Participants' characteristics and descriptive statistics.

		Control	Intervention
		n = 72 (50.3%)	*n* = 71 (49.7%)
Age	Mean	72	72
	Range	65–86	65–86
Gender	Female: frequency (%)	48 (67)	50 (70)
Number of comorbidities	Mean	4	4
	Range	1–9	1–8
Number of medications	Mean	8	8
	Range	5–14	5–17

TABLE 3 Anatomical Therapeutic Classification (ATC) classification of medications among intervention and control two groups (World Health Organization, 2022).

Medication ATC class	Medications taken by the control group n (%)	Medications taken by the intervention group n (%)	Total n (%)
A: Alimentary tract and metabolism	127 (46)	152 (54)	279 (24)
B: Blood and blood-forming organs	73 (49)	75 (51)	148 (13)
C: Cardiovascular system	271 (51)	259 (49)	530 (46)
G: Genito urinary system and sex hormones	5 (45)	6 (55)	11 (1)
H: Systemic hormonal preparations excluding sex hormones and insulins	21 (43)	28 (57)	49 (4)
M: Musculoskeletal system	16 (52)	15 (48)	31 (3)
N: Nervous system	13 (34)	25 (66)	38 (3)
R: Respiratory system	34 (52)	31 (48)	65 (6)

Patients had an average of four comorbidities and were using an average of eight medications daily in both groups. See Table 2.

3.2 Drug-related problems among the study population

After assessing all patient profiles (72 control and 71 experimental), DRPs were analyzed for both groups and presented for intervention and control groups according to the Anatomical Therapeutic Classification (ATC) classification of medications indicating comparable rates of medication use in different categories. See Table 3. Overall, 25 patients (18%) had no DRPs and 83% had one or more DRPs. Those DRPs ranged from one DRP (44%) to six DRPs per patient (1%), with a total of 231 DRPs. A drug regimen that needs to be intensified counted for the highest percentage (22%), followed by a drug with no or unclear indication (16%), an unsafe medication (16%), and a drug omission (14%). Further, 66% of the screened DRPs met the STOPP/START criteria (77%, and 23% respectively). The most common DRP in the STOPP category was that Aspirin was not indicated; while in the START category, the need for an Angiotensin-Converting Enzyme Inhibitor (ACEI) was the most common DRP encountered. The remaining DRPs were revealed by matching their use to guideline-based recommendations or by running medications used through a drug-interaction checker. See Table 4.

3.3 Recommendations made to physicians and response to those recommendations

In total, 221 recommendations, divided into six categories, were provided to physicians. Of those recommendations, more than half, 52%, were to discontinue one medication, 23% were to intensify a therapeutic regimen, and 13% were to initiate one medication. Added together, deprescribing recommendations; i.e., discontinue a medication, decrease a dose, switch to an alternative, and simplify a regimen; comprised 64% of recommendations, which was almost double the sum of drug initiation and regimen intensification recommendations (36%). See Table 5. The intervention pharmacist discussed the recommendations with three cardiologists, two endocrinologists, two gastroenterologists, one pulmonologist, and one orthopaedist. The majority of the recommendations were provided to cardiologists (72%). More than half of the total recommendations were rejected (56%), 30% were accepted, and the remaining (14%) were deferred. The rate of accepting recommendations was not uniform across physicians. The pulmonologist and the orthopaedist accepted all the recommendations received, while cardiologist-1 and gastroenterologist-1 showed an acceptance rate of 42% followed by endocrinologist-1 (35%). Cardiologist-3, on the other hand, accepted only 5% of the recommendations provided (Table 6).

TABLE 4 List and number of drug-related problems (*N* = 231).

Drug-related problem type	Total n (%)	Intervention n (%)	Control n (%)
Regimen needs intensification	50 (21.7)	25 (50)	25 (50)
No or unclear indication	38 (16.4)	15 (39)	23 (61)
Unsafe medication	36 (15.7)	19 (53)	17 (47)
Omissions	33 (14.3)	18 (55)	15 (45)
Overduration of therapy	25 (10.9)	15 (60)	10 (40)
Drug-drug interaction †	23 (10)	15 (65)	8 (35)
Presence of an adverse drug reaction or drug allergy	13 (5.6)	9 (69)	4 (31)
Other DRPs[a]	13 (5.6)	6 (46)	7 (54)
Total	231 (100)	122 (53)	109 (47)

[a]Those included having a better alternative available, regimen needs simplification, medication overdosage, duplication of therapy, † All drug interactions were assessed using the Medscape interaction checker as serious, except for Amiodarone with Acenocoumarol (not found in Medscape).

3.4 Satisfaction with the intervention

Descriptive statistics of the summary medication management patient satisfaction score (MMPSS items one to nine) per group are presented in Table 7. Patients in the control and experimental groups had a meaningful difference in satisfaction in favor of the provided intervention. Cohen's d effect size of 1.75 (t (141) = −10.48, $p < 0.001$). Data in both groups were not normally distributed. Due to the non-normality of the outcome by groups, a Mann-Whitney non-parametric analysis was also completed, providing the same conclusion (Table 8). The control group had a mean score of 15.2 (SD: 3.74), which is statistically significantly lower than that of the experimental group by six points (21.1; SD: 2.9).

TABLE 5 List, number and proportion of recommendations made to physicians (*N* = 221).

Recommendation type	n (%)
Drug discontinuation	114 (51.5)
Regimen intensification	50 (22.6)
Drug initiation	29 (12.9)
Drug substitution	18 (8.3)
Regimen simplification	7 (3.3)
Dosage adjustment	3 (1.4)

4 Discussion

4.1 Key findings

This study assessed the impact of a pharmacist-led medication optimization service with a deprescribing focus targeting older adults of low income on polypharmacy while utilizing the adapted consolidated framework for implementation research in planning the service (Shoemaker et al., 2017). Results showed that problems related to medications and medication inappropriateness are widespread among the studied population providing an opportunity for a pharmacist-driven intervention. While physician acceptance of provided pharmacist recommendations was not optimal, patients provided with this service showed much greater satisfaction with the provided service compared to the regular medication dispensing service routinely provided by the facility site pharmacist.

4.2 Drug-related problems and potentially inappropriate medications

Regarding drug-related problems, the findings reported here are in line with other studies that show a high prevalence of DRPs in older adults (68%–93%) (Allard et al., 2001; Sellors et al., 2003; Milos et al., 2013; Chan et al., 2014). Of the reasons that typically cause this high DRP prevalence among the studied population in different settings, the fact that recruited patients were suffering from multiple comorbidities and hence, were followed by multiple prescribers, with insufficient coordination between them might have been a key issue driving DRPs in this patient population (Vinks et al., 2009; Tan et al., 2014; Campbell A et al., 2018; Cheong et al., 2018; Khera et al., 2019). Still, it is important to note that DRPs found in this study at this facility were comparable to the literature as indicated above. This indicates that, despite the limited resources, the quality of patient care in this setting is comparable to others.

Being the main target, PIMs, as defined by the STOPP criteria, counted for half of the DRPs in this study, with the majority of PIMs falling in the cardiovascular drug class (no indication for Aspirin and long-term use of DAPT), followed by the unsafe use of sulfonylurea in elderly. Consistent with our results, studies addressing PIM prevalence among elderly patients indicated a prevalence of PIMs of 45%–60% (Saab et al., 2006; Eze and Olowu, 2011; Zeenny et al., 2017). A study conducted in Ethiopia revealed that the inappropriate use or omission of antithrombotic medications is prevalent in Ethiopian older adults (Getachew et al., 2016). Other studies determined PPIs, antithrombotic, sulfonylurea, and benzodiazepines as the most frequent PIMs screened by STOPP criteria (Dalleur et al., 2014; Chau et al., 2016; Kimura et al., 2017), in addition to NSAIDs, skeletal muscle relaxants, antihistamines, estrogen, and drugs for the central nervous system, as described by Beer's criteria (Fadare et al., 2013; van Heerden et al., 2016; Ammerman et al., 2019; Cardwell

TABLE 6 Number of recommendations and associated responses per physician specialty (*N* = 221).

Physician speciality	Number of recommendations	Accepted Number(%)	Rejected Number(%)	Deferred[a] Number(%)
Cardiologists	158	44 (28)	94 (59)	20 (13)
Endocrinologists	31	9 (29)	15 (48)	7 (23)
Gastroenterologists	25	7 (28)	15 (60)	3 (12)
Pulmonologist	3	3 (100)	0 (0)	0 (0)
Orthopaedist	4	4 (100)	0 (0)	0 (0)
Total	221	67 (30)	124 (56)	30 (14)

[a]Deferred means the response of the physician was postponed to a later time to monitor the patient or to order laboratory tests.

TABLE 7 Descriptive statistics of the summary medication management patient satisfaction score per group.

	Group[a]	N	Mean	Median	SD	SE	Minimum	Maximum
Summary score	C	72	15.24	15	3.74	0.44	8	27
	I	71	21.11	21	2.91	0.35	14	27

[a]C:Control Group; I = Intervention Goup.

et al., 2020; Deyo et al., 2020) This diversity in reported PIMs is common among studies. In this study, patients were of low income, hence, OTC medications (NSAIDs, antihistamines), and other medications not provided by the facility (CNS drugs) were not likely to be used, to begin with, as they were not typically affordable to patients. Second, patient records that were available at the facility for the intervention pharmacist might have been missing some information on the use of those products.

4.3 Clinical pharmacist's recommendations and physician acceptance

The recommendations provided by the intervention pharmacist to the specialty physicians at the facility mainly focused on deprescribing rather than initiating new medications, with the most common being discontinuing a medication. Intensification of a regimen, on the other hand, was the second common recommendation. This comes in agreement with literature where drug discontinuation was a frequent recommendation in many pharmacist-led interventions targeting elderly patients on polypharmacy (Vinks et al., 2009; Milos et al., 2013; Chau et al., 2016; Campins et al., 2017; Hurmuz et al., 2018; Cardwell et al., 2020). Some studies described pharmacist recommendations that only focused on providing deprescribing recommendations to physicians without addressing therapy intensification. (Kurt Kroenke and Pinholt, 1990; Dalleur et al., 2014; Morrison and MacRae, 2015; Pruskowski and Handler, 2017; Wouters et al., 2017; Cheong et al., 2018; Clark et al., 2020; Deyo et al., 2020; Kua et al., 2021). On the contrary, drug initiation, patient education, laboratory monitoring, and dose adjustment were more common recommendations in other studies (Tan et al., 2014; Campbell A et al., 2018; Khera et al., 2019). One of the latter studies targeted inappropriate medication use among elderly patients without necessarily being on polypharmacy (Campbell A et al., 2018). In addition, the explicit criteria for screening for PIMs such as the STOPP/START criteria were not used in some of these studies (Tan et al., 2014; Campbell A et al., 2018). These factors could all result in differences in pharmacists' recommendations between studies.

Thirty percent of the recommendations provided to different specialty physicians were accepted in this study. This acceptance rate is in line with several studies performed in multiple settings (20%–42%) (Vinks et al., 2009; Touchette et al., 2012; Pruskowski and Handler, 2017; Clark et al., 2020). Higher acceptance rates (75%–99%), however, were observed in other studies (Blakey and Hixson-Wallace, 2000; Roth et al., 2013; Campins et al., 2017; Kimura et al., 2017; Cheong et al., 2018; Balsom et al., 2020; Kua et al., 2021). Hailu et.al, a study conducted in a hospital in Ethiopia, showed a similar rate of DRPs (82%), but a high acceptance rate (92%) (Hailu et al., 2020). The fact that many of the drugs that constituted better alternatives for patients were in shortage at the time of the study has likely contributed to a significant proportion of those physician rejections for the intervention pharmacist recommendations. Under conditions of resource scarcity, physicians tend to give patients the available medication, even if it does not provide the most optimal therapeutic effect, rather than keeping the patient without therapy. This issue is often overlooked in research that is carried out in settings where resource scarcity does not represent a significant barrier and would warrant exploration in future work. Even with this factor taken into consideration, it was interesting to note that adopting an implementation science approach in planning this study did not seem to increase the acceptance rate of physicians in this setting above average rates reported in the literature. This suboptimal acceptance rate for recommendations provided by pharmacists should be explored in the future implementation of science-driven interventions building on and complementing this work.

4.4 Patient satisfaction with the intervention

The fact that patients receiving services in the facility welcomed the intervention provided by the intervention

TABLE 8 Difference in patient satisfaction between groups.

		Statistic	Df	P	Mean difference	SE difference		Effect size
Summary score	Student's *t*	−10.48	141.00	<.001	−5.88	0.56	Cohen's d	−1.75
	Welch's *t*	−10.49	133.81	<.001	−5.88	0.56	Cohen's d	−1.75
	Mann-Whitney U	508.50		<.001	−6.00		Rank biserial correlation	0.80

pharmacist is a key finding in this study. One would have suspected that patients, in this kind of setting, where medications are provided free of charge may have received an intervention focusing on a reduction in the number of offered medications with suspicion. This did not seem to be the case with the intervention producing a wide margin of increase in patient satisfaction. This finding could be promising with regards to patient satisfaction towards deprescribing in settings providing medications for little to no charge and requires further investigation. It is possible that because START/STOPP criteria were used, patients felt they would get additional medications prescribed as a result of their medication review, not just have medications deprescribed, in case their clinical condition required so. This could have further boosted their satisfaction with the provided service and reduced the likelihood of the misconception that the economic saving from deprescribing medications was the key driver for the work.

Earlier research assessed patient satisfaction with pharmacist-provided care in the community, primary care, and hospital settings (Alhomoud et al., 2016; Soeiro et al., 2017; Nigussie and Edessa, 2018; Jordan et al., 2021; Kabba et al., 2021; Kebede et al., 2021). In most of these studies, research indicated that patient satisfaction with pharmacist services was linked to interpersonal aspects such as communication with and being respectful to patients, as well as disease and therapy management offered by pharmacists. In Sierra Leone and Ethiopia, where health resources are relatively limited, an important factor leading to patient satisfaction was having those services provided by the pharmacist for free (Kabba et al., 2021; Kebede et al., 2021). This is in line with our study, where the intervention pharmacist reviewed therapeutic regimens for patients of low income and completed the service for no charge.

An implementation science approach was used to guide the provision of the pharmacist intervention in this study. The CFIR, which was applied here, was previously used in implementing various health interventions such as the implementation of fall prevention projects, clinical practice guidelines in nursing practice, and the HPV vaccine schedule among adolescents (Shaw et al., 2013; Breimaier et al., 2015; Garbutt et al., 2018). Taken together and in agreement with this study, these findings indicate that the application of CFIR proved to be a helpful framework in organizing the implementation process of those projects being particularly valuable in managing barriers and facilitators behind the success of the implementation.

Further, the literature indicates that patient satisfaction with health interventions guided by implementation science is promising. The application of implementation science in family planning and in providing life narrative interviews for medical inpatients led to high satisfaction and acceptance among participants (Rybarczyk et al., 2019; Weis and Festin, 2020). Moreover, an initiative to implement a measurement program of office and home blood pressure in primary care demonstrated favorable satisfaction among patients and providers towards the service that might decrease the use of unnecessary antihypertensive medications and enhance hypertension control (Doane et al., 2018). These findings are consistent with our study, where patient satisfaction with the provided intervention that was guided by implementation science was high.

4.5 Implications for practice

This study calls for increased attention to this population in future research and targeted medication optimization interventions. Pharmacists and other health professionals should be proactive in pursuing deprescribing-focused interventions in settings with limited resources noting the benefits of such interventions in these settings including increased patient satisfaction. In countries where deprescribing has not been integrated into practice, as in Lebanon, measures could be taken to facilitate the transition using an implementation science approach that considers as many implementation science considerations as possible. This includes providing facilities with different resources for intervention success; education and training of physicians, pharmacists, and medical staff; together with the incorporation of deprescribing guidelines and tools such as the STOPP/START criteria into routine practice. It is also recommended that mechanisms of financing deprescribing related activities would be established to promote its sustainability. These mechanisms should be informed by cost effectiveness analyses of interventions such as this, which are typically done and presented separately. This would be interesting to pursue and could be investigated in future research.

Another area for future research would consider the benefits vs. risks of deprescribing medication using tools such as STOPP/START criteria accounting for risks such as rebound of conditions as a result of the withdrawal of specific medications. Clinicians would benefit from extra training on managing those risks as part of different aspects to effectively and safely implement deprescribing. This along with the facilitation of interprofessional therapeutic management of medication regimens would lead to better patient satisfaction and outcomes.

4.6 Strengths and limitations

This prospective experimental study has specific strengths. It is unique in coupling the deprescribing approach with the use of an

implementation science framework in planning the intervention while assessing patients' satisfaction with the medication management pharmacist's service. Still, this study had its limitations. It was conducted in a single center in Lebanon, limiting its generalizability. In addition, for logistical reasons, the implementation and outcomes of recommendations were not monitored. Studies spanning those areas could be targeted by future research.

5 Conclusion

This intervention conducted in a facility serving patients of low income found a high prevalence of inappropriate medications taken by these patients comparable to the literature indicating that, despite the limited resources, the quality of patient care in this facility is comparable to other settings. Further, in a facility where medications are provided free of charge, patients enrolled in the study were highly satisfied with the new service they received from the pharmacist showing promise for future interventions addressing deprescribing in similar settings. The pharmacist performing the intervention provided suggestions to physicians yielding an average acceptance rate, which calls for further research into the best ways of integrating implementation science principles in guiding pharmacist interventions. Future work should assess how specific CFIR constructs contribute to the outcomes of deprescribing interventions.

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 human participants were reviewed and approved by Beirut Arab University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

NA: Conducting a research and investigation process, formal analysis, Writing Original Draft JS: Design of methodology; data analysis; Writing—Review & Editing AE-Y: data analysis; Implementation of intervention; Writing—Review & Editing HS: Implementation of intervention; Writing—Review & Editing MA: Conceptualization of research, Development of methodology; Implementation of intervention; data analysis; Writing Original Draft.

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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

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A national survey of individualized pharmaceutical care practice in Chinese hospitals in 2019

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Background: Individualized pharmaceutical care, which consists of therapeutic drug monitoring (TDM), pharmacogenetic (PGx) testing and pharmacist-managed clinic (PMC), is one of the most important trends in clinical pharmacy development in the future. While relevant studies in China were primarily single-center or regional. This study aims to explore the current status of individualized pharmaceutical care in China, find out the existing problems and provide references for its further development.

Methods: An electronic questionnaire was used and national hospitals' pharmaceutical administration data from January to December 2019 were collected. The data were sorted into Excel for further statistical analysis. All analyses were descriptive.

Results: The proportions of hospitals that performed TDM and PGx testing were 12.83% and 9.48%, respectively. The major responsible departments were the clinical laboratory and pharmacy department. External quality control was carried out in around 70% of hospitals for both TDM and PGx testing. More than half of hospitals provided TDM services for valproate sodium, digoxin, carbamazepine, vancomycin and cyclosporine. And an average of 6.84 drugs were performed TDM in 540 hospitals. Clopidogrel and warfarin were the top two drugs that performed PGx testing. As for the PMC, 10.03% of hospitals opened PMC, of which 60.00% had independent PMC. Approximately 80% of PMC services were free of charge.

Conclusion: The development of individualized pharmaceutical care in China is still in the early stage. Different sectors have to coalesce to promote its implementation, including the appropriate education, coverage, reimbursement policies, high-quality evidence, data systems, health system processes and health policies, *etc.*

KEYWORDS

China, development, individualized pharmaceutical care, pharmacist-management clinic, pharmacogenetic testing, therapeutic drug monitoring

1 Introduction

Considerable attention has been paid to "precision medicine" in recent years. It refers to treatments using individuals' genetic, biomarker, phenotypic, or psychosocial characteristics to distinguish a specific patient from others with similar clinical manifestations (Jameson and Longo, 2015). Individualized pharmaceutical care is a component of precision medicine that mainly aims at individualized pharmacotherapy. Therapeutic drug monitoring (TDM) and pharmacogenetic (PGx) testing are two essential approaches to making scientific drug regimens based on individual differences among patients. Meanwhile, opening a pharmacist-managed clinic (PMC), or a medication therapy management clinic (MTMC) is another significant step toward giving patients individualized pharmaceutical treatment. The implementation of TDM, PGx testing and PMC are all important references to evaluate the quality of individualized pharmaceutical care.

Having an overall grasp of individualized pharmaceutical care is conducive to identifying the existing problems and better promoting its further development. However, many recent studies concerning TDM, PGx or PMC in China were single-center or regional in nature (Zhang C. et al., 2021; Zhang J. et al., 2021; Liu et al., 2021). Some studies have explored healthcare providers' and researchers' understanding of PGx and factors that hindered the PGx clinical application (Guo et al., 2021), but the overall situation of individualized pharmaceutical care in China (including the implementation rate, responsible departments, the conduction of quality control and so on) is still unknown. We thus perform this national questionnaire survey regarding TDM, PGx and PMC in clinical practice to comprehensively know about the current situation of individualized pharmaceutical care in China and raise potential solutions to existing problems, hoping to promote the long-term, healthy growth of this field.

2 Materials and methods

2.1 Data collection

This study was nested within a nationwide survey, undertaken by the National Institute of Hospital Administration to collect data on pharmaceutical administration and quality control in medical institutions. Chinese hospitals are rated in 3 grades based on a series of indicators (hospital scale, research capabilities, medical facilities, etc.). The top grade among these is the tertiary hospital. Given the difficulty of collecting data from grade-I hospitals, our target hospitals were confined to secondary and above general hospitals, and the ownership had no limitation (Figure 1 introduced the grade, ownership and type of hospitals in China). Heads of medical affairs departments in these hospitals were requested to register and log on to the accompanying website National Clinical Improvement System (National Clinical Improvement System, 2019) to fill out questionnaires concerning pharmaceutical administration, including individualized pharmaceuticals care. The guideline for data collection was provided in (Supplementary material S1). The collected data ranged from January 2019 to December 2019. To ensure the accuracy and reliability of the data, each hospital was requested to designate a responsible person to check the reported data. Additionally, the questionnaire's data quality will serve as a benchmark for hospital evaluation and key specialty settings. This survey was approved and organized by the National Institute of Hospital Administration in the national layer and was

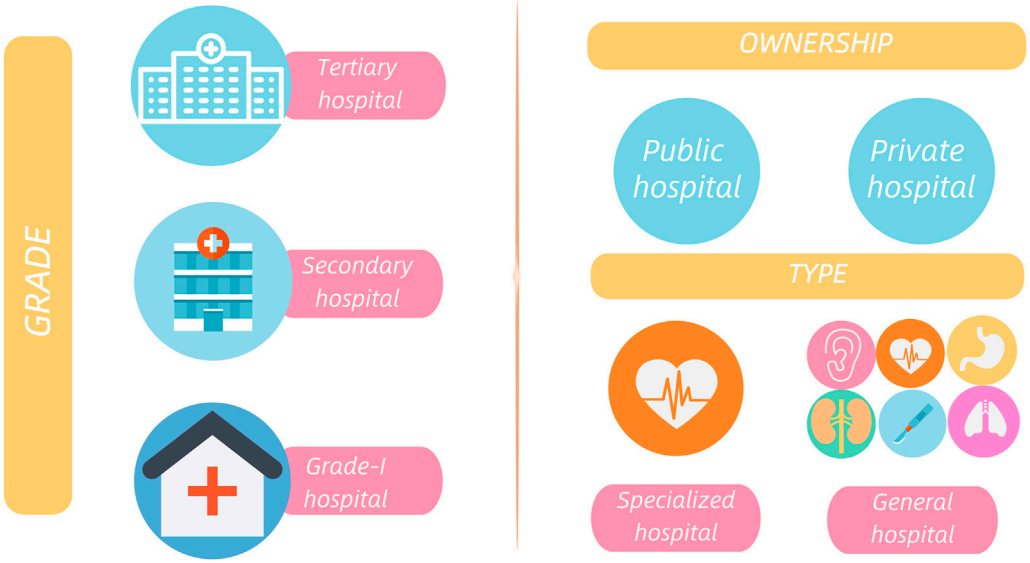

FIGURE 1
The grade, ownership and type of hospitals in China, Grade of hospitals: According to the *Hospital Grading Management Standard*, Chinese hospitals are divided into 3 grades, i.e., tertiary, secondary and grade-I hospitals, based on a series of indicators (hospital scale, research capabilities, medical facilities, *etc.*). Among these grades, the tertiary hospital is the premier. Ownership of hospitals: Public hospitals are hospitals funded by the country and taken into the government's financial budget. Being the mainstay of Chinese medical service system, public hospitals are directly managed by local health authorities, emphasizing public welfare. Private hospitals refer to health institutions funded by societies and dominated by for-profit institutions. The establishment of private hospitals must be approved by local health authorities. Type of hospitals: includes general and specialized hospitals.

TABLE 1 Indexes analyzed in our survey.

Section	Evaluation Indexes	Details
TDM	Hospitals with TDM (%)	The number of hospitals implementing TDM/Total number of hospitals with valid data
	Responsible department	Pharmacy department; Clinical laboratory; Others
	EQC[a] (%)	The number of hospitals conducting EQC for TDM/Total number of hospitals with valid data
	Drugs tested	All hospitals filled in this index according to the actual situation in their own hospitals
PGx	Hospitals with PGx testing (%)	The number of hospitals implementing PGx testing/Total number of hospitals with valid data
	Responsible department	Pathology department; Clinical laboratory; Pharmacy department; Multi-department; others
	EQC (%)	The number of hospitals conducting EQC for PGx testing/Total number of hospitals with valid data
	Drugs and genes tested	All hospitals filled in this index according to the actual situation in their own hospitals
PMC/MTMC	Hospitals with PMC (%)	The number of hospitals providing PMC/Total number of hospitals with valid data
	Types[b]	Collaborative PMC; Independent PMC (Specialized/General)
	Charge	Yes or No

TDM: Therapeutic drug monitoring; PGx: Pharmacogenomics; PMC: Pharmacist-managed clinic; MTMC: Medication therapy management clinic; EQC: External Quality Control, or External Quality Assessment (EQA).

[a]External quality control is organized by the clinical laboratory center (or reference laboratory) under the leadership of the health department, to ensure the reliability of the testing results in hospital laboratories. The reference laboratory delivers quality control samples to hospital laboratories and requires them to report the testing results in a limited time. Then reference laboratory will analyze the submitted results to find out existing problems, eventually improving the testing abilities in hospital laboratories.

[b]Collaborative PMC, refers to a service mode in which pharmacists provide pharmaceutical care for patients together with doctors or personnel from other departments; Independent PMC, refers to a service mode in which pharmacists provide pharmaceutical care independently. Independent PMC, includes specialized clinics and general clinics.

approved by the Ethical Committee of the Peking Union Medical College and Chinese Academy of Medical Sciences (Beijing, China).

2.2 Questionnaire development

The questionnaire was designed by experts from the National Institute of Hospital Administration, covering a wide range of items concerning pharmaceutical management and quality control. Two rounds of Delphi survey through online questionnaire were conducted and 105 expert opinions were collected in total. The survey was modified based on the results of expert opinions. A consensus was reached after an experts' face-to-face discussion. In this paper, we focus on items related to individualized pharmaceutical care. Concerning questions were excerpt from the questionnaire of Medical Quality Management and Control in 2019 (Supplementary material S2). These questions can be divided into five parts, (1) basic hospital information; (2) TDM implementation situation; (3) PGx testing implementation situation; (4) the situation of PMC and (5) supplementary information. Explanations for specific notions (such as PGx testing) have been given in the questionnaire and the hotline was available for any inquiries.

2.3 Data analyses

The data collected from the network survey was sorted into Microsoft Excel 2016 for further statistical analysis and chart drawing. We analyzed the data as a single cohort or stratified by grade and ownership of hospitals. Indexes analyzed in our survey were summarized in Table 1. The indices of hospitals with TDM/PGx/PMC and the conduction of external quality control were analyzed by percentage. On account of the indexes of drugs (or genes) tested in TDM and PGx testing services, the content filled in by different hospitals varies greatly because of the fill-in-the-blank form, adding difficulties for further analysis. To make data standardized for further analysis, we first sorted out hospitals with valid information, then extracted the data according to the kind of drugs (or genes) and counted the total number of drugs (or genes) for each hospital. In the specific analysis, we excluded hospitals in which data was missing or deviated from reality. All of our analyses were descriptive.

3 Results

Overall, we delivered electronic questionnaires to 4 750 hospitals nationwide, and the total numbers of respondents were 4 637 for TDM, 4 640 for PGx and 4 638 for PMC, respectively.

3.1 Status of therapeutic drug monitoring

3.1.1 Hospitals with TDM

In total, 4 637 hospitals with valid data were included in this item. Of these, 595 (12.83%) hospitals carried out TDM service, the number and percentage of hospitals with TDM classified by grade and ownership were shown in Table 2. The percentage of hospitals with TMD ranged from 35.28% (in tertiary public hospitals) to 1.70% (in secondary private hospitals), which indicated that the clinic implementation of TDM was not widespread throughout the country. The percentage of tertiary hospitals with TDM was higher than secondary hospitals, and the public was higher than private.

TABLE 2 The percentage of hospitals with TMD, PGx testing and PMC.

Hospitals	Hospitals with TMD%	Hospitals with PGx testing%	Hospitals with PMC%
Tertiary Public hospitals	35.28 (471/1 335)	27.02 (361/1 336)	24.70 (330/1 336)
Secondary Public hospitals	3.84 (96/2 502)	2.24 (56/2 503)	4.44 (111/2 502)
Tertiary Private hospitals	17.20 (16/93)	12.90 (12/93)	6.45 (6/93)
Secondary Private hospitals	1.70 (12/707)	1.55 (11/708)	2.55 (18/707)
All hospitals	12.83 (595/4 637)	9.48 (440/4640)	10.03 (465/4638)

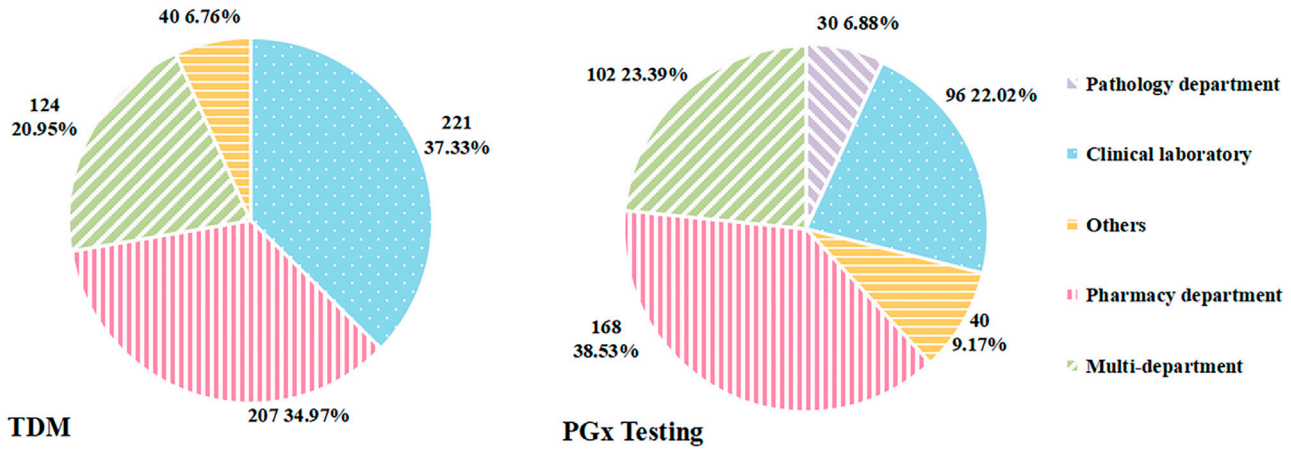

FIGURE 2
The proportion of different departments in charge of TDM and PGx testing.

3.1.2 Responsible department

As for the department in charge of TDM service, three of the 595 hospitals that carried out TDM were excluded from further analyses for data deficiency. As shown in Figure 2, the major departments in charge of TDM were the clinical laboratory and pharmacy department. TDM was conducted independently by the clinical laboratory in 221 hospitals (37.33%), followed by the pharmacy department in 207 hospitals (34.97%).

3.1.3 External quality control for TDM

External quality control (EQC), also called external quality assessment (EQA), is a crucial part of clinical laboratory quality management. It is organized by the Clinical Laboratory Center (or Reference Laboratory) under the leadership of the Health Department, to ensure the reliability of the testing results in hospital laboratories. The reference laboratory delivers quality control samples to hospital laboratories and requires them to report the testing results in a limited time. Then the reference laboratory will analyze the submitted results to find out existing problems, eventually improving the testing abilities in hospital laboratories. Of 595 hospitals that provided TDM service, 412 (69.24%) conducted external quality control (EQC) for TDM. Then we stratified the hospitals by grade and ownership. It showed that the proportions in tertiary public, secondary public, tertiary private and secondary private hospitals were 73.04% (344/471), 57.29% (55/96), 56.25% (9/16) and 33.33% (4/12), respectively.

3.1.4 Drugs tested

Of 595 hospitals, only 540 offered valid information about specific drugs carried out TDM. We firstly sorted out all kinds of drugs for TDM from the provided information and then counted the total number of drugs for each hospital. As shown in Figure 3, more than half of hospitals provided TDM services for valproate sodium, digoxin, carbamazepine, vancomycin and cyclosporine. And an average of 6.84 drugs were performed TDM in 540 hospitals. After we stratified these hospitals by grade and ownership, it revealed that tertiary public hospitals performed 7.43 drugs for TDM on average, which was the highest among these four types of hospitals (Table 3).

3.2 Status of pharmacogenetic testing

3.2.1 Hospitals with PGx testing

Of 4 640 hospitals with available data, 440 (9.48%) implemented PGx testing. Table 2 showed the number and proportion of hospitals with PGx testing stratified by grade and ownership. It also presented that the proportion of tertiary hospitals with PGx testing was higher than that of secondary hospitals. Furthermore, the proportion was higher in public hospitals than that in private hospitals.

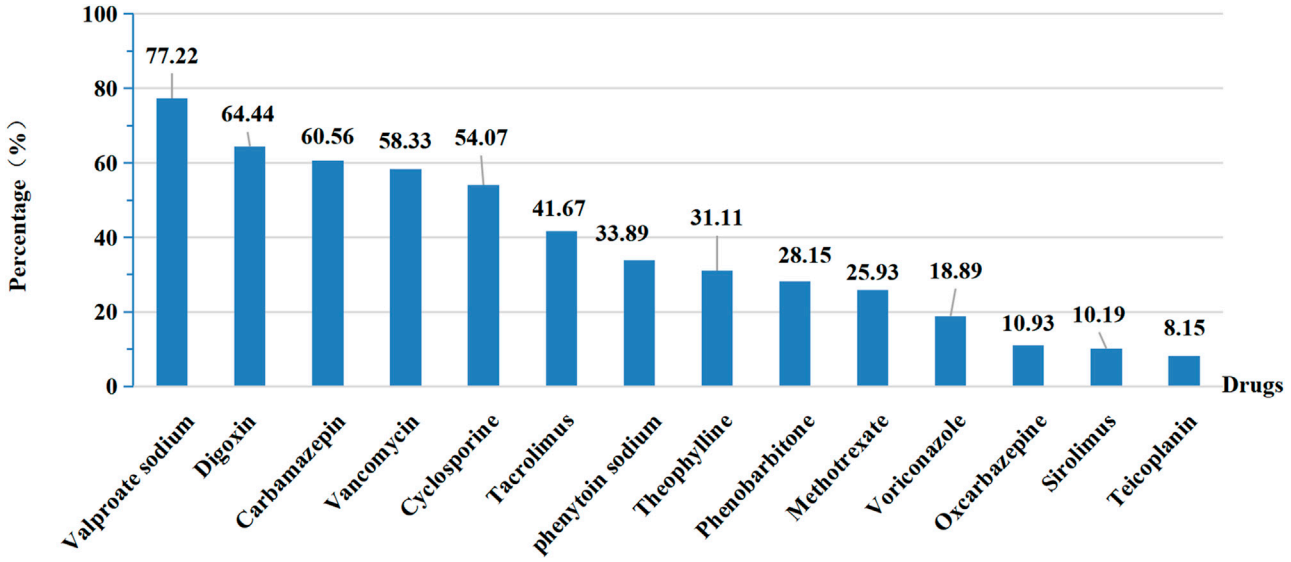

FIGURE 3
The percentage of drugs performed TDM in 540 hospitals.

TABLE 3 Drugs performed TDM on average in 540 hospitals.

Hospitals	Total	Drugs performed TDM on average
	*N**	
Tertiary Public hospitals	448	7.43
Secondary Public hospitals	73	3.81
Tertiary Private hospitals	12	5.71
Secondary Private hospitals	7	3.29
All hospitals	540	6.84

*N**: indicates the number of respondents provided valid information.

3.2.2 Responsible department

After excluding four hospitals with missing data of this index, the number of hospitals with valid data was 436. Of these, PGx testing in 168 hospitals was undertaken by the pharmacy department, accounting for the largest proportion (38.53%), followed by multi-department in 102 (23.39%) hospitals (Figure 2).

3.2.3 EQC for PGx testing

Among the 440 hospitals with PGx testing, 309 (70.23%) conducted EQC for PGx testing. And the proportions in tertiary public, secondary public, tertiary private and secondary private hospitals were 72.00% (260/361), 66.07% (37/56), 58.33% (7/12) and 45.45% (5/11), respectively.

3.2.4 Drugs and genes tested

Most hospitals filled this index with drugs and/or genes, but a few hospitals filled it with disease or irrelevant information, making it impossible to determine whether a specific drug performed PGx testing in those hospitals. We therefore excluded these hospitals to ensure the accuracy of our results. Ultimately, a total of 368 hospitals were included. As shown in Figure 4, we ranked drugs and genes by the number of hospitals offering PGx testing for them. Clopidogrel, warfarin, statins, folic acid and aspirin were the top five drugs that performed PGx testing in 368 hospitals. As for genes, the top five were the cytochrome P450 (*CYP*) *2C19* gene, 5,10-methylenetetrahydrofolate reductase (*MTHFR*), Aldehyde dehydrogenase 2 (*ALDH2*), *CYP2C9* and Vitamin K epoxide reductase complex subunit 1 (*VKORC1*).

3.3 Status of pharmacist-managed clinic

3.3.1 Hospitals with PMC

A total of 4 638 hospitals were included in this index, among these, 465 (10.03%) hospitals set up PMC. From Table 2 we can see that the proportion of hospitals with PMC varied by grade and ownership.

3.3.2 Types of PMC

We excluded five hospitals that did not fill in this index. Among 460 hospitals, 85 (18.48%) hospitals had collaborative PMC, 276 (60.00%) had independent PMC, including 99 (21.52%) specialized

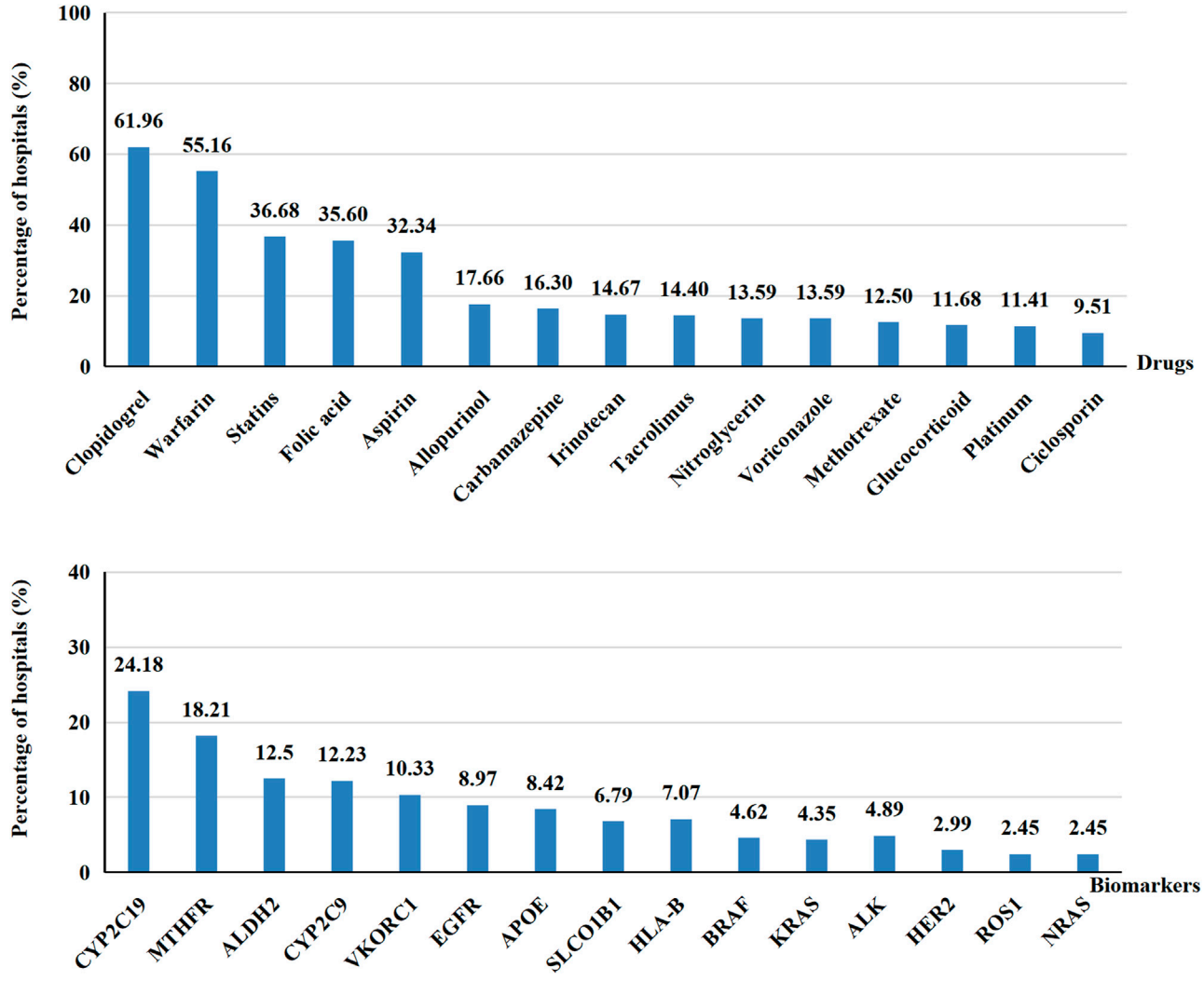

FIGURE 4
The percentage of drugs and genes performed PGx testing.

and 177 (38.48%) general clinics. Besides, 99 (21.52%) hospitals had more than one type of PMC. When these hospitals were stratified by grade and ownership, we found that in all kinds of hospitals, general PMC accounted for the largest share (Figure 5).

3.3.3 Charge

In this index, all hospitals provided valid data. Of 465 hospitals with PMC, only 98 (21.08%) were charged. PMC in six tertiary private hospitals were all free of charge. And the proportions of charging PMC in tertiary public hospitals, secondary public hospitals and secondary private hospitals were 27.27%, 5.41% and 11.11%, respectively.

4 Discussion

Our study intends to investigate the state of individualized pharmaceutical care in China, find out any unsolved issues, and offer solutions for its further advancement. We found that the implementation rate of TDM, PGx and PMC is relatively low (12.83%, 9.48% and 10.03%, respectively). The responsible departments of TDM and PGx testing among hospitals are not unified yet, and the clinical laboratory and pharmacy department were the major responsible departments. About 70% of hospitals conducted EQC for TDM, and the proportion is similar for PGx testing. TDM services for valproate sodium, digoxin, carbamazepine, vancomycin, and cyclosporine were offered by more than 50% of hospitals. Clopidogrel and warfarin were the top two drugs that performed PGx testing. Approximately 80% of PMC services were free of charge. Based on the results of this survey, we discussed the proportion of hospitals with individualized pharmaceutical care, responsible departments, the conduction of quality control, specific implementing projects for TDM/PGx and the development of PMC in turn.

4.1 The proportion of hospitals with individualized pharmaceutical care

Our survey provides fresh reference regarding the current situation of individualized pharmaceutical care all over China. In

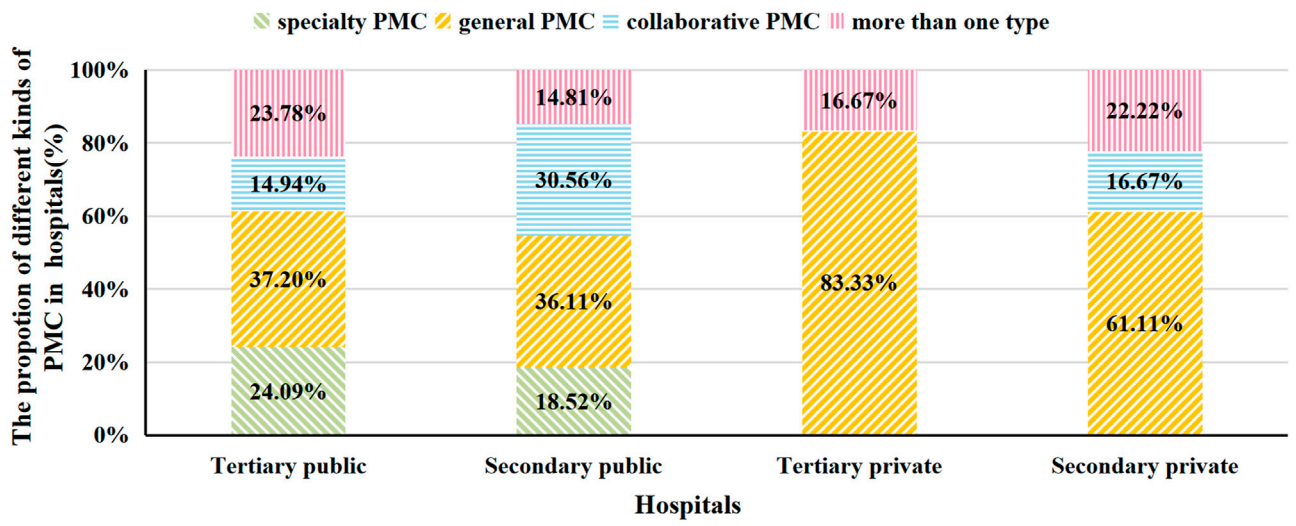

FIGURE 5
The proportion of different kinds of PMC in hospitals.

general, tertiary hospitals had higher proportions of hospitals with TDM, PGx testing, or PMC services than secondary hospitals, and public hospitals had higher proportions than private hospitals, reflecting the unbalanced development situation among hospitals. Besides, there is still a big gap between China and the United States in the implementation of TDM. According to the American Society of Health-System Pharmacists (ASHP) national survey findings in 2015, 70.6% of hospitals used TDM to routinely monitor patients for adverse events (Pedersen et al., 2016), which was around two-fold the rate in our tertiary public hospitals (35.28%). However, it is noteworthy that multiple metrics from different dimensions need to be measured to comprehensively assess the advance of individualized pharmaceutical care, including the implementing rate of TDM, PGx or PMC, the conduction of quality control, the number of drugs performed TDM or PGx, patient satisfaction, and so on. It cannot be inferred merely from the implementing rate of TDM. Quantitative methods are needed to evaluate the quality of pharmaceutical care more scientifically and roundly.

Interestingly, we discovered that the proportions of hospitals with TDM were even lower than the proportions from older studies in China. A study conducted by Chen et al., in 2013 reported that 89.89% (80/89) hospitals had provided TDM service (Chen et al., 2015), and another survey conducted by Zhang et al., in 2019 showed that 75.86% (22/29) hospitals offered TDM service (Zhang C. et al., 2021), which was much higher than our results in 2019. We speculated that the excessively high rates in these studies were mainly caused by the inclusion of unrepresentative hospitals. Chen et al. selected 89 public hospitals as objects, and Zhang et al. only included 29 tertiary public hospitals in northern China. Moreover, results can also be influenced by the attitude of staff filling out the questionnaire. The data Chen et al. used were submitted by hospitals to evaluate key specialty departments, thus data providers were more likely to show their situation in an overly flattering light. On the contrary, our survey was carried out for the aim of pharmaceutical quality control and had nothing to do with the hospital evaluation.

As a whole, our results indicated that the popularization of TDM, PGx and PMC in China is at a relatively low level. However, in recent years, the Chinese authorities strongly support the implementation of pharmaceutical care. In 2018, the National Health Commission (NHC) and the National Administration of Traditional Chinese Medicine promulgated *Opinions on accelerating the high-quality development of pharmaceutical care*, emphasizing the importance of pharmaceutical care for people's health (National Health Commission, 2018). Two transformations for the mode of pharmaceutical care are proposed: shifts from "drug-centric" to "patient-centric"; and from "focusing on ensuring drug supply" to "focusing on providing professional pharmaceutical services and participating in clinical practice of drug use on the premise of ensuring drug supply". To further promote and standardize pharmaceutical care, the NHC has formulated service specifications for pharmacist-managed clinics, drug use education and pharmaceutical monitoring service in medical institutions in 2021 (National Health Commission, 2021). These documents all reflect that the Chinese authorities have attached great importance to pharmaceutical care. On account of lacking longitudinal data about TDM, PGx and PMC, it was impossible to analyze the impact of policies on the implementation of individualized pharmaceutical care. We will pay close attention to its development tendency and discuss it in the follow-up research.

4.2 The situation of responsible departments of TDM and PGx testing

Our results showed that the responsible departments for TDM and PGx varied greatly among Chinese hospitals. The responsible departments are largely concentrated in the pharmacy department, clinical laboratory and multi-department. The different educational backgrounds among these departments contribute to the discrepancy in clinical practice. Practitioners in the clinical

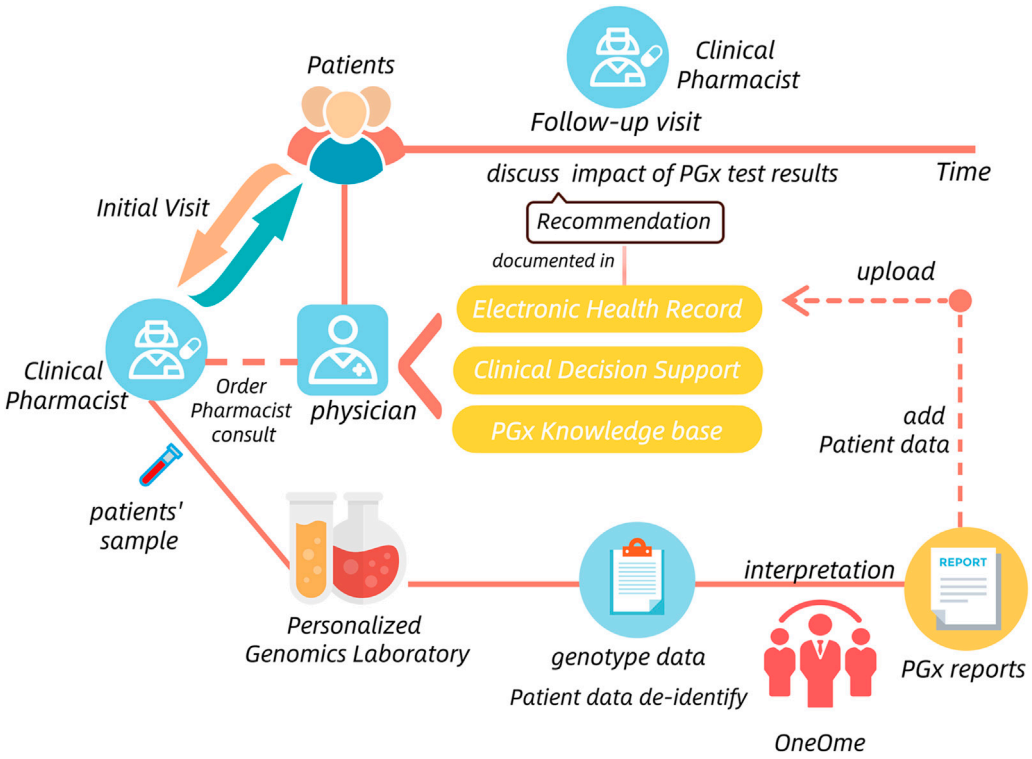

FIGURE 6
The process and involved departments of PGx Testing in the Mayo Clinic.

laboratories tend to stress the operation standards and internal or external quality control, while pharmacists are more likely to focus on pharmacokinetics and the adjustment of drug regimens according to the interpretation of testing results. The diversity of responsible departments inevitably increases the difficulty of standardization and conducting quality control for clinical practice.

The responsible departments need to be standardized urgently. In China, guidelines for the management of TDM practice have not yet been published. Only *the Expert Consensus on the Standards of Therapeutic Drug Monitoring* was published in 2019 (Zhang et al., 2019), putting forward that the qualification certification for TDM professionals ought to be conducted, but the detailed information about responsible departments was not mentioned. Given that TDM is a multidisciplinary field, one possible strategy is that different departments specialized in different fields took corresponding responsibilities in TDM procedure. Physicians could submit test requests in clinical practice; sample collection and concentration determination could be conducted by professionals in clinical laboratories; clinical pharmacists could be responsible for data processing and interpretation of results for patients. Through the collaboration of multiple departments and a clear division of responsibility, the management of clinical practice will be standardized and the working efficiency will be improved.

The situation of PGx testing was similar to TDM. Four published guidelines concerning the management of PGx testing only stressed the importance and necessity of PGx-staff qualification certification, the detailed information for responsible departments was also omited (National Health and Family Planning Commission, 2015). Fortunately, many pilot hospitals where PGx testing has been successfully implemented provide us with good models to learn from. For example, the Mayo Clinic had implemented the Nine-gene pharmacogenomics profile service, which was a pre-emptive PGx testing process. It established a care model including the Center for Individualized Medicine and pharmacy operations teams, clinical decision support team, Personalized Genomics Laboratory and OneOme (a commercial vendor) that provided reports of PGx results (Matey et al., 2022) (Figure 6). In China, Beijing Chaoyang hospital also conducted PGx testing in the charge of clinical pharmacists and pharmacogenetic technicians. They all show that the clinical practice of PGx testing usually involves multiple departments and institutions.

Additionally, although TDM and PGx testing in most of hospitals are multi-sectoral participation, a backbone is still needed. Given that clinical pharmacists work on the front line with patients and have a solid foundation of pharmacy knowledge, they are theoretically well-suited to promote the application of both TDM and PGx testing in clinical practice. It is suggested that the clinical pharmacy department should play a leading role in these related departments and coordinate the clinical implementation of TDM and PGx testing on the whole.

However, most of clinical pharmacists today are unable to interpret the TDM and PGx testing results professionally, especially for PGx testing. Zhang et al. reported that the majority of pharmacists in the First Affiliated Hospital of Zhengzhou University had no or little knowledge about the PGx because of the absence of PGx education in their major during the master or

doctor school year (Zhang J. et al., 2021). Hu et al. also reported that approximately 60% of pharmacists believed they had poor or fair capacity to offer PGx testing and related services (Hu et al., 2022). In Japan, only 12.4% of pharmacists had received specific PGx-related education (Tsuji et al., 2021). Therefore, the educational system should be established as soon as possible. Post-graduate opportunities, such as easily accessing continuing education courses and Graduate certifications or Master's Programs could be provided for pharmacists; colleges of pharmacy may offer courses focused on TDM and PGx in their curriculum as part of pharmacology curricula or as an elective course for students (Kisor et al., 2018; Marcinak et al., 2018; Mayo Clinic, 2019; University of Florida Health, 2022).

4.3 The conduction of quality control for TDM and PGx testing

Conducting quality control is important to ensure the reliability of the TDM and PGx testing results in hospital laboratories, which is the prerequisite for guiding patients to use drugs rationally. EQC plays a significant role in the quality control system. Its primary goal is to determine whether testing systematic mistakes exist in laboratories' clinical practice and identify the sources of errors so as to enhance the reliability of testing findings and advance laboratory analysis technology. In our survey, the proportions of hospitals conducting EQC for TDM and PGx were comparable to each other (69.24% and 70.23%, respectively). There is also obtained information regarding quality control or quality assessment in other countries. In South Korea, 20%–29% of respondents did not participate in proficiency testing for EQC in 2018 (Choi et al., 2019), which was roughly the same percentage as in Chinese hospitals. Similarly, in Malaysia, 77.4% of hospitals reported having quality assurance programs for TDM in their hospitals (such as international quality assessment programs, and the hospital's internal quality assessment programs) (Ab Rahman et al., 2013).

In the United States, to guarantee the reliability of testing results, laboratories performing PGx testing are subject to federal regulatory standards through College of American Pathologists accreditation and Clinical Laboratory Improvement Amendment certification or stricter state requirements (Vo et al., 2017). In China, EQA is routinely organized by pharmaceutical quality control institutions, clinical laboratory centers or other pharmaceutical societies approved by national/provincial/municipal health commissions (Division of Therapeutic Drug Monitoring et al., 2021). In general, the National Center for Clinical Laboratories organizes quality control of clinical laboratories nationwide, mainly for large medical institutions (National Center for Clinical Laboratories, 2022), while the provincial clinical laboratory centers are responsible for quality control of local clinical laboratories, primarily in regional, city, county or some township medical institutions (Wenxiang, 2013). Typically, quality control institutions will specify a catalogue of projects that they are qualified for conducting EQA, and laboratories can choose from the catalogue according to the projects conducted in their own laboratories (National Center for clinical Laboratories et al., 2013). However, in certain situations, projects implemented in laboratories are not all included in the catalogue. That is to say, the diversity of testing projects and methods is one of the reasons that hinders the conduction of EQC for TDM and PGx testing. It is recommended that quality control institutions build connections with corresponding laboratories, collect up-to-date testing projects from subordinate laboratories regularly, and then develop standard operation procedures (SOP) accordingly. For testing projects that have no SOP of EQA currently, other laboratories conducting the same or related projects could be references.

Our survey collected information about the conduction of EQC for TDM and PGx testing, which can reflect the testing abilities of laboratories but cannot point out the testing stability (or precision) for a specific testing project in clinical practice. Only through conducting internal quality control can we discover and remedy existing problems in time to ensure the consistency of testing results for patients. In addition, other processes such as sample collection, transportation and reporting of test results all require quality control. Further investigations about quality control remain to be conducted.

4.4 Analysis for implementing projects of TDM and PGx testing

In general, the drugs performed TDM and PGx testing in our survey were consistent with other contemporary small-scale studies in China (Zhang C. et al., 2021; Zhang J. et al., 2021). The results indicated that over 50% of hospitals performed TDM for valproate sodium, digoxin, carbamazepine, vancomycin and cyclosporine. Of note, most of these drugs have narrow therapeutic ranges and high intra- and inter-individual variability (Patsalos et al., 2018; He et al., 2020; Deprez and Stove, 2021; Ballotari et al., 2022). In these scenarios, TDM is useful to adjust medication dosages of treatments to maximize clinical effectiveness and decrease their toxicity. Situations that require TDM to guide medication are summarized in Table 4 (Muller et al., 2018; Alrabiah et al., 2021).

Yan Liu et al. reviewed published research for TDM over the past 30 years and summarized that the hotspots of TDM drugs in the last 5 years were vancomycin and medications related to inflammatory bowel disease (IBD) (Liu et al., 2022). In China, there has been a clinical practice guideline on vancomycin TDM since 2015, updated in 2020 (He et al., 2020), which has greatly promoted vancomycin TDM implementation. The proportion of hospitals implementing TDM for vancomycin is also higher (58.33%) than for many other drugs. For IBD therapy, monoclonal antibodies against tumor necrosis factor such as infliximab, adalimumab, certolizumab pegol and golimumab have all been approved worldwide for the treatment of moderate-to-severe active Crohn's disease and/or ulcerative colitis (Argollo et al., 2020). Reactive TDM and proactive TDM have been proven as useful tools for optimizing biologic therapy, specifically anti-TNF therapy (Papamichael et al., 2019; Sparrow et al., 2020; Syed et al., 2020). While our data showed that no hospital conducted TDM for adalimumab, and only one hospital performed Infliximab TDM (data not shown). Furthermore, as the incidence of antimicrobial resistance has increased globally and the "average" human host has changed as well, except for antibiotics with narrow therapeutic windows such as

TABLE 4 Scenarios that require TDM.

Types of scenarios	Scenarios
Drug-related scenarios	drugs with narrow therapeutic ranges
	drugs that have non-linear pharmacokinetics
	drugs that interindividual pharmacokinetics vary greatly
	antibiotic drugs that need to prevent drug resistance
Clinical practice-related scenarios	requiring long-term medication but lacking a clear, observable endpoint or indicator of treatment
	to seek causes of therapeutic failure
	the toxicity of drug therapy is difficult to distinguish from the patient's underlying disease
Patient-related scenarios	patients' clearance ability of drugs with narrow therapeutic indexes has been impaired
	to monitor patient's compliance
	for patients with social habits and lifestyle may affect the pharmacokinetics of drugs (eg, smoking, alcohol)

TABLE 5 Drugs and corresponding Genes in PharmGKB.

Drug	Genes in drug labels				
	FDA	EMA	Swissmedic	HSCS	PMDA
Clopidogrel	*CYP2C19*[d]	*CYP2C19*[d]	*CYP2C19*[d]	*CYP2C19*[d]	*CYP2C19*[d]
Warfarin	*CYP2C9*[d]/*VKORC1*[d]	/	/	*CYP2C9*[d]/*VKORC1*[d]	/
Statins[a] (Atorvastatin)	*SLCO1B1*[e]	/	/	/	/
Folic acid	/	/	/	/	/
Aspirin	/	/	*G6PD*[d]	/	/
Allopurinol	*HLA-B*[c]	/	*HLA-B*[d]	/	*HLA-B*[e]
Carbamazepine	*HLA-B*[b]/*HLA-A*[d]	/	*HLA-B*[b]	*HLA-B*[c]/*HLA-A*[c]	*HLA-B*[d]/*HLA-A*[d]
			/*HLA-A*[c]		
Irinotecan	*UGT1A1*28*[d]	*UGT1A1*28*[d]	*UGT1A1*28*[d]	*UGT1A1*28*[d]	*UGT1A1*[c]
Tacrolimus	*CYP3A5*[e]	/	/	/	/
Nitroglycerin	/	/	*G6PD*[d]	/	/
Voriconazole	*CYP2C19*[d]	*CYP2C19*/*CYP2C9*/*CYP3A4*[e]	*CYP2C19*[d]	*CYP2C19*[d]	*CYP2C19*[d]
Methotrexate	/	/	/	/	/
Glucocorticoid	/	/	/	/	/
Platinum	/	/	/	/	/
Ciclosporin	/	/	/	/	/

[a]Atorvastatin is listed as a representative of stains. FDA: US, Food and Drug Administration; EMA: European Medicines Agency; Swissmedic: Swiss Agency of Therapeutic Products; HSCS: Health Canada (Santé Canada); PMDA: Pharmaceuticals and Medical Devices Agency, Japan. The human gene symbols have been italicized.
[b]"Testing required", refers to genetic testing, functional protein assays, cytogenetic studies, *etc.*, should be conducted before using this drug.
[c]"Testing recommended", refers to genetic testing, functional protein assays, cytogenetic studies, *etc.*, is recommended before using this drug.
[d]"Actionable PGx", refers to a gene, protein or chromosomal testing are not required or recommended.
[e]"Informative PGx", refers to particular variants or phenotypes affect a drug's efficacy, dosage, metabolism or toxicity, but this effect is not "clinically" significant.

vancomycin and aminoglycosides, TDM of beta-lactam antibiotics is also becoming necessary, especially for patients in ICU (Muller et al., 2018). While our results showed that only eight hospitals performed TDM of beta-lactam antibiotics (data not shown).

Overall, the clinical practice of TDM in China lagged behind the frontiers of TDM research in some fields. Confronted with this situation, staff in the responsible departments such as clinical pharmacists could form keeping-up groups. In this way,

pharmacists track the cutting-edge TDM research, conduct promotion and education on drugs with the latest high-quality evidence-based research or published consortium guidelines that support conducting TDM. Furthermore, the standardized procedures of TDM and internal/external quality control for new projects should also be formulated in time to ensure the feasibility in clinical practice.

PharmGKB is a comprehensive resource that gathers knowledge about the impact of genetic variation on drug response for clinicians and researchers (PharmGKB, 2022a). According to PGx-based drug dosing guidelines annotates by the website, PGx testing at present could guide the clinical application of hundreds of drugs encompassing anticoagulant, anti-tumor, antiviral, anti-inflammatory, analgesic, anesthetic, anti-ulcer, anti-depression, anti-asthma and so on.

Based on the results of our survey and the information on Drug Label Annotations from PharmGKB (PharmGKB, 2022b), we matched the drugs conducted PGx testing with corresponding genes in Table 5. Clopidogrel and warfarin performed PGx testing in more than half of Chinese hospitals with PGx testing in our survey. Being an oral antiplatelet prodrug, clopidogrel is metabolized by *CYP2C19* gene into the active form. *CYP2C19* gene variants are known to be associated with increased or decreased response to clopidogrel (Wang et al., 2016). It has been demonstrated that patients with *CYP2C19* loss-of-function alleles have a higher risk of major adverse cardiovascular outcomes when treated with clopidogrel (Mega et al., 2010). Warfarin is a classic oral anticoagulant with a narrow therapeutic window and large inter-patient variability. About 53%–54% of dose variance of warfarin could be explained by taking into consideration both *VKORC1* and *CYP2C9* genetic polymorphisms (Gage et al., 2008). The guidelines published by the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) and the Chinese Society of Cardiology all recommended that gene polymorphism testing of *CYP2C9* and *VKORC1* is beneficial to optimize the dosage regimen of Warfarin (Sun, 2013; Shaw et al., 2015; Johnson et al., 2017). PGx testing of clopidogrel and warfarin prior to initiating treatment is widely accepted and the clinical significance is generally recognized by clinicians.

As compared with clopidogrel and warfarin, the conducting rate of PGx testing of other drugs in hospitals with PGx testing was relatively low, for instance, carbamazepine and allopurinol were both performed PGx testing in less than 20% of hospitals with PGx testing. However, it is necessary for patients to perform a PGx testing before using these drugs, for the severe adverse reactions maculopapular exanthem, Stevens-Johnson syndrome and toxic epidermal necrolysis are all related to Human leukocyte antigen B (*HLA-B*) genotype polymorphism (Saito et al., 2016; Phillips et al., 2018). One of the reasons limited PGx testing implementation of these drugs is the lack of approved reagent kits. On account of the user-friendliness and lower requirement for hardware environment when using PGx testing reagent kits, the number of approved kits could directly exert an impact on drugs tested. On the website of National Center for Clinical Laboratories and the National Medical Products Administration (National Medical Products Administration, 2022), the approved kits of clopidogrel and warfarin were 15 and seven respectively in 2019, which could meet the demand for clinical PGx testing well. On the contrary, only three kits were approved for PGx testing of the *HLA-B* gene.

Based on our results, recently, few PGx testing projects have successfully transformed from basic medical research into clinical practice. The latency of clinical implementation was contributed by many factors: the paucity of sufficiently powered trials that can quantify the added value of PGx testing in the real world (Lauschke and Ingelman-Sundberg, 2020); the negative attitude of physicians and the insufficient awareness of patients towards PGx (Guo et al., 2021); lack of approved reagent kits and equipment for conducting PGx testing; the shortage of qualified personnel (Owusu Obeng et al., 2018; Zhang J. et al., 2021; Tsuji et al., 2021); the high cost and unsound reimbursement policies, and so on. To promote the integration of basic research and clinical practice of PGx testing, it is significant to build good cooperation among the pharmaceutical industry, scientific research system and health system. The formulation of national policies and the innovation of testing technologies are also indispensable for the development of PGx transformation.

However, the utility of PGx testing in clinical practice should be viewed rationally and objectively. PGx testing results alone cannot determine medication regimens, even if the project is at a high level of evidence. For example, the TAILOR-PCI randomized clinical trial compared the genotype-guided selection of an oral *P2Y12* inhibitor with conventional clopidogrel therapy without point-of-care genotyping, resulting in no statistically significant difference in a composite endpoint of cardiovascular death (Pereira et al., 2020). Clinicians and pharmacists still need to combine individual pathophysiological status and other clinical indications to achieve precise medication.

4.5 The situation of PMC development in hospitals

As mentioned previously, the proportion of hospitals with PMC services in China was not satisfactory enough, and the development in different kinds of hospitals was unbalanced. Recently, the NHC has provided development proposals and created a promising environment to support the development of PMC in China. It is suggested that the implementation of PMC will be included in the evaluation index for hospital grade in the future.

The major types of PMC in China include independent PMC (specialized/general) and collaborative PMC. Our results showed that general PMC accounted for the largest proportion in all kinds of hospitals with PMC. Specialty PMCs include medication management for pregnancy/lactation, anticoagulant/antithrombotic, chronic disease management, pain management and so on, which are more suitable for patients with a single system disease. A general PMC refers to a pharmacist-managed clinic that does not differentiate specialties, being suitable for patients with multi-system diseases. Correspondingly, the requirements for pharmacists are much higher than specialty PMCs. The two types of PMC can complement each other in clinical practice. As for collaborative PMCs, pharmacists usually provide patients with pharmaceutical care together with physicians. This kind of pharmaceutical care might be relatively more easily accepted by patients. However, on account of the high dependence

on physicians, only in hospitals with good physician-pharmacist partnerships can it be implemented, which also explains why this type of PMC was not common in our survey. Recently, online medical consultation services have been set up in more and more hospitals, and so does the online pharmaceutical care service. In this way, the timeliness and accessibility of high-quality medical care have been considerably improved, and the turnover can be reduced, which is meaningful during the COVID-19 pandemic (Wu et al., 2020). It was reported that most urological patients (84.7%) had a good acceptance of telemedical consultation (Boehm et al., 2020). Accordingly, it might be a practicable way for hospitals to establish online pharmaceutical care services in clinical practice.

In 2013, it was raised by the International Pharmaceutical Federation that pharmaceutical care without payment is not sustainable. This may lead to an inactive attitude of pharmaceutical practitioners, and the service quality cannot be well guaranteed. However, our survey showed that most PMCs in China were free of charge (only 21.08% were charged) and there is no uniform charge standard across China currently. In Japan, patients need to pay for the pharmacy information provision service and the medication management service, as well as in Korea. Policymakers should learn from these countries and enact the *Pharmacist Law* as soon as possible to help pharmacists increase enthusiasm for PMC service, which will also help with the translation of patients' attitude towards PMC and improve the patients' confidence in pharmacists.

Moreover, PMC is also an important way to bridge the gap between TDM or PGx testing and their clinical implementation. In October 2021, the NHC issued the standards for the pharmacist-managed clinic service in medical institutions, patients who require pharmacists to interpret the results of drug monitoring (e.g., blood drug concentration and PGx testing) are the targeted population for service (National Health Commission, 2021). Therefore, it is highly recommended that related departments integrate PMC, TDM and PGx testing services into an entirety, thereby spurring the development of individual pharmaceutical care.

4.6 Advantages and limitations

Our study for all we know is the first nationwide survey on individualized pharmaceutical care in China. That is, the biggest advantage of our survey is its large size, being able to represent the overall situation of individualized pharmaceutical care in China. And the quality of our data was well guaranteed by the support of the National Institute of Hospital Administration. Because our survey was conducted for pharmaceutical quality control and did not involve hospital-grade evaluation, the objectivity of the data was well guaranteed. And the items set in the e-questionnaire were mostly choice questions, which was also beneficial for improving the response rate and data reliability. It can be seen that the response rate is excellent. Furthermore, given that PMC is an indispensable part of individualized pharmaceutical care as well, it is quite meaningful to raise the awareness of PMC among medical practitioners. Our survey not only gathered data about TDM and PGx but paid attention to the status of PMC as well, which will be useful for policymakers to formulate strategies to promote further development of PMC.

There are also some limitations to our study. As mentioned above, a few hospitals filled the index of drugs and genes tested for PGx with diseases or irrelevant information, making it impossible to make sure whether a specific drug performed PGx testing in these hospitals or not. After careful consideration, we think that it was mainly because Part 2, question eight of the questionnaire (Supplementary material S2) was not clarified, contributing to some people's misunderstanding concerning "PGx tests". The fill-in-blank form with the indeterminate filling format is also one of the reasons leading to this problem. To cope with this situation, we excluded the non-standard data and outliers, ensuring the reliability and accuracy of our analyses as far as possible. Additionally, our test results were similar to concurrent studies in northern China (Zhang C. et al., 2021), so we conclude that there was no big influence on our test results. The National Institute of Hospital Administration should compile all test items based on the results of this survey and all reagent kits approved by the National Health Commission, match genes to drugs, present these questions as multiple choices when designing follow-up questionnaires.

In addition, our evaluation indexes were relatively not detailed enough. It was mainly because the scale of our study was too large to make a further survey on the premise of ensuring data accuracy and reliability. Furthermore, our study was a cross-sectional one and was the first study of this nature in China, so it was inevitable that actual patients' longitudinal outcomes about TDM or PGx were unavailable. However, the National Institute of Hospital Administration will conduct regular research on individualized pharmaceutical care in the future. In this way, the prospective longitudinal data will be available and the trend of this field can be analyzed and discussed.

More studies focused on one field in individualized pharmaceutical care should be conducted for in-depth research. For example, researchers can also collect data such as the analytical methods and the implementation way for TDM service and PGx testing. As for PMC, further studies can be launched about the types of specialty PMC, the content of pharmaceutical care, education background and the degree of patient satisfaction, *etc.* Besides, more attention should be paid to the practice of addressing difficulties in the development of individualized pharmaceutical care. That is, sharing the practical experience of pilot hospitals with others should be encouraged and the construction of a curriculum system for cultivating professional pharmacists ought to be accelerated.

5 Conclusion

Overall, the development of individualized pharmaceutical care in China is still in the early stage. The implementation rate of TDM, PGx and PMC is relatively low, uniform clinical standards are deficient, the proportion of hospitals conducting EQC needs to be further improved, and the clinical practice in some fields lagged behind the cutting-edge research. Many different sectors and activities have to coalesce to promote the implementation and adoption of individualized pharmaceutical care, including the appropriate education, coverage, reimbursement policies, high-quality evidence, data systems, health system processes and health policies. To establish a completed and sophisticated

individualized pharmaceutical care system, there is still a long way to go.

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 survey was approved and organized by the National Institute of Hospital Administration. This research was reviewed and approved by the Ethical Committee of the Peking Union Medical College and the Chinese Academy of Medical Sciences (Beijing, China).

Author contributions

WZ and QY designed and performed the research; MC and LZ wrote the manuscript; DG and MC analyzed the data; DM, BZ and WZ revised the manuscript.

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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.2023.1022134/full#supplementary-material

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A systematic review on sex differences in adverse drug reactions related to psychotropic, cardiovascular, and analgesic medications

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Background and objective: Adverse drug reactions (ADRs) are the main safety concerns of clinically used medications. Accumulating evidence has shown that ADRs can affect men and women differently, which suggests sex as a biological predictor in the risk of ADRs. This review aims to summarize the current state of knowledge on sex differences in ADRs with the focus on the commonly used psychotropic, cardiovascular, and analgesic medications, and to aid clinical decision making and future mechanistic investigations on this topic.

Methods: PubMed search was performed with combinations of the following terms: over 1,800 drugs of interests, sex difference (and its related terms), and side effects (and its related terms), which yielded over 400 unique articles. Articles related to psychotropic, cardiovascular, and analgesic medications were included in the subsequent full-text review. Characteristics and the main findings (male-biased, female-biased, or not sex biased ADRs) of each included article were collected, and the results were summarized by drug class and/or individual drug.

Results: Twenty-six articles studying sex differences in ADRs of six psychotropic medications, ten cardiovascular medications, and one analgesic medication were included in this review. The main findings of these articles suggested that more than half of the ADRs being evaluated showed sex difference pattern in occurrence rate. For instance, lithium was found to cause more thyroid dysfunction in women, and amisulpride induced prolactin increase was more pronounced in women than in men. Some serious ADRs were also found to exert sex difference pattern, such as clozapine induced neutropenia was more prevalent in women whereas simvastatin/atorvastatin-related abnormal liver functions were more pronounced in men.

KEYWORDS

sex differences, adverse drug reactions, psychotropic, cardiovascular, analgesic

1 Introduction

Adverse drug reactions (ADRs), or drug side effects, are defined as harmful, unintended events resulting from the use of medications. For a new drug entity to be approved by the US Food and Drug Administration (FDA), its safety and potential ADRs must be assessed during the investigational stage. According to a recent study,

about 17% of the investigational drugs failed in phase 3 or pivotal trials because of safety concerns (Hwang et al., 2016). Even for the drugs that have been approved for clinical use, their ADRs can still be concerning. Serious ADRs were shown to result in over 100,000 deaths per year, making it the fourth leading cause of death in the US (Giacomini et al., 2007). Other less severe ADRs have been associated with drug discontinuation, poor adherence, and suboptimal treatment outcomes (DiBonaventura et al., 2012). Therefore, it is of great translational value to identify the risk factors for common or serious ADRs, so that clinical monitoring or medication change can be applied accordingly.

As an easy-to-use patient characteristic, sex has been identified as an important predictor in both disease incidence and treatment outcomes. For instance, among non-smokers, women are found to have higher risk of developing lung cancer compared to men (Ragavan and Patel, 2022), whereas women tend to respond better to epidermal growth factor receptor (EGFR) inhibitors, a targeted therapy for lung cancer, than men (Chen et al., 2013). Likewise, the role of sex in the likelihood of ADRs has been evaluated in numerous medications. One illustrative example is zolpidem, a medication used to treat insomnia. Twenty years after its approval to the market, FDA issued Drug Safety Communication (U.S. Food and Drug Administration, 2022) to require a decreased initial dose of zolpidem in women, due to the accumulating evidence indicating that women experience more driving impairment than men under the same recommended dose (Verster and Roth, 2012; Farkas et al., 2013). Subsequent pharmacokinetic studies found that the same dose resulted in significantly higher zolpidem plasma concentration in women than in men (Olubodun et al., 2003; Greenblatt et al., 2014; Greenblatt et al., 2022), which might be able to explain the higher incidence of zolpidem-related ADRs in women. Even though sex difference has gained increasing awareness nowadays, many of the existing clinical trials did not provide sex specific data when evaluating drug efficacy and safety (Hayes and Redberg, 2008; Beery and Zucker, 2011), making it challenging to promote sex-aware prescribing for most of the medications.

Here, we systematically review and summarize the existing literature evaluating sex differences in ADRs to address the fundamental question that whether sex should be considered in drug prescription to prevent/minimize ADRs. If so, for which drugs/drug classes. To summarize and discuss the findings of the included literature, we classified the medications into their therapeutic area. We chose to focus on psychotropic, cardiovascular, and analgesic medications because the above three drug classes are the top categories with sex difference studies available from our web scraping results. Furthermore, the above three drug categories yield the largest number of the "most prescribed drugs" in the US (Fuentes et al., 2018), supporting their broad use and clinical impact. It is to note that oncology mediations were not evaluated in this review due to the inherent cytotoxic effects and the different standard in the ADR recordings (Nguyen et al., 2019). By summarizing the main findings of the commonly used medications in the three drug classes, we aim to facilitate clinical decision making by improving the current understanding of sex differences in ADRs. More importantly, this review highlights the need of further research on sex-aware evaluation of ADRs.

2 Materials and methods

2.1 Search strategy

To search for evidence of sex difference in ADRs, we performed web scraping in PubMed using a R package "easyPubMed" (Fantini, 2019). The keywords used for searching were drugs of interests, sex difference (and its related terms), and side effects (and its related terms). The full list of searching terms and other restrictions can be found in Supplementary Table S1. For the drugs of interests, we used a list of 1,819 drugs which have established human targets and the corresponding ADRs recorded in clinical trials from a previously published paper by (Nguyen et al., 2019). Web scraping was performed in March 2022.

2.2 Study selection

All studies resulted from web scraping were considered regardless of study design or date of publication. We first performed an initial screening on the title and abstract to exclude unrelated literature. Then, we did full-text review with the focus on psychotropic, cardiovascular, and analgesic medications. To ensure the drugs included in the review belong to the above three categories, we used Anatomical Therapeutic Chemical (ATC) Classification developed by WHO, (2023) as the reference. Studies were excluded during the full-text review if 1. language was not English; 2. the drug of interest was not in the 1,819 drug list; 3. sex difference was evaluated in drug efficacy rather than ADRs; 4. sex difference in ADRs were caused by a combination of drugs rather than a specific drug; 5. significance level was not reported; 6. The ADR being evaluated is not a well-established ADR as endorsed by Micromedex (IBM MICROMEDEX, 2022). Review articles were also inspected to identify additional original studies to be included.

2.3 Data collection

For each of the study included in this review, the following information was collected: 1. study design; 2. race and age (adults or children) of the study population; 3. health status of the participants (healthy volunteers or patients with specific diseases); 4. number of male and female participantsin the study; 5. drug of interest; 6. dosing regimen; 7. ADRs being inspected in the study; 8. results for sex difference study in ADRs (male-biased ADR, female-biased ADR, or ADR with no sex difference); 9. any pharmacokinetic (PK) measurement if applicable.

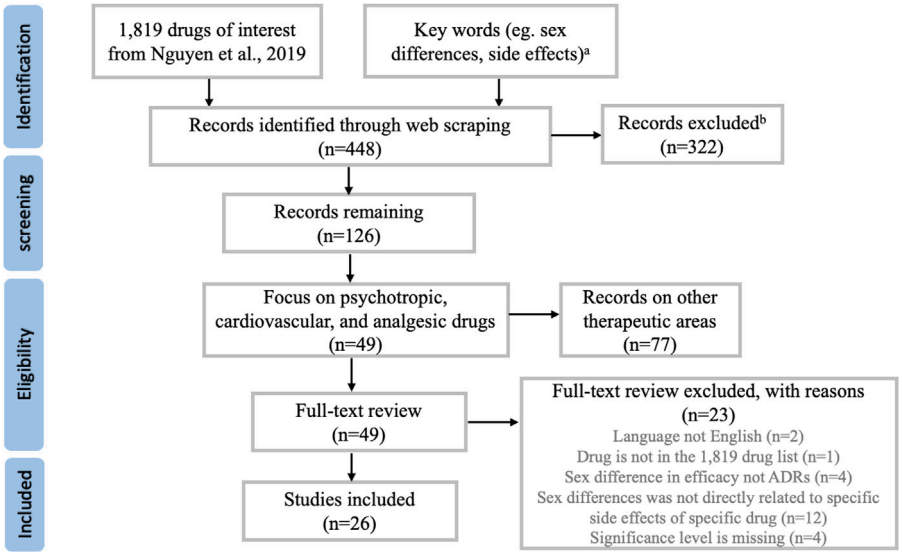

FIGURE 1
Overview of the study selection process. Note (A) A complete list of the keywords used in web scraping can be found in Supplementary Table S1. Note (B) Most studies being excluded here were not related to drug side effects, or not related to human subjects.

3 Results

3.1 Study characteristics

Literature search for the 1,819 drugs through web scraping retrieved 448 unique publications. Figure 1 summarized the process of study selection, which resulted in a total of 26 studies included in this review. The characteristics of each study such as drug of interest, study design, number of subjects, dosing regimen, etc. were recorded in Table 1. Sex differences in ADRs were summarized for six psychotropic medications, ten cardiovascular medications, and one analgesic medication. The rest of the result session was structured to first briefly introduce the clinical significance and common ADRs of the medications, followed by the evidence of sex difference in common or serious ADRs related to the drug of interest.

3.2 Psychotropic medications

3.2.1 Lithium

Lithium is recommended as the first-line treatment for both acute mania and maintenance phase in bipolar disorder (Yatham et al., 2018). Recent evidence has also suggested the value of lithium in reducing suicidal rate in patients with bipolar or major depression disorder (Smith and Cipriani, 2017). Despite its significant clinical benefits, lithium has gradually become less widely utilized due to its narrow therapeutic index and requirement for frequent blood tests. Some common ADRs of lithium are tremor, polyuria, hypothyroidism, weight gain, and increased thirst. Other more severe ADRs such as bradycardia, sinus node dysfunction, and seizure might happen at a lower rate.

Sex differences were identified in lithium-related thyroid dysfunction, tremor, weight gain, and oedema. Özerdem et al. (2014) assessed sex differences in lithium associated thyroid dysfunction through a retrospective, naturalistic study. One hundred four men and 136 women taking lithium for bipolar disorder with thyroid-stimulating hormone (TSH) level available were included in the study. Using 0.3–3 μIU/mL as the normal range of TSH, the researchers found that significantly fewer female patients (55.9%) were within the normal range compared to male patients (71.2%) ($p = 0.016$). Notably, the difference in the proportion of normal TSH between male and female patients was not significant in the non-lithium treated group, which suggested that the observed sex differences in thyroid dysfunction is related to lithium treatment rather than the disease state. The vulnerability to thyroid dysfunction in lithium-treated women has also been observed by Chantal Henry in another retrospective study (Henry, 2002). By interviewing 22 male and 38 female patients about lithium ADRs, the researcher found that more female patients than male patients reported new diagnosis of hypothyroidism during the first year of lithium treatment (37% vs. 9%, $p < 0.05$). Weight gain was also shown to affect more female than male patients (47% vs. 18%, $p < 0.05$) in the same study whereas tremor was more pronounced in male than female patients (54% vs. 26%, $p < 0.05$). There is a more recent retrospective study investigating reasons for lithium discontinuation performed by Öhlund et al. (2018). The results showed that female patients were more likely to discontinue lithium due to weight gain ($p < 0.01$) and oedema ($p < 0.01$) compared to male patients. To conclude, current evidence suggested that lithium-associated thyroid dysfunction, weight gain, and oedema affect more female patients, while lithium-associated tremor affect more male patients in the treatment of bipolar disorder.

TABLE 1 Characteristics of studies included.

Studies	Drugs	Study design	Number of subjects (Male/ Female)	Dosing regimen	Race	Children/ Adults	Patients/ volunteers	PK measurement
Psychotropic medications								
Özerdem et al. (2014)	lithium	Retrospective naturalistic study	240 (104/136)	Individualized dosing	NR	adults	bipolar disorder patients	Serum lithium level was higher in women
Henry (2002)	lithium	Retrospective study	60 (22/38)	Individualized dosing	NR	adults	Type I bipolar disorder patients	NR
Öhlund et al. (2018)	lithium	Retrospective cohort study	423 (185/238)	Individualized dosing	Swedish	adults	bipolar disorder patients	NR
Hoekstra et al. (2021)	amisulpride aripiprazole olanzapine	Prospective randomized study	144 (93/51)	aripiprazole 15 mg/day olanzapine 10 mg/day amisulpride 400 mg/day	Predominantly Caucasian	adults	schizophrenia patients	amisulpride and aripiprazole level were higher in women
Düring et al. (2019)	amisulpride	Prospective cohort study	56 (35/21)	Individualized dosing	NR	adults	schizophrenia patients	NR
Müller et al. (2006)	amisulpride	Prospective naturalistic study	99 (61/38)	400–1,200 mg/ day	NR	adults	schizophrenia patients	amisulpride plasma level was higher in women
Kraal et al. (2017)	clozapine olanzapine	Cross-sectional study	79 (51/28)	Individualized dosing	63% White 25% Black 12% Other	adults	schizophrenia patients	NR
Lau et al. (2016)	clozapine	Retrospective cohort study	117 (67/50)	Individualized dosing	NR	NR	patients	NR
Hollingworth et al. (2018)	clozapine	Retrospective descriptive study	2,194 (1,470/724)	Individualized dosing	NR	NR	patients	NR
Pu et al. (2020)	olanzapine aripiprazole risperidone	Prospective cohort study	569 (283/286)	risperidone 3–6 mg/day olanzapine 10–25 mg/day aripiprazole 15–30 mg/day	East Asian	adults	schizophrenia patients	NR
Belmonte et al. (2016)	Aripiprazole	Retrospective meta-analysis	157 (89/68)	10 mg single dose	NR	adults	healthy volunteers	AUC and Cmax were higher in women
Labelle et al. (2001)	risperidone	Prospective cohort study	330 (232/98)	6 mg/day	NR	adults	schizophrenia patients	NR
Cardiovascular Medications								
Essebag et al. (2007)	amiodarone	Prospective cohort study	973 (583/390)	Individualized dosing	NR	adults	AF patients	NR
Roten et al. (2009)	amiodarone	Retrospective chart review	264 (192/72)	Individualized dosing	NR	adults	AF patient	NR
Lehmann et al. (1996)	d,l-sotalol	Retrospective study	3,135 (2,336/799)	Individualized dosing	NR	Adults	patients	NR
Smiderle et al. (2014)	simvastatin atorvastatin	Prospective cohort study	495 (164/331)	Individualized dosing	European descent	adults	hypercholesterolemia patients	NR
Sadanaga et al. (2009)	enalapril	Prospective cohort study	199 (101/98)	Individualized dosing	NR	adults	HF patients	NR

(Continued on following page)

TABLE 1 (*Continued*) Characteristics of studies included.

Studies	Drugs	Study design	Number of subjects (Male/ Female)	Dosing regimen	Race	Children/ Adults	Patients/ volunteers	PK measurement
Ishani et al. (2005)	enalapril	Retrospective study	6,436 (5,458/978)	10 mg bid	86% Caucasian 7% AA 2% Hispanic 6% other	adults	HF patients	NR
Wood (1995)	enalapril captopril lisinopril	Retrospective cohort study	1,013 (547/466)	Individualized dosing	NR	adults	HTN patients	NR
Fan et al. (2008)	captopril nifedipine HCTZ atenolol	Prospective, randomized study	3,535 (1,209/ 2,326)	captopril 25–50 mg/day Nifedipine 20–40 mg/day HCTZ 12.5–25 mg/day atenolol 12.5–25 mg/day	East Asian	adults	HTN patients	NR
Os et al. (1994)	lisinopril Nifedipine	Prospective, randomized study	828 (424/404)	Individualized dosing	NR	adults	HTN patients	NR
Coulter and Edwards (1987)	captopril enalapril	Retrospective postmarketing surveillance	unknown	Individualized dosing	NR	children and adults	HTN patients	NR
Abad-Santos et al. (2005)	amlodipine	Prospective, randomized study	36 (18/18)	10 mg single dose	Caucasian	adults	healthy volunteers	similar AUC and Cmax in both sexes
Analgesic Medications								
Sadhasivam et al. (2015)	morphine	Prospective cohort study	219 (105/114)	0.1–0.2 mg/kg, additional 0.05 mg/kg PRN.	Caucasian	children	children undergoing tonsillectomy	NR
Fillingim et al. (2005)	morphine	Prospective, randomized, double-blind study	100 (39/61)	0.08 mg/kg single dose	Predominately Caucasian	adults	healthy volunteers	NR
Bijur et al. (2008)	morphine	Retrospective meta-analysis	355 (144/211)	0.1 mg/kg single dose	predominately Latino and African American	adults	patients with acute pain	NR

Individualized dosing: participants used their original dosage and might adjust the dose according to their heathy condition during the study. The researchers did not assign dose for participants. *HCTZ, hydrochlorothiazide; AF, atrial fibrillation; HF, heart failure; HTN, hypertension; AA, african american; bid, twice daily; PRN, as needed; NR, not reported; AUC, area under the curve; Cmax, maximum serum concentration.

3.2.2 Amisulpride

Amisulpride is an atypical antipsychotic with selective blockade of dopamine 2 and dopamine 3 receptors. It has been reported by multiple studies to be an effective and well-tolerated treatment for schizophrenia (Puech et al., 1998; Leucht et al., 2013). More recently, the clinical significance of amisulpride has been evaluated in combination therapies with other antipsychotics such as olanzapine in treatment-resistant schizophrenia (Schmidt-Kraepelin et al., 2022; Woo et al., 2022). On the safety prospective, amisulpride is associated with increased prolactin level, weight gain, hypotension, sexual dysfunction, and prolonged QT interval.

As one of the well-established adverse events of amisulpride, increased prolactin level was reported to be sex-biased by multiple studies (Düring et al., 2019; Hoekstra et al., 2021). In the BeSt InTro study, 93 men and 51 women with schizophrenia diagnosis were randomized to different antipsychotics including amisulpride (Johnsen et al., 2020). When comparing amisulpride induced ADRs between sexes, the researchers found that women had significantly higher mean prolactin level (1,869 mIU/L) then men (920 mIU/L) under amisulpride treatment ($p < 0.001$) (Hoekstra et al., 2021). Further evaluations showed that the serum level of amisulpride was higher in women than in men after adjusting for the

daily dose ($p = 0.019$), which might explain the observed female-biased ADR. As a potential consequence of elevated prolactin level (Halbreich et al., 2003), sexual disturbance was also evaluated in this study. Using Udvalg for Kliniske Undersøgelser side effect score (UKU score) as the measurement for sexual disturbance, the researchers found that women had more sexual disturbance compared to men with marginal significance ($p = 0.051$). Notably, similar findings were observed in a separate study conducted by Düring et al., 2019. By following 35 men and 21 women with schizophrenia taking amisulpride monotherapy, the researchers found that prolactin level was higher in women ($p < 0.01$) compared to men after 6 weeks of amisulpride treatment. Women also reported higher sexual dysfunction load than men did ($p < 0.01$). In conclusion, amisulpride related prolactin elevation and sexual dysfunction are more common in women than in men in treating schizophrenia, even though the average daily dose is similar between two sexes.

3.2.3 Clozapine and olanzapine

Clozapine and olanzapine are both atypical antipsychotics with similar molecular structures. Clozapine is known as one of the most effective antipsychotics and it is the gold standard for treatment resistant schizophrenia. However, studies have shown that the use of clozapine in schizophrenia is suboptimal (Warnez and Alessi-Severini, 2014), which might involve several reasons including a range of serious adverse events of this medication. For instance, clozapine is associated with myocarditis, cardiomyopathy, and neutropenia, all of which can be life-threatening. Recently, the use of olanzapine in treatment resistant schizophrenia has been widely discussed, as several studies have shown that olanzapine is non-inferior to clozapine in terms of safety and efficacy in hard-to-treat schizophrenia (Tollefson et al., 2001; Bitter et al., 2004; Naber et al., 2005). In terms of common adverse events, both clozapine and olanzapine are recognized as being high risk for weight gain, hyperglycemia, and dyslipidemia (Rummel-Kluge et al., 2010; Kraal et al., 2017).

Even though clozapine and olanzapine have similar profiles in metabolic ADRs, the impact of sex on some of those ADRs were observed to be different between the two medications. In the BeSt InTro study (Hoekstra et al., 2021), sex differences in BMI increase was evaluated in patients randomized to olanzapine group. BMI increase was found to be more pronounced in men (1.48 kg/m^2) than in women (0.24 kg/m^2) ($p < 0.001$). Interestingly, the direction of sex difference in treatment-related weight gain was shown to be opposite in patients taking clozapine. In a retrospective study conducted by Lau et al., 2016, 67 men and 50 women attending the outpatient clozapine clinic were recruited and their weight change from 3 months to 12 months after clozapine initiation was calculated. The percentage weight change (weight change divided by the 3-month weight) was found to be significantly higher in women (+5.5%) than in men (+1.3%) ($p = 0.01$). To analyze sex differences in more serious ADRs of clozapine, Hollingworth et al. reviewed all reported clozapine related neutropenia, myocarditis, and cardiomyopathy cases in Australia monitoring database from 1993 to 2014 (Hollingworth et al., 2018). Sex differences were observed with neutropenia happening more in women (OR 1.45, CI 1.28–1.67), while cardiomyopathy (OR 2.53, CI 1.9–3.37) and myocarditis (OR 1.58, CI 1.34–1.87) happened more in men. These findings suggest sex as an important factor in clozapine and olanzapine related weight gain as well as in more serious adverse events of clozapine.

3.2.4 Aripiprazole

Aripiprazole is an atypical antipsychotic with numerous FDA approved indications including schizophrenia, bipolar I disorder, autistic disorder, Tourette's syndrome, and major depressive disorder. Because of its unique receptor binding profile, aripiprazole has different mechanism of actions from other antipsychotics and is sometimes referred as a third-generation antipsychotic (Freudenreich and Freudenreich, 2020). In addition to its confirmed efficacy in various disease areas, aripiprazole has also been shown to induce less adverse events compared with other antipsychotics (Leucht et al., 2013). Some common ADRs of aripiprazole are weight gain, nausea, vomiting, tremor, and fatigue. More serious ADRs such as prolonged QT interval, myocardial infarction, and neutropenia have been observed at a lower rate.

Among aripiprazole-related ADRs, weight gain and some cardiovascular ADRs were shown to impact men and women differently. In a study evaluating sex differences in pharmacokinetics and ADRs of aripiprazole, 89 men and 68 women from multiple aripiprazole bioequivalence clinical trials were recruited (Belmonte et al., 2016). PK parameters were calculated, and physical assessments were performed several times before and after a single dose of 10 mg aripiprazole. The study found that AUC and C_{max} of aripiprazole were significantly higher in women ($p < 0.05$), which indicated a higher aripiprazole exposure in women even under the same dose. In concordance with the observed difference in PK parameters, the blood pressure lowering effects of aripiprazole were found to be more pronounced in women at all measured times ($p < 0.01$). At 8 h after the dose, the mean systolic blood pressure in women was 105 mmHg versus 116 mmHg in men ($p < 0.001$). In addition, women were found to have higher heart rate and larger QTc interval compared to men at multiple measured times ($p < 0.001$). As a well-established ADR of aripiprazole, weight gain has also been shown to impact women and men differently. In the BeSt InTro study (Hoekstra et al., 2021), men were observed to have higher BMI increase compared to women after 52 weeks of aripiprazole use (0.64 kg/m^2 vs. −0.04 kg/m^2, $p = 0.016$). In conclusion, sex differences have been observed in multiple aripiprazole related ADRs including weight gain, blood pressure reduction, increased heart rate and QTc. Since some of the conclusions were based on a single dose of aripiprazole, further investigation is warranted to explore the sex difference in long-term aripiprazole use.

3.2.5 Risperidone

Risperidone is a second-generation antipsychotic with serotonin 5-hydroxytryptamine receptor 2 (5-HT$_2$) blocking activities at low doses and dopamine D$_2$ receptor blocking activities at higher doses (Megens et al., 1994). Risperidone is proven to mitigate both positive and negative symptoms of schizophrenia, with less concern about dyskinesia which is a prevalent ADR of most antipsychotics (Labelle et al., 2001). Some common ADRs of risperidone are rash, weight gain, hyperprolactinemia, parkinsonism, and fatigue.

Sex differences in risperidone-associated rash, weight gain, parkinsonism, and dystonia have been evaluated. In a randomized study, 100 men and 90 women taking daily risperidone were followed up for 1 year to assess drug-related ADRs (Pu et al., 2020). At the end of the follow-up period, more female patients reported rash related to risperidone than male patients ($p = 0.03$). In another *post hoc* analysis on an open-label study, ADRs in 232 men and 98 women taking risperidone were analyzed for differences between sexes (Labelle et al., 2001). Weight gain was found to happen more in men compared to women with marginal significance ($p = 0.085$). No sex difference was identified for parkinsonism ($p = 0.889$) or dystonia ($p = 0.512$). To conclude, risperidone-related rash is more prevalent in women, whereas no significant sex difference was found in weight gain, parkinsonism, or dystonia related to risperidone treatment in schizophrenia.

3.3 Cardiovascular medications

3.3.1 Amiodarone

Amiodarone is a class III antiarrhythmic drug which is highly effective and widely used in both supraventricular and ventricular arrhythmias (Connolly, 1999). However, amiodarone is also well-known for its potential ADRs on different organs such as thyroid, heart, lung, liver, and eyes. A previous study showed that the prevalence of amiodarone-related ADRs is 15% in the first year, and may increase to 50% in long term use, which would ultimately lead to medication discontinuation in 20%–50% of the patients (van Erven and Schalij, 2010). Some common ADRs of amiodarone are thyroid dysfunction, photosensitivity, and visual disturbance. Amiodarone can also cause more serious adverse events such as bradyarrhythmia, sinus arrest, and hepatotoxicity.

In a prospective cohort study (Essebag et al., 2007), Essebag et al. enrolled 583 men and 390 women with new onset atrial fibrillation (AF) and followed the participants for up to 30 months for amiodarone related ADRs. The researchers found that amiodarone use was associated with increased risk of pacemaker insertion only in women but not in men (HR: 4.69, 95% CI: 1.99–11.05, vs. HR: 1.05, 95% CI: 0.42–2.58, $p = 0.02$). This significant difference remained after adjusting for daily dose, weight, and the use of other antiarrhythmic medications. In another retrospective study (Roten et al., 2009), Roten et al. reviewed amiodarone associated ADRs in 192 men and 72 women who were referred to clinic for AF management. Their analysis showed that women overall experienced more amiodarone-related ADRs than men (56% vs. 36%, $p = 0.046$), and there were significant sex differences in the occurrence of phototoxicity under amiodarone treatment (21% in women vs. 8% in men, $p = 0.047$). The results above suggest that closer monitoring is needed in female population taking amiodarone since they are more likely to experience ADRs such as bradyarrhythmia requiring pacemaker insertion and phototoxicity.

3.3.2 Sotalol

Sotalol is a class III antiarrhythmic agent which is approved for treatment of AF and ventricular arrhythmia. Its efficacy in reducing death and preventing recurrence of arrhythmia has been proven to be superior to other antiarrhythmic drugs (Mason, 1993). However, along with its high efficacy, sotalol can induce some lethal ADRs such as Torsades de pointes (TdP), which may lead to sudden cardiac death. To unveil whether sex is a risk factor for sotalol induced TdP, Lehmann et al. assessed the prevalence of TdP development under sotalol treatment in 3,135 adult patients and compared the results between sexes (Lehmann et al., 1996). TdP was observed in 44 of 2,336 men (1.9%) and in 33 of 799 women (4.1%), and the difference was statistically significant ($p < 0.001$). Further logistic regression also suggested female sex as a significant risk factor in TdP development ($p < 0.0001$), even after adjusting for sotalol dose. Since TdP is such a lethal ADR, the results above emphasize the need for closer monitoring of cardiac function in female patients taking sotalol.

3.3.3 Simvastatin and atorvastatin

Despite the recent advancement in the treatment options for hyperlipidemia and in the prevention of coronary artery disease, statins remain the first line therapy due to their high efficacy, low cost, and relatively safe profile. The pharmacological effects of statins have been proven in lowering the low density lipoprotein cholesterol (LDL-C) by 20%–50%, as well as lowering triglyceride by 10%–20% (Taylor et al., 2013). In terms of safety, statins are well tolerated by the vast majority of patients, but they can still cause some ADRs such as myalgias, urinary tract infection, and increased liver enzymes, which can all lead to treatment interruption or discontinuation. Sex differences in the ADRs of two commonly used statins, simvastatin and atorvastatin, have been evaluated in a prospective cohort study (Smiderle et al., 2014). A total of 164 men and 331 women on simvastatin or atorvastatin treatment participated in the study, and they were evaluated every 3 months for statin related ADRs. The researchers observed higher occurrence of myalgia in women than in men (25.9% vs. 20.3%, $p = 0.002$), while more creatinine phosphokinase (CPK) increase and/or elevated liver enzymes were observed in men than in women (11.1% vs. 7.6%, $p = 0.017$) under simvastatin or atorvastatin treatment. These results request more attention on the role of sex in statin associated ADRs, and further studies are warranted to explore the potential mechanism of the observed sex differences.

3.3.4 Enalapril, lisinopril, and captopril

Angiotensin converting enzyme (ACE) inhibitors are effective antihypertensives working through inhibition of renin-angiotensin system. ACE inhibitors are recommended by multiple guidelines as first-line treatment for hypertension (Williams and Mancia, 2018), and their use has been expanded to other disease areas such as acute myocardial infarction, heart failure, and kidney diseases. While most patients tolerate ACE inhibitors well, some patients can still experience hypotension, dizziness, dry cough, and other more serious ADRs such as angioedema and renal impairment during the treatment.

Evidence of sex differences in ACE inhibitor induced ADRs was found in lisinopril, enalapril, and captopril. Interestingly, most of the sex difference analysis has been focused on ACE inhibitor induced bronchospasm and cough. In a retrospective study (Wood, 1995), the prevalence of new onset bronchospasm and cough was assessed in 1,013 patients taking captopril,

lisinopril, or enalapril. Women were found to experience more bronchospasm (58% vs. 42%) and cough (59% vs. 41%) reactions compared to men; however, the difference was not statistically significant. Notably, patients under the three different treatments were not separated when the prevalence was reported, which means that the rate of bronchospasm and cough in each individual medication group was unknown. In another randomized, double-blind clinical trial investigating sex differences in efficacy and safety of antihypertensives, 3,535 hypertensive patients (1,209 men and 2,326 women) were recruited and followed during 8 weeks of treatment (Fan et al., 2008). In patients randomized to captopril group, the prevalence of cough was found to be significantly higher in women than in men (14.3% vs. 8.4%, $p = 0.005$). This female-biased ACE inhibitor induced cough was also observed in lisinopril by Os et al. in a randomized, double-blind clinical trial (Os et al., 1994). In this study, 206 men and 206 women were randomized to lisinopril group, and cough was found to happen three times more often in women than in men (12.6% vs. 4.4%, $p = 0.0027$). Overall, although some non-significant findings exist, more evidence suggests an increased risk of ACE inhibitor induced cough in women.

3.3.5 Amlodipine and nifedipine

Both amlodipine and nifedipine are dihydropyridine calcium channel blockers (CCBs) which are widely used for treating hypertension, stable and variant angina. Although structurally similar, amlodipine differs from nifedipine and other dihydropyridine CCBs by its long half-life, enabling once daily dosing (Haria and WagstaffAmlodipine, 1995). In terms of ADRs, both amlodipine and nifedipine are observed to cause hypotension, palpations, edema, and flushing with slightly different occurrence rate.

Sex difference studies are available for amlodipine-related neurological ADRs and nifedipine-related cough and edema. Abad Santos et al. conducted a bioequivalent study in 36 healthy volunteers (18 men and 18 women) to study sex differences in amlodipine induced ADRs as their secondary objective (Abad-Santos et al., 2005). All subjects received a single 10 mg dose of each amlodipine formulation with a 14-day washout period. After statistical analysis, the researchers did not find any significant difference between men and women in amlodipine related headache (44% vs. 28%), dizziness (11% vs. 28%), or tiredness (17% vs. 6%). Sex difference in nifedipine-related edema was studied in a prospective study by Fan et al. (Fan et al., 2008). A total of 327 men and 620 women were randomized to nifedipine sustained release (SR) group and were followed up for 8 weeks to evaluate drug related ADRs. Women were found to be more susceptible to ADRs related to nifedipine SR than their men counterpart (15.8% vs. 9.8%, $p = 0.017$), with intolerable edema being the main type of ADR observed. In another study assessing the role of sex in nifedipine associated cough, 218 men and 198 women were randomized to nifedipine group and were followed up for 10 weeks (Os et al., 1994). No sex difference was identified by this study in nifedipine related cough (men 3% vs. women 2.8%). To conclude, women were found to experience more intolerable edema from nifedipine SR, while no sex difference was found in nifedipine associated cough or amlodipine associated headache, dizziness, or tiredness.

3.3.6 Atenolol

Atenolol is one of the drugs classified as beta-blocker, and it is used to treat several conditions such as hypertension, cardiac dysrhythmia, angina pectoris, etc. Recently, the effectiveness of atenolol has been assessed in other disease areas including anxiety (Armstrong and Kapolowicz, 2020). In terms of its safety profile, most patients tolerate atenolol well. Bradyarrhythmia, hypotension, dizziness, and fatigue are the most common ADRs observed with atenolol treatment. There is one study evaluating sex difference in ADRs related to atenolol in treating hypertension. After following 191 men and 403 women on atenolol therapy for 8 weeks, the researchers found that fatigue and bradycardia were most common ADRs during treatment period, and there was no sex difference in the occurrence rate of those ADRs (men 15.8% vs. women 11.6%, $p = 0.497$) (Fan et al., 2008).

3.4 Analgesic medications

3.4.1 Morphine

Opioids are widely used in the management of moderate to severe pain. As one of the potent opioid analgesia, morphine is recommended for pain management in various disease types such as cancer, acute pulmonary edema, and myocardial infarction (Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology ESC, 2012; Wiffen et al., 2016). However, the use of morphine has been cautioned due to a wide range of ADRs including pruritus, nausea, vomiting, dizziness, urinary retention, and more seriously, drug dependence, respiratory depression, and cardiac arrest.

Sex differences have been investigated in multiple morphine induced ADRs such as gastrointestinal ADRs and respiratory depression. In a prospective observational study undertaken by Sadhasivam et al. (Sadhasivam et al., 2015), 219 children undergoing tonsillectomy or adenotonsillectomy (T/TC) surgery were recruited and the efficacy and safety of morphine were compared between boys and girls. No sex difference was observed in respiratory depression (10% in boys vs. 7% in girls, $p = 0.81$), postoperative nausea and vomiting (6% in boys vs. 9% in girls, $p = 0.2$), and pruritus (41% in boys vs. 33% in girls, $p = 0.54$). Likewise, sex differences in morphine related ADRs were also assessed by Fillingim et al. in healthy adult women (n = 61) and men (n = 39) (Fillingim et al., 2005). All subjects in the study were intravenously administered 0.08 mg/kg single dose of morphine, after which the incidence of pruritus, nausea, and emesis were assessed. Similar to the previously described study, no evidence of sex difference was found in pruritus (8% in men vs. 10% in women). However, the prevalence of nausea and emesis were found to be significantly higher in women than in men (nausea 35% vs. 3%, emesis 18% vs. 0, $p < 0.005$). The results from the two studies above indicates that the role of sex in morphine related nausea and vomiting might be different in different disease states and/or age groups.

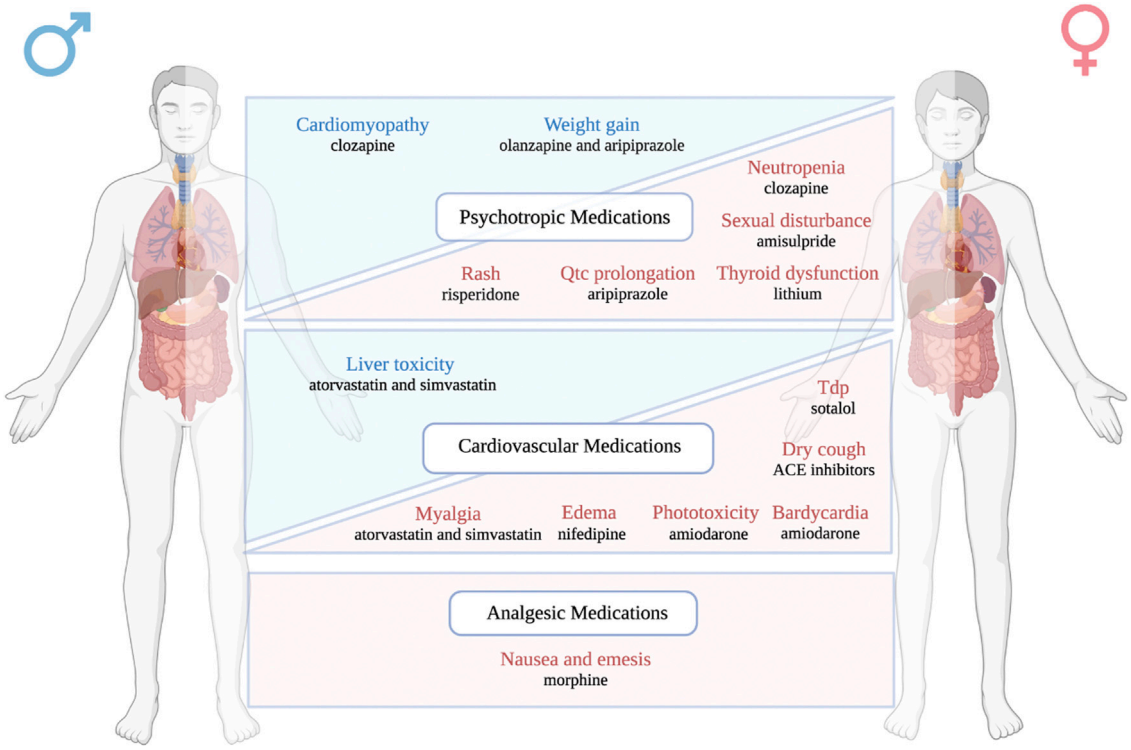

FIGURE 2
A schematic figure listing the main ADRs showing sex differences in occurrence rate. The adverse drug reactions highlighted in blue are male-biased ADRs, while the adverse drug reactions highlighted in red are female-biased ADRs. Drugs and their associated sex biased ADRs are classified into three different therapeutic categories: psychotropic medications, cardiovascular medications, and analgesic medications.

4 Discussion

Despite the careful premarketing evaluation and postmarketing surveillance, adverse drug reactions remain a global public health issue leading to morbidity, mortality, and huge financial loss. In the United States, severe ADRs have been estimated to occur more than 2 million times in hospitalized patients every year, which ultimately result in 100,000 deaths (Giacomini et al., 2007). The financial burden caused by ADRs has been calculated to be equivalent to 16% of total healthcare expenditures in the US in 2016 (Watanabe et al., 2018). Although some recent efforts have been invested into ADR prediction (Lounkine et al., 2012; Mohsen et al., 2021; Zhang et al., 2021), it remains challenging to identify patients with high risk to develop certain ADRs clinically, which might be due to lack of data, limited sample size of ADR studies, and the complex nature of ADR generation, etc. As a ready-to-use clinical character, sex has recently been shown to be an influencer in the risk of ADR development (Tharpe, 2011; Nakagawa and Kajiwara, 2015). Here, we systematically reviewed the role of sex in the risk of ADRs caused by commonly used psychotropic, cardiovascular, and analgesic medications. Our findings suggested that several common and/or severe ADRs have difference prevalence in men versus in women as shown in Figure 2.

Quantitively, we included studies evaluating sex differences in ADR occurrence for 6 psychotropic medications, with 18 drug-specific ADRs showing sex differences, 15 drug-specific ADRs showing no sex difference; 10 cardiovascular medications, with 8 drug-specific ADRs showing sex differences, 4 drug-specific ADRs showing no sex difference; 1 analgesic medication with 3 drug-related ADRs showing no sex difference. The 17 drugs discussed in this review cover a variety of disease areas such as bipolar disorder, schizophrenia, arrhythmia, hypertension, hyperlipidemia, pain, etc. Notably, as an important class of psychotropic medication, the antidepressant medications in our searching list did not result in any study showing sex differences in ADR, which implies that more sex-awareness is needed for this particular drug class. A complete list of the sex difference findings in ADR can be found in Table 2.

Intriguingly, we identified some well-established ADRs which were shown to exert sex difference patterns by multiple studies. For instance, lithium was found to cause more thyroid dysfunction in women than in men (Henry, 2002; Özerdem et al., 2014), and amisulpride was shown to increase prolactin level more in women than in men (Düring et al., 2019; Hoekstra et al., 2021). In addition to the consistent findings on sex biased ADRs, sex difference research in serious ADRs is also worth mentioning. As a rare but life threatening ADR of clozapine, neutropenia was found to happen more in women than in men in a retrospective study (Hollingworth et al., 2018), suggesting that more surveillance is needed for women with long-term clozapine use. Similarly, after reviewing the ADRs in patients treated with sotalol for arrhythmia, researchers found that more women developed TdP, a fatal ADR of sotalol, than men (Lehmann et al., 1996). These clinically observed ADRs should serve as stimulants for both consideration of sex in drug selection and

TABLE 2 Summary of findings of sex difference research.

Drug	Consistent findings			Conflicting findings
	Male-biased	Female-biased	No sex difference	
Psychotropic medications				
Lithium	Tremor (Henry, 2002)	Edema (Öhlund et al., 2018) Weight gain (Henry, 2002; Öhlund et al., 2018) Thyroid dysfunction (Henry, 2002; Özerdem et al., 2014)	Acne (Henry, 2002) Polyuria (Henry, 2002)	—
Amisulpride	—	Increased prolactin levels (Düring et al., 2019; Hoekstra et al., 2021)	Extrapyramidal symptoms (Müller et al., 2006; Hoekstra et al., 2021) Agitation (Müller et al., 2006) Sedation (Müller et al., 2006) Blurred vision (Müller et al., 2006) Metabolic ADRs (Hoekstra et al., 2021) Hypersalivation (Müller et al., 2006)	Sexual dysfunction (female-biased (Düring et al., 2019) vs. no sex difference (Müller et al., 2006; Hoekstra et al., 2021))
Clozapine	Cardiomyopathy and myocarditis (Hollingworth et al., 2018)	Weight gain (Lau et al., 2016) Neutropenia (Hollingworth et al., 2018)	—	—
Olanzapine	Increased BMI (Hoekstra et al., 2021) Increased glucose level (Hoekstra et al., 2021)	Dermatological symptoms (Pu et al., 2020) Higher prolactin level (Hoekstra et al., 2021) Autonomic ADRs (Pu et al., 2020)	Dystonia, rigidity, hypo/hyperkinesia, tremor, seizure (Hoekstra et al., 2021) Sexual dysfunction (Hoekstra et al., 2021)	—
Aripiprazole	BMI increase (Hoekstra et al., 2021)	BP lowering, higher HR, prolonged QTc interval (Belmonte et al., 2016) Nausea and vomiting (Belmonte et al., 2016) Psychotic ADRs (Pu et al., 2020)	Dystonia, rigidity, hypo/hyperkinesia, tremor, seizure (Hoekstra et al., 2021) Increased glucose level (Hoekstra et al., 2021) Sexual dysfunction (Hoekstra et al., 2021)	—
Risperidone	—	Rashes (Pu et al., 2020)	Weight gain (Labelle et al., 2001) Parkinsonism, dystonia (Labelle et al., 2001)	—
Cardiovascular medications				
Amiodarone	—	Phototoxicity (Roten et al., 2009) Bradyarrhythmia requiring pacemaker insertion (Essebag et al., 2007)	—	—
d,l-sotalol	—	Torsade de pointes (TdP) (Lehmann et al., 1996)	—	—
Simvastatin/atorvastatin	Abnormal liver function (Smiderle et al., 2014) Increased CPK levels (Smiderle et al., 2014)	Myalgia (Smiderle et al., 2014)	—	—
Enalapril	Anemia (Ishani et al., 2005)	—	—	Cough (female-biased (Coulter and Edwards, 1987) vs. no sex difference (Wood, 1995; Sadanaga et al., 2009))
Captopril	—	—	—	Cough (female-biased (Coulter and Edwards, 1987; Fan et al., 2008) vs. no sex difference (Wood, 1995))
Lisinopril	—	—	—	Cough (female-biased (Os et al., 1994) vs. no sex difference (Wood, 1995))
Amlodipine	—	—	Headache, dizziness, and tiredness (Abad-Santos et al., 2005)	—

(Continued on following page)

TABLE 2 (*Continued*) Summary of findings of sex difference research.

Drug	Consistent findings			Conflicting findings
	Male-biased	Female-biased	No sex difference	
Nifedipine	—	Intolerable edema (Fan et al., 2008)	Cough (Os et al., 1994)	—
Atenolol	—	—	Bradycardia (Fan et al., 2008) Fatigue (Fan et al., 2008)	—
Analgesic medications				
Morphine	—	—	Pruritus (Fillingim et al., 2005; Sadhasivam et al., 2015) Dizziness (Fillingim et al., 2005) Respiratory depression (Sadhasivam et al., 2015)	Nausea and vomiting (female-biased (Fillingim et al., 2005) vs. no sex difference (Bijur et al., 2008; Sadhasivam et al., 2015))

*BMI, body mass index; BP, blood pressure; HR, heart rate; CPK, creatinine phosphokinase.

ADR monitoring, as well as future studies to explore the underlying mechanism behind the observed sex differences.

In addition to the findings showing consistent sex differences in certain ADRs, conflicting results also exist, which makes it difficult to draw a certain conclusion. For instance, morphine-associated nausea and vomiting was concluded as female-biased by Fillingim et al. (Fillingim et al., 2005), whereas no sex difference was observed in the same ADR in another study (Sadhasivam et al., 2015). After carefully reviewed the two studies, we found that the former study recruited healthy adult volunteers, while the latter one recruited children undergoing tonsillectomy or adenotonsillectomy (T/TC) surgery. The distinct target populations made it difficult to compare the results between the two studies, since both age and disease state can impact the risk of drug ADRs (Lavan and Gallagher, 2016). Similarly, other discrepancies in the study design (dosing regimen, follow-up time, definition of certain ADR, ethnicity group of the participants, etc.) also introduce complexities when results were compared between studies. Therefore, we suggest that more thorough study design and more robust methods such as meta-analyses are needed to better understand sex differences in the risk of ADR generation.

For all the studies that are included in this review, we searched the article for potential mechanisms that may explain the observed sex differences. Surprisingly, only five out of the twenty-six studies discussed the putative underlying mechanisms, all of which are related to differences in the serum concentration of the medication between men and women. However, in-depth discussion on the reason of the differences in PK profile between sexes is missing in those studies. In fact, there are recent publications summarizing how sex might impact PK and drug response. It is believed that the intracellular and extracellular water volumes, amount of fat mass, expression of drug metabolizing enzymes and transporters, and glomerular filtration might be different between men and women, which can impact every aspect of absorption, distribution, metabolism, and elimination of a medication (Gandhi et al., 2004; Soldin et al., 2011; Yang et al., 2012). More broadly speaking, other factors such as genetics, hormone, immune system, microorganisms, and environment could also contribute to sex differences in drug efficacy and safety by impacting PK and/or pharmacodynamic of medications (Arnold, 2017; Weersma et al., 2020; Cheng et al., 2022; Huang et al., 2023). Therefore, we suggest that future studies need to consider a wider range of potential mechanisms to better understand the observed sex differences in drug ADRs.

Our study has some limitations. Although the 1,819 drug list used for web scraping covers the majority of the most prescribed cardiovascular, psychotropic, and analgesic medications (Fuentes et al., 2018) (22/24 top 100 cardiovascular medications, 15/15 top 100 psychotropic medications, 9/9 top 100 analgesic medications are in drug list), we are missing two commonly prescribed cardiovascular medications which are furosemide and aspirin. We manually searched evidence of sex differences in ADR related to the above two medications using the same criteria as listed in Figure 1, which resulted in one study showing sex differences in reported bleeding events related to aspirin (Rydberg et al., 2014). This retrospective study found that women were at a lower risk of aspirin related bleeding compared to men (RR 0.8, 95% CI 0.66-1.96). Since we did not use an exhaustive list of cardiovascular, psychotropic, and analgesic medications, one limitation of our study is that we might miss evidence of sex differences in ADRs related to some less commonly used medications under the three categories above. Second, the distinct quality and study design (dosage, route of administration, target population, etc.) of the included studies introduce complexities when comparing the results among the studies. For instance, we found that differences in the risk of bias of the included studies may contribute to conflicting results. Using Risk Of Bias In Non-randomized Studies - of Intervention (ROBINS-I) as the tool (Sterne et al., 2016), we found that the study conducted by Müller et al. (2006) has a moderate risk of bias due to confounding because of its naturalistic study design and the different dosage of amisulpride used by participants. In comparison, the study conducted by Hoekstra et al. (2021) has a low risk of bias due to confounding since the patients received the same dose of amisulpride. This difference in risk of bias may be able to explain the conflicting finding of the two studies on sex differences in sexual disfunction related to amisulpride. Therefore, we suggest that the results of this review should be

carefully interpreted with the quality and design of the original study. Third, our search results are exclusively generated from PubMed search. A more comprehensive list of relevant studies might be achieved by including other databases such as Cochrane Library and Web of Science.

Overall, sex differences in ADRs have been studied and identified in a handful of psychotropic, cardiovascular, and analgesic medications. However, to better understand the underlying mechanism of the observed sex differences in ADRs, further studies with more comprehensive study design are warranted. Some key factors to consider are clearly documented ADRs in each sex group, collection of PK data, pharmacogenomic data, measurement of microorganism, document of environmental exposure, etc. It is of great clinical significance to understand how sex can impact the risk of ADRs so that more personalized approaches could be applied to minimize the burden caused by ADRs.

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

YS, LC, and RSH conceived the idea. YS and YH performed the web scraping. YS, LC, and YZ screened the literature resulted from web scraping, and collected the characteristics and main findings of each paper included in this review. YS wrote the manuscript. All authors contributed to the article and approved the submitted version.

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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.2023.1096366/full#supplementary-material

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Inpatient prescribing patterns of long-acting injectables and their oral or short-acting injectable equivalent formulations

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Background: Long-acting injectable (LAI) antipsychotics (APs) each have an oral equivalent formulation, while aripiprazole, olanzapine, and ziprasidone each also have a short-acting injectable (SAI) equivalent formulation. Inpatient prescribing patterns of LAIs and their oral/SAI equivalents are less characterized in populations other than Medicaid, Medicare, and Veterans Affairs populations. Mapping out inpatient prescribing patterns remains an important first step to ensure appropriate use of antipsychotics during this critical juncture of patient care prior to discharge. This study determined inpatient prescribing patterns of first- (FGA) and second-generation antipsychotic (SGA) LAIs and their oral/SAI formulations.

Methods: This was a large retrospective study using the Cerner Health Facts® database. Hospital admissions due to schizophrenia, schizoaffective disorder, or bipolar disorder from 2010 to 2016 were identified. AP utilization was defined as the proportion of inpatient stays during which at least 1 AP was administered to the total number of inpatient visits over the observed period. Descriptive analyses were used to determine prescribing patterns for APs. Chi-square tests were used to determine utilization differences across years.

Results: 94,989 encounters were identified. Encounters during which oral/SAI of SGA LAIs were administered were most common (n = 38,621, 41%). Encounters during which FGA LAIs or SGA LAIs were administered were the least common (n = 1,047, 1.1%). Prescribing patterns differed across years ($p < 0.05$) within the SGA LAI subgroup analysis (N = 6,014). Paliperidone palmitate (63%, N = 3,799) and risperidone (31%, N = 1,859) were the most frequently administered. Paliperidone palmitate utilization increased from 30% to 72% ($p < 0.001$), while risperidone utilization decreased from 70% to 18% ($p < 0.001$).

Conclusions: Compared with their oral or SAI formulations, LAIs were underutilized from 2010 to 2016. Among SGA LAIs, the prescribing patterns of paliperidone palmitate and risperidone changed significantly.

KEYWORDS

long-acting injectable antipsychotic medications, prescribing patterns (physician), schizophrenia, schizoaffective disorder, bipolar disorder, real-world evidence

Introduction

Schizophrenia and bipolar disorder are two of the costliest mental health diseases in the United States, accounting for approximately $281 (Schizophrenia and Psychosis Action Alliance, 2021) and $202 billion per year (Cloutier et al., 2018) in U.S. healthcare costs, respectively. Schizophrenia affects 0.8% (Schizophrenia and Psychosis Action Alliance, 2021), schizoaffective disorder affects 0.3% (Perälä et al., 2007; Olfson et al., 2009), and bipolar disorder affects 2.4% of the U.S. population (Merikangas et al., 2007). A sizable portion of these costs are driven by non-adherence to antipsychotics (APs) (Olivares et al., 2013), treatment interruptions that increase the risk of re-hospitalization (Weiden et al., 2004) and emergency psychiatric services (Hong et al., 2011).

Long-acting injectables (LAIs) include first- (FGA) and second-generation antipsychotic (SGA) LAIs. Before FGA and SGA LAIs were introduced to the market, they were preceded by their oral and short-acting injectable (SAI) equivalent formulations. Of note, ziprasidone is available in an oral formulation and as a SAI, but not as a LAI. Except for risperidone and paliperidone palmitate, each LAI also has a short-acting injectable equivalent formulation. LAIs are appropriate for patients with more severe illness, limited social supports, or at high-risk of relapse (Sajatovic et al., 2018), all of which are risk factors for medication non-adherence. Real-world studies illustrate that LAIs reduce hospitalization and non-adherence amongst Medicaid (Bera et al., 2013; Marcus et al., 2015; Pilon et al., 2017a; Pilon et al., 2017b), Medicare (Offord et al., 2013) and Veterans Affairs (VA) populations (Baser et al., 2015). A recent meta-analysis also illustrate that LAIs reduce the likelihood of non-adherence and hospitalization (Lin et al., 2021). Despite these promising findings in conjunction with a recent trend of increased LAI use, LAIs remain underutilized within those diagnosed with persistent psychiatric disorders (Rittmannsberger et al., 2017).

Although previous utilization studies provide evidence of underuse, large retrospective studies focus only on outpatient prescribing. Outpatient LAI use amongst Medicaid beneficiaries diagnosed with schizophrenia range from 10% for any LAI (Brown et al., 2014), to 3.1% and 3.8% for Risperdal, and FGA LAIs, respectively (Jackson et al., 2018). Outpatient LAI use amongst commercially insured beneficiaries with schizophrenia range from 6.9% to 9.3% for atypical and typical LAI, respectively (Fu et al., 2022). Inpatient prescribing studies are fewer in number with much smaller sample sizes. One inpatient study found that only 25%–33% of patients having clear indications for LAIs were prescribed LAIs prior to discharge (Kishimoto et al., 2017). Another study of 179 patients hospitalized for schizophrenia reported a 42% LAI utilization rate (Yee et al., 2021). Taken together, no studies to our knowledge leverage large retrospective databases to determine inpatient prescribing patterns within and among LAIs, oral APs, or SAIs.

Although SGA LAIs have emerged as treatment options with potential advantages including enhanced tolerability, dosing flexibility, and extended dosing time intervals, their prescribing patterns have not been widely reported in literature, as they are still relatively new medication administration technologies. Identifying gaps in inpatient prescribing patterns across a larger cross-section of APs is a critical step in achieving a better understanding of disparities, similarities, and differences within LAIs, oral APs, and SAIs, in turn informing better pharmacotherapy strategies prior to patients being discharged. Understanding prescribing patterns also has clinical merits, such as determining which SGA LAI is favored by prescribers.

Determining inpatient prescribing patterns provides insights into medication utilization during a critical period in which patients with schizophrenia are being stabilized, underscoring the need for studies measuring inpatient prescribing patterns. Furthermore, conducting these analyses using the Cerner Health Facts® Data representing hospitals across the US has the advantage of capturing real-world prescribing behaviors across a large dataset that would otherwise not be captured in randomized trials or smaller studies focused on inpatient prescribing.

Objectives

Our primary objectives were to determine and describe FGA and SGA LAI and oral/SAI equivalent prescribing patterns within a sample of US patients hospitalized for schizophrenia, schizoaffective disorder, or bipolar disorder from 2010 to 2016. Our secondary objective was to identify SGA LAI prescribing pattern changes from 2010 to 2016.

Methods

The Health Facts® database (Cerner Corp., Kansas City, MO) was used to examine prescribing patterns of APs for patients hospitalized for schizophrenia, schizoaffective disorder, or bipolar disorder between 2010 and 2016. The Cerner Health Facts® Data Warehouse includes records for over 64 million patients treated at over 863 hospitals and clinics throughout most states within the U.S. Currently, the database contains data from the inpatient setting on 11.4 million hospital inpatient stays and 22.9 million emergency department visits, and contains patient demographics, diagnosis, medications, and procedures. Only medications administered through hospital pharmacies are captured, such as National Drug Codes (NDCs), and the dates and times when drugs were dispensed.

The unit of analysis was an inpatient encounter. We included inpatient encounters (hospital stays or emergency department visits) for which the primary diagnosis was schizophrenia, schizoaffective disorder, or bipolar disorder, and during which at least one LAI or an oral/SAI equivalent formulation was prescribed. The diagnoses were based on ICD-9 and ICD-10 codes. ICD-9 codes were schizophrenia and schizoaffective disorder (ICD-9 Codes 295.0 to 295.9, including all the double digits), or bipolar disorder (ICD-9 Codes 296.0, 296.4 to 296.8, including all the double digits). ICD-10 codes were schizophrenia (ICD-10 Codes F20.0 to F20.9), schizoaffective disorder (ICD-10 Code F25), or bipolar disorder (ICD-10 Code F31).

Generic and brand-named FGA and SGA LAIs and their oral/SAI equivalent formulations were identified using NDCs. The Health Facts® database contained multiple NDCs corresponding to varying dosage forms for each of these generic and brand name drugs. FGA LAIs included haloperidol decanoate (Haldol®, Haldol

TABLE 1 Inpatient prescribing patterns of APs 2010–2016 (N = 94,989).

Inpatient prescribing patterns	N (%)
LAI only	
FGA LAI only	494 (0.52)
SGA LAI only	553 (0.58)
FGA and SGA LAI only	0 (0)
Subtotal	**1,047 (1.1)**
Oral/SAI formulations only	
FGA oral/SAI only	22,926 (24.1)
SGA oral/SAI only	38,621 (40.7)
FGA and SGA oral/SAI only	22,644 (23.8)
Subtotal	**84,191 (88.6)**
Concurrent LAI and oral/SAI equivalent	
FGA oral/SAI and FGA LAI	2,496 (2.6)
SGA oral/SAI and SGA LAI	2,148 (2.3)
FGA oral/SAI and SGA LAI	481 (0.51)
SGA oral/SAI and FGA LAI	274 (0.29)
FGA oral/SAI, FGA LAI, and SGA oral/SAI	1,587 (1.7)
FGA oral/SAI, FGA LAI, and SGA LAI[a]	18 (0.02)
SGA oral/SAI, SGA LAI, and FGA oral/SAI	2,615 (2.75)
SGA oral/SAI, SGA LAI, and FGA LAI[a]	15 (0.02)
FGA oral/SAI, SGA oral/SAI, FGA LAI, and SGA LAI[a]	117 (0.12)
Subtotal	**9,751 (10.3)**
Total	**94,989 (100)**

Notes.
FGA, LAIs: haloperidol decanoate (Haldol®, Haldol Decanoate®) and fluphenazine decanoate (Prolixin®).
SGA, LAIs: aripiprazole monohydrate (Abilify Maintena®), aripiprazole lauroxil (Aristada®), paliperidone palmitate (Invega Trinza®, Invega Sustenna®), risperidone (Risperdal Consta®), and olanzapine pamoate (Zyprexa Relprevv®).
FGA, oral equivalents of FGA, LAIs.
SGA, oral- oral equivalents of SGA, generation LAIs.
[a]Pattern did not differ significantly across years.

Decanote®) and fluphenazine decanoate (Prolixin®). SGA LAIs included aripiprazole monohydrate (Abilify Maintena®), aripiprazole lauroxil (Aristada®), paliperidone palmitate (Invega Trinza®, Invega Sustenna®), risperidone (Risperdal Consta®), and olanzapine pamoate (Zyprexa Relprevv®). Of note, Risperidone (Perseris®) and aripiprazole lauroxil nanocrystal technology (Aristada Initio®) were not commercially available during the 6-year follow-up period of this study.

AP utilization consisted of inpatient encounters (hospital stays or emergency department visits) during which at least one LAI, oral AP, or SAI was dispensed. SAIs were included because agitated or acutely psychotic patients often receive a short-acting intramuscular form of the medication they eventually will be administered orally during their hospitalization. Including SAIs enabled us to capture total use of all different formulations of the AP class. We divided the inpatient encounters into fifteen mutually exclusive medication categories corresponding to fifteen different combinations of prescribing patterns (Appendix). Descriptive analyses were conducted for these fifteen inpatient prescribing patterns. For each prescribing pattern, Chi-square tests were used to examine whether the pattern differed across years.

In the sub-group analysis, we examined inpatient encounters during which any of the SGA LAIs was dispensed. Descriptive analyses were used to determine utilization rates within the 6,014 encounters. For each year, the utilization rate was calculated as the number of encounters associated with a particular SGA LAI divided by the number of encounters associated with all SGA LAIs. For each SGA LAI, Chi-square tests were used to determine if the utilization rates differed across years. All analyses were completed using IBM SPSS Statistics Version 25 (IBM Corp., Armonk, NY), and this study was under a long-standing IRB approval for all Health Facts® projects at our institution.

Results

A total of 94,989 encounters were identified, including 80,648 hospital stays (84.9%) and 14,341 emergency department visits (14.9%). FGA oral/SAI formulations were administered in 88.6% of the inpatient encounters, and SGA oral/SAI formulations were administered in 40.7% of encounters (Table 1). LAIs as monotherapy were administered in 1.1% of inpatient encounters, while LAI and oral/SAI equivalents were administered concomitantly in 10.3% of inpatient encounters. In addition, FGA LAIs and SGA LAIs were only administered as monotherapy in 0.52% and 0.58% of inpatient encounters, respectively.

Figure 1 displays the trends of FGA LAI, SGA LAI, and LAI monotherapy. Overall, the utilization of FGA LAI and LAI monotherapy increased between 2013 and 2016. The utilization of SGA LAI monotherapy increased between 2013 and 2015. Chi-square tests for each prescribing pattern across years were statistically significant ($p < 0.05$), except the following three categories.

1. The concurrent use of oral/SAI formulations of FGA LAIs, FGA LAIs, and SGA LAIs.
2. The concurrent use of oral/SAI formulations of SGA LAIs, SGA LAIs, and FGA LAIs.
3. The concurrent use of oral/SAI formulations of FGA LAIs, oral/SAI formulations of SGA LAIs, FGA LAIs, and SGA LAIs.

Sixty-three percent of encounters were associated with patients who were Caucasian, and 28% were associated with patients who were African American (Table 2). Fifty-six percent of encounters were associated with male patients, and 69% were associated with single patients. The average age across encounters was 44.8 years old (±15.5), and the average length of stay was 8.7 days (±13.7). In addition, 83% of encounters were associated with urban hospitals, and 91% were associated with acute hospitals (Table 2).

In the sub-group analysis of SGA LAIs, 6,014 encounters were identified. Of note, the identification method was different from the

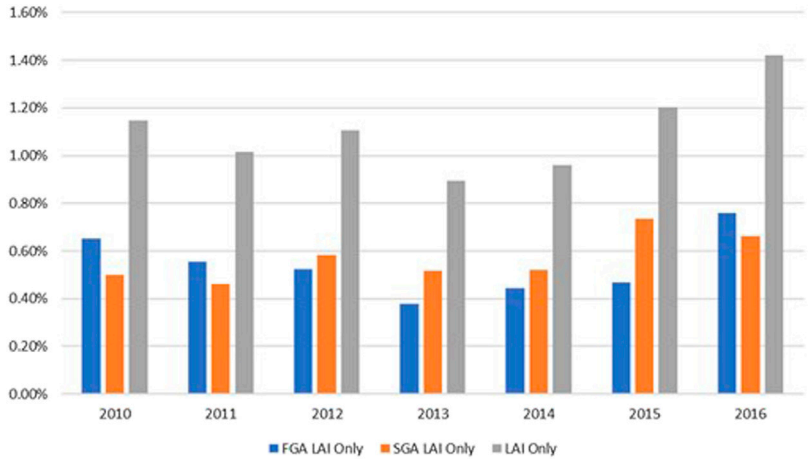

FIGURE 1
Trends of Prescribing Patterns for FGA LAI, SGA LAI, and LAI monotherapy 2010–2016.

method used in Table 1. For example, if an encounter was associated with both paliperidone palmitate and olanzapine pamoate, it was counted as two (one for paliperidone palmitate and one for olanzapine pamoate) but counted as one in the category of "SGA LAI only" in Table 1. As shown in Figure 2, Aripiprazole was administered in 5% (N = 323) of encounters, paliperidone palmitate was administered in 63% (N = 3,799) of encounters, risperidone was administered in 31% (N = 1,859) of encounters, and olanzapine was administered in less than 1% (N = 33) of encounters. Aripiprazole monohydrate (Abilify Maintena®) and aripiprazole lauroxil (Aristada®) were combined as one category of aripiprazole due to only four encounters related to Aristada®. Breaking these 6,014 encounters out across 7 years revealed paliperidone palmitate utilization increased from 29.6% to 71.6% (p p< 0.001), while risperidone decreased from 70.4% to 18.4% (p < 0.001) (Figure 3; Table 3).

Discussion

According to our knowledge, this was the first study to utilize a large nationwide sample to examine inpatient prescribing patterns of LAIs and concomitant oral/SAI APs for schizophrenia, schizoaffective disorder, or bipolar disorder. Our findings of low inpatient LAI utilization are consistent with previous studies conducted in smaller settings (Kishimoto et al., 2017; Yee et al., 2021). Previous studies determining inpatient LAI prescribing patterns had smaller sample sizes and focused on single sites such as psychiatric hospitals. In addition, for each of fifteen prescribing patterns, this study performed detailed comparisons across years, whereas previous studies only included certain APs. Moreover, this study compared the utilization rates among SGA LAIs. The Chi-square results for each prescribing pattern across years demonstrated that LAIs were underutilized. Figure 1 shows that paliperidone palmitate (63%) and risperidone (31%) were the two primary SGA LAIs utilized between 2010 and 2016. Furthermore, Figure 2 with Chi-square test results demonstrate a trend of increasing utilization for paliperidone palmitate since 2010, and for aripiprazole since 2013; and a trend of decreasing utilization for risperidone since 2010.

Our analysis reported lower LAI inpatient prescribing rates (e.g., 1.1% for LAI monotherapy, and 10.3% for concurrent use of LAI and oral/SAI formulation), compared to previous studies. Kishimoto et al. (2017) found LAIs were prescribed in 25%–33% of patients admitted to a 208-bed psychiatric hospital. Yee et al. (2021) found LAIs were prescribed in 42% of hospitalized patients participating in a community hospital-based community treatment program. The higher prescribing rates observed in these studies were potentially attributed to the fact they included individuals with a history of hospitalization due to AP non-adherence (Kishimoto et al., 2017) or individuals who experience the most intractable symptoms or level of dysfunction (Yee et al., 2021). The lower utilization rates in our study could be due to a host of differences in patient preferences, clinician knowledge and attitudes, coverage policies, or pharmaceutical company promotions - all of which have been shown to impact utilization trends in schizophrenic patients (Horvitz-Lennon et al., 2009). For example, familiarity with treatment guidelines and frequent contact with pharmaceutical representatives influence the physician prescribing behaviors of SGA LAIs (Arbuckle et al., 2008). The higher utilization rates in psychiatric hospitals admitted patients with more severe conditions and had providers who were intimately familiar with treatment guidelines, compared to our sample of patients at primarily general acute care facilities.

For SGA LAIs, we found 4% (3,799/94,989), 2% (1,859/94,989) and 0.3% (323/94,989) of hospitalizations had at least one administration of paliperidone, risperidone, and aripiprazole (Abilify Maintena® and Aristada® combined), respectively. In contrast, Yee et al. found 14%, 17% and 9% for paliperidone, risperidone, and aripiprazole (Abilify Maintena® only), respectively (Yee et al., 2021). Because Yee et al. conducted

TABLE 2 Patient demographics and facility characteristics associated with encounters (N = 94,989).

Variables	Frequency	Percent
Patient demographics		
Race		
Caucasian	60,008	63.2
African American	26,562	28
Asian or Pacific Islander	1,701	1.7
Hispanic	1,310	1.4
Native American	1,028	1.1
Other	4,380	4.6
Total	94,989	100
Gender		
Male	52,812	55.6
Female	42,177	44.4
Total	94,989	100
Marital Status		
Single	65,638	69.1
Divorced	11,712	12.3
Married	11,281	11.9
Widowed	3,565	3.8
Other	2,793	2.9
Total	94,989	100
Facility characteristics		
Urban vs. Rural		
Urban	78,976	83.1
Rural	16,013	16.9
Total	94,989	100.0
Acute vs. Non-Acute		
Acute	86,063	90.6
Non-Acute	8,926	9.4
Total	94,989	100.0

their study in 2018, when SGA LAIs became more widely available, and they focused on a designated clinical program in which patients might have more severe conditions, it is reasonable that the utilization rates were higher than our findings. However, the advantage of our study is offering longitudinal perspectives for a variety of prescribing patterns across healthcare facilities. As mentioned earlier, two noteworthy trends we observed were the upward and downward utilization trends of paliperidone and risperidone, respectively between 2010 and 2016. The proportion of encounters during which paliperidone was administered increased from 29.6% to 71.6%, yet the proportion of encounters during which risperidone was administered decreased from 70.4% to 21.9%. This reversed trend can partly be explained by prescribers preferring paliperidone over risperidone due to dosing interval extensions or improved tolerability. For example, patients initiated on paliperidone palmitate (Invega Sustenna®) have a longer injection cycle of 1 month which could later be extended to 3 months by switching to Invega Trinza®.

Despite these increasing trends over time, our results still affirm LAI underutilization within inpatient settings between 2010 and 2016. Underutilization can result in negative health outcomes by reducing symptom control, worsening symptoms, increasing hospitalization or readmission, and increasing healthcare expenditures related to non-adherence and associated psychiatric decompensation (Lacro et al., 2002; Nosé et al., 2003). Examining prescribing patterns of APs in the inpatient setting is the first step to address issues related to underutilization. The variation in prescribing patterns of APs and specifically SGA LAIs indicates disparities in medication utilization. The variation is clinically relevant because discharging patients on appropriate regimens would reduce readmissions and improve health outcomes. The variation could also lead to hypotheses about what patient, provider, or organizational factors would drive the differences. Therefore, future studies should focus on two directions: 1) exploring the relationship between prescribing patterns and patients' health outcomes, especially how the underutilization of LAIs impacts patients' health outcomes; and 2) identifying patient, provider, or organizational factors affecting the disparities of medication utilization or health outcomes. Furthermore, future studies could compare costs and quality of life measures between FGA LAIs and SGA LAIs, or among prescribing patterns of APs. If differences in quality of life were minimal, and differences in costs were significant, results would have important implications for prescribing behaviors and clinical recommendations.

This study had three limitations. First, the results are generalizable to only the types of facilities included in Health Facts® database and associated with Cerner Corp. Second, given the absence of data, we were not able to capture prescribing patterns in outpatient prescribing patterns, which also provide important context of prescribing patterns outside the hospital stay. Despite this, examining solely inpatient prescribing enables us to focus on a population of patients with more severe disease compared to those represented in outpatient clinics. Third, we were not able to measure prescriber-specific factors such as attitude or behavior, because specific providers were not identifiable in Health Facts® database. Despite these limitations, this is the first known study to using a large dataset of inpatient prescribing to evaluate the LAI prescribing patterns amongst US hospitals. The size of dataset provides results that are more generalizable compared to previous inpatient utilization studies focused on smaller sample sizes and fewer study sites. Furthermore, the detailed time and date stamps for medication administration in combination with the substantial number of hospitals represented within the

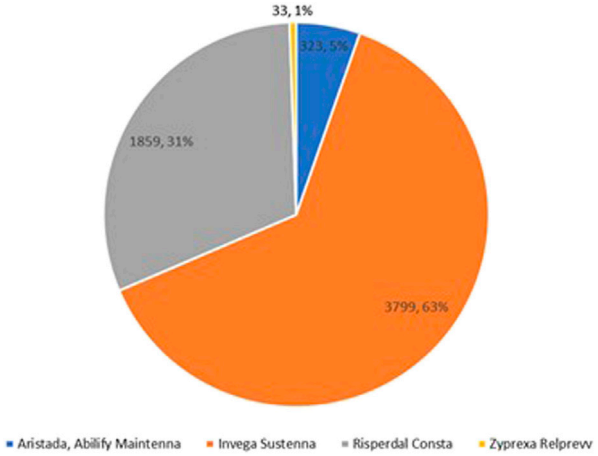

FIGURE 2
Proportion of medications within the subgroup of SGA LAIs 2010–2016 (N = 6,014).

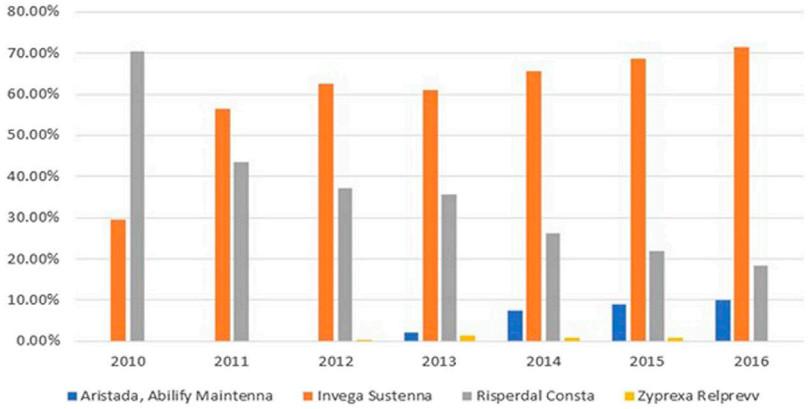

FIGURE 3
Year-specific utilization rates at the admission level for brand-named SGA LAIs.

TABLE 3 Year-specific utilization rates for SGA LAIs (N = 6,014).

SGA LAIs	Overall	2010	2011	2012	2013	2014	2015	2016	*p*-value
	N (col %)	N (col %)	N (col %)	N (col %)	N (col %)	N (col %)	N (col %)	N (col %)	
Aripiprazole	323 (5.4)	0 (0)	0 (0)	0 (0)	21 (2.1)	86 (7.5)	113 (8.9)	103 (10)	<0.0001
Paliperidone palmitate	3799 (63.2)	108 (29.6)	286 (56.5)	451 (62.5)	600 (61.1)	750 (65.5)	869 (68.5)	735 (71.6)	<0.0001
Risperidone	1859 (30.9)	257 (70.4)	220 (43.5)	267 (37)	349 (35.5)	300 (26.2)	277 (21.9)	189 (18.4)	<0.0001
Olanzapine pamoate	33 (0.5)	0 (0)	0 (0)	3 (0.4)	12 (1.2)	9 (0.8)	9 (0.7)	0 (0)	0.003
Total	6,014	365	506	721	982	1,145	1,268	1,027	

HealthFacts® database offers robust "real-world" data to accurately capture physician prescribing patterns across a large representative sample of US hospitals.

Conclusion

Our study reported fifteen inpatient prescribing patterns of APs for schizophrenia, schizoaffective disorder, or bipolar disorder from 2010 to 2016. Compared with their oral/SAI formulations, LAIs were underutilized at the time of acute mental health crisis and acute hospitalizations. In addition, among SGA LAIs, the prescribing patterns of paliperidone palmitate and risperidone changed significantly. Further study is needed to explore the extent to which patient, provider, or organizational factors are associated with FGA or SGA LAI utilization, and in turn, the extent to which higher LAI utilization is associated with lower incidence of emergency room visits or hospitalizations.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Health Facts is a proprietary dataset only available to entities who have a data use agreement established with Cerner.

Author contributions

YL, MP, and SCS contributed to conception and design of the study. SS queried and created original datasets. YL and MP refined and updated final analytic datasets. YL performed the statistical analyses. YL, MP wrote the first draft of the manuscript. SCS wrote sections of the manuscript. YL, MP, and SCS contributed to manuscript revision, read and approved the submitted version.

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Conflict of interest

SCS has served in an advisory board capacity with Alkermes, Inc., Sunovion Pharmaceuticals, and Neurocrine Pharmaceuticals. SCS is on the Speaker's Bureau for Neurocrine Pharmaceuticals and has received honoraria from TEVA Pharmaceuticals.

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.

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Appendix: Classification method of medications

LAI only:

1. First-generation antipsychotic (FGA) LAIs
2. Second-generation antipsychotic (SGA) LAIs
3. Concurrent FGA and SGA LAIs

Oral AP/SAI Formulations only:

4. Oral AP/SAI formulations of FGA LAIs
5. Oral/SAI formulations of SGA LAIs
6. Concurrent oral/SAI formulations of FGA and SGA LAIs

Concurrent use of LAI and oral/SAI equivalents:

7. Oral/SAI formulations of FGA LAIs, and FGA LAIs
8. Oral/SAI formulations of SGA LAIs, and SGA LAIs
9. Oral/SAI formulations of SGA LAI APs, and SGA LAIs
10. Oral/SAI formulations of SGA LAIs, and FGA LAIs
11. Oral/SAI formulations of FGA LAIs, FGA LAIs, and oral/SAI formulations of SGA LAIs
12. Oral/SAI formulations of FGA LAIs, FGA LAIs, and SGA LAI APs
13. Oral/SAI formulations of SGA LAIs, SGA LAIs, and oral/SAI formulations of FGA LAIs
14. Oral/SAI formulations of SGA LAIs, SGA LAIs, and FGA LAIs
15. Oral/SAI formulations of FGA LAIs, oral/SAI formulations of SGA LAIs, FGA LAIs, and SGA LAIs

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Pharmacological interventions for preventing opioid-induced hyperalgesia in adults after opioid-based anesthesia: a systematic review and network meta-analysis

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Background: Opioid-induced hyperalgesia (OIH) is an adverse event of prolonged opioid use that increases pain intensity. The optimal drug to prevent these adverse effects is still unknown. We aimed to conduct a network meta-analysis to compare different pharmacological interventions for preventing the increase in postoperative pain intensity caused by OIH.

Methods: Several databases were searched independently for randomized controlled trials (RCTs) comparing various pharmacological interventions to prevent OIH. The primary outcomes were postoperative pain intensity at rest after 24 h and the incidence of postoperative nausea and vomiting (PONV). Secondary outcomes included pain threshold at 24 h after surgery, total morphine consumption over 24 h, time to first postoperative analgesic requirement, and shivering incidence.

Results: In total, 33 RCTs with 1711 patients were identified. In terms of postoperative pain intensity, amantadine, magnesium sulphate, pregabalin, dexmedetomidine, ibuprofen, flurbiprofen plus dexmedetomidine, parecoxib, parecoxib plus dexmedetomidine, and S (+)-ketamine plus methadone were all associated with milder pain intensity than placebo, with amantadine being the most effective (SUCRA values = 96.2). Regarding PONV incidence, intervention with dexmedetomidine or flurbiprofen plus dexmedetomidine resulted in a lower incidence than placebo, with dexmedetomidine showing the best result (SUCRA values = 90.3).

Conclusion: Amantadine was identified as the best in controlling postoperative pain intensity and non-inferior to placebo in the incidence of PONV. Dexmedetomidine was the only intervention that outperformed placebo in all indicators.

Clinical Trial Registration: https://www.crd.york.ac. uk/prospero/display_record.php?, CRD42021225361.

KEYWORDS

opioid-induced hyperalgesia, pharmacological interventions, general anesthesia, network meta-analysis, postoperative pain, postoperative nausea and vomiting

What is already known about this subject?

OIH is highly prevalent in surgery patients, contributing to various undesirable outcomes, such as more severe postoperative pain, increased opioid demand, and a high incidence of side effects.

In clinical routine, multiple medications with various mechanisms were proven to prevent the increase in postoperative pain caused by OIH. However, the comparative effects of different pharmacological interventions are urgently needed for a better guideline for the individualized anesthesia protocols.

What this study adds

Amantadine, magnesium sulphate, pregabalin, dexmedetomidine, ibuprofen, flurbiprofen plus dexmedetomidine, parecoxib, parecoxib plus dexmedetomidine, and S (+)-ketamine plus methadone all have statistically significantly lower pain intensity than placebo. Amantadine was the most effective compared to placebo but failed to demonstrate superiority in the incidence of PONV.

Dexmedetomidine is not the best option, but it is the most well-balanced choice because it is the only intervention that outperforms placebo in all indicators.

1 Introduction

Opioids are the most commonly used analgesics during the perioperative period as a part of balanced anesthesia. Timely opioid administration during surgery reduces the need for general anesthetics, resulting in faster recovery (Lang et al., 1996), and post-surgery patient-controlled opioid analgesia improves patient comfort and satisfaction (McNicol et al., 2015). However, a state of nociceptive sensitization with reduction in nociceptive thresholds and paradoxical increase in pain after exposure to opioids (Koppert et al., 2003), referred to as opioid-induced hyperalgesia (OIH), have been demonstrated in animal models (Minville et al., 2010), human volunteers (Vinik and Kissin, 1998) and surgical patients (Fletcher and Martinez, 2014). Patients who experience more severe postoperative pain due to nociceptive sensitization may be obliged to accept more opioids unless alternatives are considered (He et al., 2020). Furthermore, opioid-related adverse drug events have been associated with increased inpatient mortality, prolonged stay, and a high cost of hospitalization (Shafi et al., 2018).

Although the precise molecular mechanism underlying OIH is unknown, it is widely assumed to be triggered by neuroplastic changes in the peripheral and central nervous systems (Lee et al., 2011). Previous research has demonstrated that opioids contribute to the occurrence of OIH by inhibiting glutamate recapture and inducing production of pro-inflammatory molecules (Roeckel et al., 2016). The inhibition of the glutamate transporter leads to increased synaptic concentrations of glutamate, which, in turn, activates the N-methyl-D-aspartate (NMDA) receptor, thus triggering OIH (Antal et al., 2008; Arout et al., 2015). Previous electrophysiological studies also identified the rapid and persistent upregulation of NMDA receptor function by clinically relevant concentrations of remifentanil, mirroring the potential target for the pathologic activation of NMDA receptor in the intervention of OIH (Guntz et al., 2005; Zhao and Joo Daisy, 2008). Furthermore, neuroinflammation mediated by opioid-triggered release of pro-inflammatory molecules and the activation of glial cells can sensitize pain pathways, lower pain thresholds, and contribute to the development of OIH (Grace et al., 2015). Additionally, the interactions between mu and delta opioid receptors (Beaudry et al., 2015),α-2 adrenoreceptors (Mercieri et al., 2017), neurokinin-1 receptor mediated transmission (Vera-Portocarrero et al., 2007), and spinal dynorphin expression (Vanderah et al., 2001) also have been reported to play a role in the development and maintenance of OIH.

In light of these findings, clinical investigators mainly focused on manipulating the glutaminergic system through modulation of the NMDA receptor and blocking the neuroinflammation to prevent the occurrence and development of OIH. Various interventions have been explored, including NMDA receptor antagonists (amantadine (Snijdelaar Dirk et al., 2004), magnesium sulphate (Ryu et al., 2008), methadone (Tognoli et al., 2020), and ketamine (Leal et al., 2015)), non-steroidal anti-inflammatory drugs (NSAIDs) (Ibuprofen (Koo et al., 2016), flurbiprofen (Zhang et al., 2016), and parecoxib (Du et al., 2019)), opioid receptor antagonist (naloxone (Du et al., 2019)), agonist-antagonist opioid analgesics (nalbuphine (Hu et al., 2020) and buprenorphine (Mercieri et al., 2017)) and α-2 adrenoceptor agonist (dexmedetomidine (Wu et al., 2021)). These interventions, with different mechanisms of action, have been shown the potential in reduce pain intensity and the need for postoperative analgesics due to OIH. Regretfully, clinical routines are still debatable about the optimal intervention strategy to prevent the increase in postoperative pain intensity caused by OIH due to small sample sizes and varying medication dosages in existing literature (Wu et al., 2015). Importantly, the relative effects of different types of medications remain unknown.

Given these uncertainties, we conducted a systematic review and network meta-analysis of various pharmacological interventions to prevent the increase in postoperative pain intensity caused by OIH in adults following general anesthesia, hoping better to guide clinical practice for more individualized general anesthesia protocols.

2 Methods

This network meta-analysis was registered on https://www.crd.york.ac.uk/PROSPERO. The registration number is CRD42021225361.

2.1 Search strategy and selection criteria

According to PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses (Hutton et al., 2015), MEDLINE, Embase, The Cochrane Central Register of Controlled Trials, and Web of Science were searched in English with language restrictions. The search strategy combined free text words and medical subject heading (MeSH) terms to maximize the results. The following keywords were used in the search: 1) opioid, 2) hyperalgesia, and 3) magnesium, naloxone, buprenorphine,

ketamine, dexmedetomidine, butorphanol, propofol, flurbiprofen, morphine, methadone, lornoxicam, nitrous oxide, parecoxib, clonidine, amantadine, nalbuphine, paracetamol, pregabalin, nefopam, acetazolamide.

2.2 Selection of studies and data extraction

Two investigators (WJX and HFC) reviewed all titles, abstracts, and full texts sequentially. Finally, eligible trials were identified, and data on eligibility, quality, and outcomes were independently retrieved. Disagreements between the two reviewers on eligibility were resolved through mutual discussion. A third reviewer (YCL) was requested for the final decision when needed. Relevant data were extracted from eligible literature using a standard extraction formula and cross-checked.

Retrieved data included: 1) first author, year of publication, study location, study design, sample size, gender, age, American Society of Anesthesiologists (ASA) status, types of surgery, premedication, anesthesia maintenance, intervention description, control description, dose of opioid, postoperative analgesic strategies, and 2) pain intensity in the form of the various pain scores during the 0 to 24 postoperative hours, pain threshold or normalized area of hyperalgesia during the 0 to 48 postoperative hours, cumulative morphine consumption at 24 h after surgery, time to first rescue analgesic, and incidence of postoperative opioid-related side-effects, such as postoperative nausea and vomiting (PONV), shivering, dizziness and hypotension. Dichotomous data were extracted as the number of patients (%). Continuous data were extracted in the form of mean ± standard deviation (SD).

We tried to contact the author via e-mail twice when the target data in the article were incomplete, but no responses were received. Range and median estimation (Grace et al., 2015) were used to convert the data when the standard deviation was missing.

2.3 Type of outcome measures

Our primary outcomes were postoperative pain intensity at rest after 24 h and the incidence of PONV. Postoperative pain intensity was measured using pain scores scaling from 0 (no pain) to 10 (worst possible pain). Intensity scores reported on a visual analogue scale (VAS: 0: no pain to 100: worst possible pain) were transformed to a 0–10 scale. PONV, the most common adverse event, contributes to the highly distressing experience and severe patient dissatisfaction (Myles et al., 2000; Eberhart et al., 2002), with an incidence as high as 80% in high-risk cohorts (Apfel Christian et al., 1999).

Secondary outcomes include pain thresholds at 24 h after surgery, cumulative morphine consumption over the 24 h period, time to first postoperative analgesic requirement, and shivering incidence.

2.4 Assessment of risk of bias

Two investigators (WJX and HFC) read the eligible articles independently. They assessed their methodological validity using the Cochrane Collaboration's tool of Review Manager software (RevMan version 5.4, Cochrane Community, London, England) for evaluating the risk of bias in randomized controlled trials (RCTs), and disagreements were resolved through discussion (Higgins et al., 2011). The tool includes seven items that describe random sequence generation, allocation concealment, participants and personnel blinding, outcome assessment, blinding, incomplete outcome data, selective reporting, and other biases. Each item was assigned a risk of material bias judgment of high, low, or unclear.

2.5 Statistical analysis

For dichotomous outcomes, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated, as were standardized mean differences (SMDs) or mean differences (MDs) with 95% CIs for continuous outcomes.

This network meta-analysis was performed within a frequentist framework using the STATA 16.0 (StataCorp, Texas, United States) command 'mvmeta' (White, 2011). First, a network geometry plot for each outcome was created, which provided a visual and concise description of the relationship between pairs of interventions (Chaimani et al., 2013). Second, the node-splitting method and loop inconsistency mode were used to assess the statistical consistency. p-value ≥0.05 or 95% CI for each closed-loop containing 0 means direct and indirect comparisons were considered consistent (van Valkenhoef et al., 2016). Third, a comparison-adjusted funnel plot was used to assess publication bias. A symmetrical graph indicated that publication bias had a low influence, whereas an asymmetric graph indicated possible publication bias. Finally, the forest plot was used to report the results of the mixed comparison of interventions and placebo, and the league table was used to illustrate all head-to-head comparisons. We assumed that 95% of CIs that did not contain 0 were statistically significant for SMDs or MDs, and those that did not have 1 were statistically significant for ORs. The two-dimensional graph is prepared to visualize comprehensive drug for placebo comparisons. The point in the lower-left portion of the coordinate system that does not intersect with the dark grey dashed line indicates that this pharmacological intervention outperforms the placebo regarding postoperative pain intensity and PONV incidence. Furthermore, the ranking probabilities of all interventions at each possible intervention rank were estimated (Chaimani et al., 2013). The treatment hierarchy was summarized and reported as the surface under the cumulative ranking curve (SUCRA) (Chaimani et al., 2013) the ranking probabilities. The higher the SUCRA value, the higher the rank of the treatment outcomes.

2.6 Inclusion and exclusion criteria

RCTs that met the following criteria were considered eligible: 1) anesthesia was induced and maintained with opioids; 2) pharmacological interventions were administered to patients at any dose before or during the operative period; and 3) pharmacological interventions were compared to the placebo.

Articles were excluded based on the following criteria: 1) combination with regional nerve block during the anesthesia

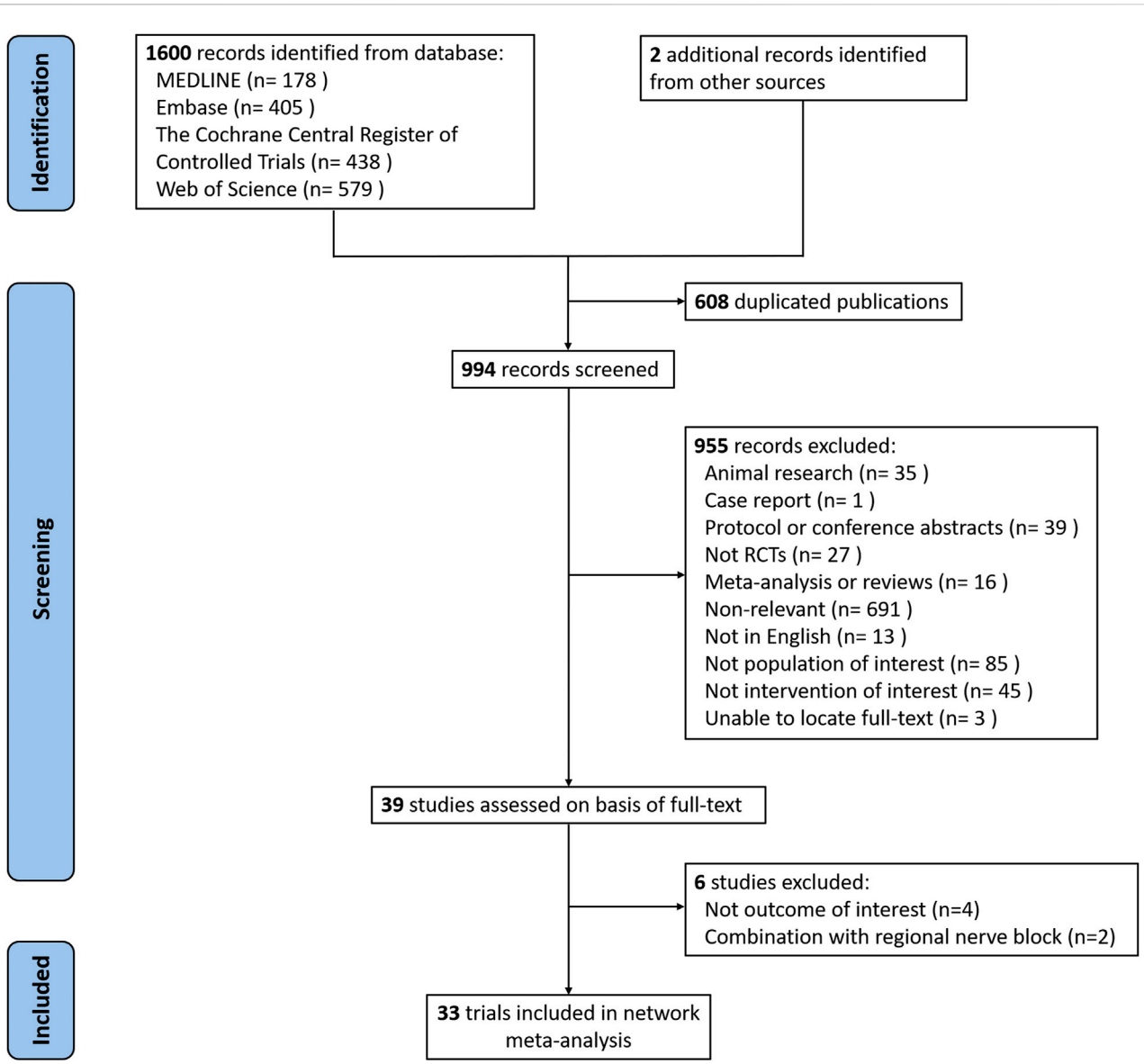

FIGURE 1
Flow chart of search strategy to identify the eligible randomized controlled trials (RCTs).

induction or maintenance period, and 2) data from healthy volunteer or pediatric studies, abstracts, letters, or reviews.

3 Results

3.1 Study selection and characteristics

We identified 1,602 potentially relevant studies in total. After adjusting for duplicates and reviewing the title/abstract, the remaining 39 full-text manuscripts were reviewed. Following the study protocol, six trials were excluded due to a lack of outcome of interest (n = 4) and a combination with a regional nerve block (n = 2). In total, 33 RCTs with a total of 1711 patients were identified. Figure 1 depicts the process of literature selection.

A total of 960 subjects were randomly assigned to pharmacological intervention and 751 to placebo. The included RCTs were published between 2002 and 2020 and included orthopedic (n = 2), urinary (n = 4), abdominal (n = 10), gynecologic (n = 9), thyroid surgery (n = 5), thoracic (n = 1) and ear-nose-throat surgery (n = 2). Table 1 describes the basic characteristics of the enrolled studies.

3.2 Risk of bias assessment

Supplementary Appendix S2 contains the details for the risk of bias assessment. The random sequence generation was specified in 24 trials (72.7%). Although 18 trials (54.5%) reported allocation concealment, one trial had a high risk of bias. Only one trial did not

TABLE 1 Characteristics of studies.

Study (author/ year)	Country	Sample Size (intervention/ control)	Gender (M/F)	Mean Age	ASA Status (I/II/III)	Intervention	Type of Surgery	Does of Opioid
W. Jaksch 2002	Austria	15/15	15/15	31.5	NA	S (+)-ketamine 0.5 mg/kg IV + 2.0 μg/kg· min continuous infusion	Arthroscopic anterior cruciate ligament repair	Remifentanil 0.125–1.0 μg/kg· min
B. Guignard 2002	France	25/25	14/16	62.5	9/35/7	Ketamine 0.15 mg/kg IV + 2.0 μg/kg· min continuous infusion	Open colorectal surgery	Remifentanil 0.25 μg/kg· min
A. Sahin 2004	Turkey	17/16	16/17	47.4	NA	Ketamine 0.5 mg/kg IV	Lumbar disk operation	Remifentanil 0.1 μg/kg· min
A. C. Van Elstraete 2004	France	20/20	20/20	29.0	NA	Ketamine 0.5 mg/kg IV + 2.0 μg/kg· min continuous infusion	Elective electrodissection tonsillectomy	Remifentanil 0.125–1.0 μg/kg· min
D. G. Snijdelaar 2004	Canada	11/10	21/0	60.0	8/12/1	Amantadine 200 mg orally at night and at 1 h before surgery and 100 mg at 8, 20, and 32 h after surgery	Radical prostatectomy	NA
V. Joly 2005	France	24/25	18/32	57.5	21/22/7	Ketamine 0.5 mg/kg IV + 5.0 μg/kg· min continuous infusion +2.0 μg/kg· min for 48 h after surgery	Abdominal surgery	Remifentanil 0.4 μg/kg· min
J. H. Ryu 2008	Korea	25/25	0/50	42.4	37/13/0	Magnesium sulphate 50 mg/kg IV + 15 mg/kg· h continuous infusion	Total abdominal hysterectomy	Remifentanil TCI 4 ng/mL
S. Kaya 2009	Turkey	20/20	NA	50.0	NA	Magnesium sulphate 30 mg/kg IV + 500 mg/h continuous infusion	Elective abdominal hysterectomy	Remifentanil 0.25 μg/kg· min
H. R. Jo 2011	Korea	20/20	0/40	46.1	34/6/0	Pregabalin 150 mg orally	Non-malignant total abdominal hysterectomy	Remifentanil TCI 3–4 ng/mL
C. Lee 2011	Korea	25/25	50/0	63.4	NA	Magnesium sulfate 80 mg/kg IV	Robot-assisted laparoscopic prostatectomy	Remifentanil 0.3 μg/kg· min
C. Lee 2011	Korea	30/30	38/22	38.2	NA	Adenosine 80 μg/kg· min continuous infusion	Tonsillectomy	Remifentanil 0.1 μg/kg· min
J. W. Song 2011	Korea	28/28	11/45	46.0	NA	Magnesium sulphate 30 mg/kg IV + 10 mg/kg· h continuous infusion	Thyroidectomy	Remifentanil 0.2 μg/kg· min
H. Bornemann-Cimenti 2012	Germany	13/13	11/15	56.9	NA	Pregabalin 300 mg orally	Elective transperitoneal nephrectomy	Remifentanil 0.1–0.5 μg/kg· min
C. Lee 2013	Korea	28/29	0/57	48.7	NA	Dexmedetomidine 1.0 μg/kg IV + 0.7 μg/kg· h continuous infusion	Laparoscopically assisted vaginal hysterectomy	Remifentanil 0.3 μg/kg· min
C. Lee 2013	Korea	31/29	31/29	50.7	NA	Pregabalin 300 mg orally	Laparoendoscopic single-site urologic surgery	Remifentanil 0.3 μg/kg· min
S. Treskatsch 2014	Germany	16/17	8/25	66.0	NA	Amantadine 200 mg/ 500 mL solution	Intra-abdominal surgery	Remifentanil 0.2 μg/kg· min

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TABLE 1 (*Continued*) Characteristics of studies.

Study (author/ year)	Country	Sample Size (intervention/ control)	Gender (M/F)	Mean Age	ASA Status (I/II/III)	Intervention	Type of Surgery	Does of Opioid
E. Choi 2015	Korea	25/25	0/50	44.1	NA	Ketamine 0.5 mg/kg IV + 5.0 μg/kg· min continuous infusion	Elective laparoscopic gynecological surgery	Remifentanil 0.3 μg/kg· min
P. C. Leal 2015	Brazil	28/28	9/47	44.6	28/28/0	Ketamine 5.0 μg/kg· min continuous infusion	Laparoscopic cholecystectomy	Remifentanil 0.4 μg/kg· min
H. Bornemann-Cimenti 2016	Austria	37/19	31/25	60.5	4/24/28	S (+)-ketamine 0.25 mg/kg IV + 0.125 mg/kg· h continuous infusion or S (+)-ketamine 0.015 mg/kg· h continuous infusion	Elective major abdominal surgery	Remifentanil 0.1–0.3 μg/kg· min
M. Kong 2016	China	25/25	32/18	51.5	NA	Butorphanol 0.2 μg/kg IV + 0.02 μg/kg· min continuous infusion	Laparoscopic cholecystectomy	Remifentanil 0.3 μg/kg· min
C.-H. Koo 2016	Korea	27/26	33/20	63.7	NA	Ibuprofen 800 mg IV over 30 min	Pancreaticoduodenectomy	Remifentanil TCI 4 ng/mL
Z. Yu 2016	China	57/29	0/86	46.1	NA	Dexmedetomidine 0.5 μg/kg IV + 0.6 μg/kg h continuous infusion or flurbiprofen 1.5 mg/kg combination with dexmedetomidine infusion	Laparoscopic assisted vaginal hysterectomy	Remifentanil 0.3 μg/kg· min
L. Zhang 2016	China	56/28	0/84	46.0	67/ NA/NA	Butorphanol 20 μg/kg IV or butorphanol 20 μg/kg combined with flurbiprofen 0.5 mg/kg	Elective laparoscopicgynaecological surgery	Remifentanil 0.3 μg/kg· min
C. H. Koo 2017	Korea	30/31	20/41	47.0	50/11/0	Naloxone 0.05 μg/kg· min continuous infusion	Thyroid surgery	Remifentanil TCI 4 ng/mL
M. Mercieri 2017	Italy	31/32	34/29	64.5	6/42/15	Buprenorphine 25 μg/h continuous infusion	Lateral thoracotomy	Remifentanil TCI 5 ng/mL
L. Zhang 2017	China	28/28	0/56	44.8	45/11/0	Flurbiprofen 1.0 mg/kg IV	Elective laparoscopic gynecologic surgery	Remifentanil 0.3 μg/kg· min
H. Qiu 2018	China	32/16	24/24	NA	NA	Dexmedetomidine 0.2 μg/kg IV or 0.6 μg/kg	Thyroidectomy	Remifentanil 0.2 μg/kg· min
B. Sng 2018	Singapore	45/44	0/89	48.1	NA	S (+)-ketamine 0.25 mg/kg IV	Open abdominal hysterectomy	NA
X. Du 2019	China	60/20	NA	NA	NA	Parecoxib 40 mg IV or dexmedetomidine 0.6 μg/kg· h continuous infusion or both	Laparoscopic cholecystectomy	NA
R. Gutiérrez 2019	Chile	23/24	4/43	44.5	18/29/0	ACTZ 250 mg IV	Total thyroidectomy without neck dissection	Remifentanil TCI 4.5 ± 0.5 ng/mL
J. Hu 2020	China	24/24	11/37	50.2	24/24/0	Nalbuphine 0.2 mg/kg IV	Laparoscopic cholecystectomy	Remifentanil 0.4 μg/kg· min

(Continued on following page)

TABLE 1 (*Continued*) **Characteristics of studies.**

Study (author/ year)	Country	Sample Size (intervention/ control)	Gender (M/F)	Mean Age	ASA Status (I/II/III)	Intervention	Type of Surgery	Does of Opioid
E. Tognoli 2020	Italy	24/24	29/19	58.6	19/24/5	S (+)-ketamine 5.0, 2.5 and 2 μg/kg· min continuous infusion + methadone 2.0 mg IV	Open laparotomy for anterior resection of the rectum	Remifentanil TCI 5–7 ng/mL
Z. Wu 2020	China	60/29	28/61	40.0	74/15/0	Dexmedetomidine 0.2 μg/kg continuous infusion or 0.5 μg/kg	Thyroidectomy	Remifentanil 0.3 μg/kg· min

use blinding methods. Eight trials (24.2%) had selective reporting. No trials were found to be at high risk of bias due to incomplete outcome data and other bias. Overall, the included studies were of relatively high quality.

3.3 Network geometry of eligible comparisons

The network geometry plot (Figure 2) represents the network of eligible comparisons for postoperative pain intensity at rest at 24 h (A) and the incidence of PONV (B). The postoperative pain intensity at rest at 24 h after surgery was reported in 28 studies involving 20 treatments, and the incidence of PONV was reported in 27 studies involving 17 treatments. There was at least one placebo-controlled trial for each treatment. When a direct comparison was performed, each treatment was represented by a node and linked by an edge. More sample sizes indicate a bigger node, while more studies demonstrate a thicker edge.

3.4 Results of primary outcomes

The forest plot (Figure 3) displays the network meta-analysis results for the primary outcomes. In terms of postoperative pain intensity, amantadine, magnesium sulphate, pregabalin, dexmedetomidine, ibuprofen, flurbiprofen plus dexmedetomidine, parecoxib, parecoxib plus dexmedetomidine and S (+)-ketamine plus methadone were all associated with milder pain intensity than placebo, with SMDs ranging between −3.06 (95% CI: −4.67, −1.45) for amantadine and −0.62 (95% CI: −1.23, −0.01) for magnesium sulphate. Regarding the PONV incidence, intervention with dexmedetomidine (OR = 0.25, 95% CI: 0.11, 0.54) or flurbiprofen plus dexmedetomidine (OR = 0.27, 95% CI: 0.08, 0.87) results in a lower incidence of PONV than placebo.

The league table (Figure 4) illustrates head-to-head comparisons of all pharmacological intervention strategies and placebo for postoperative pain intensity (lower left portion) and PONV incidence (upper right portion). The results of pairwise comparisons are expressed as SMD (95% CI) and OR (95% CI), respectively. The two-dimensional graph (Figure 5) reveals that only dexmedetomidine and flurbiprofen plus dexmedetomidine outperform placebo in terms of postoperative pain intensity and PONV incidence.

In the ranking probability plot (Supplementary Appendix S4, Figure 4), amantadine appeared to be the best agent for postoperative pain intensity among all 20 treatments with a SUCRA value of 96.2. In terms of PONV incidence, it was determined that dexmedetomidine appeared to be the best option among all 17 PONV treatments, with a SUCRA value of 90.3.

3.5 Results of secondary outcomes

3.5.1 Pain threshold at 24 h after surgery

Ten studies involving 11 interventions reported pain thresholds 24 h after surgery (measured by QST and in g) (Supplementary Appendix S4 and Supplementary Figure 4.1.1). Butorphanol (SMD = 2.43, 95% CI: 1.65, 3.22), magnesium sulphate (SMD = 1.01, 95% CI: 0.14, 1.88) and dexmedetomidine (SMD = 1.01, 95% CI: 0.14, 1.88) have higher pain thresholds than placebo at 24 h after surgery (Supplementary Appendix S4 and Supplementary Figure 4.1.2). The league table (Supplementary Appendix S4 and Supplementary Figure 4.1.3) illustrates the comparison of each intervention to one another. Flurbiprofen plus dexmedetomidine was ranked first in the ranking probability plot (Supplementary Appendix S4 and Supplementary Figure 4.1.4) among 11 interventions with a SUCRA value of 98.1.

3.5.2 Cumulative morphine consumption over the 24 h

A total of 14 studies with 11 interventions reported cumulative morphine consumption over a 24 h period (Supplementary Appendix S4 and Supplementary Figure 4.2.1). Flurbiprofen (SMD = −17.36, 95% CI: −22.13, −12.59) and dexmedetomidine (SMD = −11.83, 95% CI: −17.77, −5.90) caused more morphine consumption at 24 h after surgery than placebo (Supplementary Appendix S4 and Supplementary Figure 4.2.2). The league table (Supplementary Appendix S4 and Supplementary Figure 4.2.3) compares the outcomes of each intervention to one another. Flurbiprofen plus dexmedetomidine was ranked first in the ranking probability plot (Supplementary Appendix S4 and Supplementary Figure 4.2.4) among 11 interventions with a SUCRA value of 100.

3.5.3 The time to first postoperative analgesic requirement

The time to the first postoperative analgesic requirement was reported in 14 studies involving 13 interventions

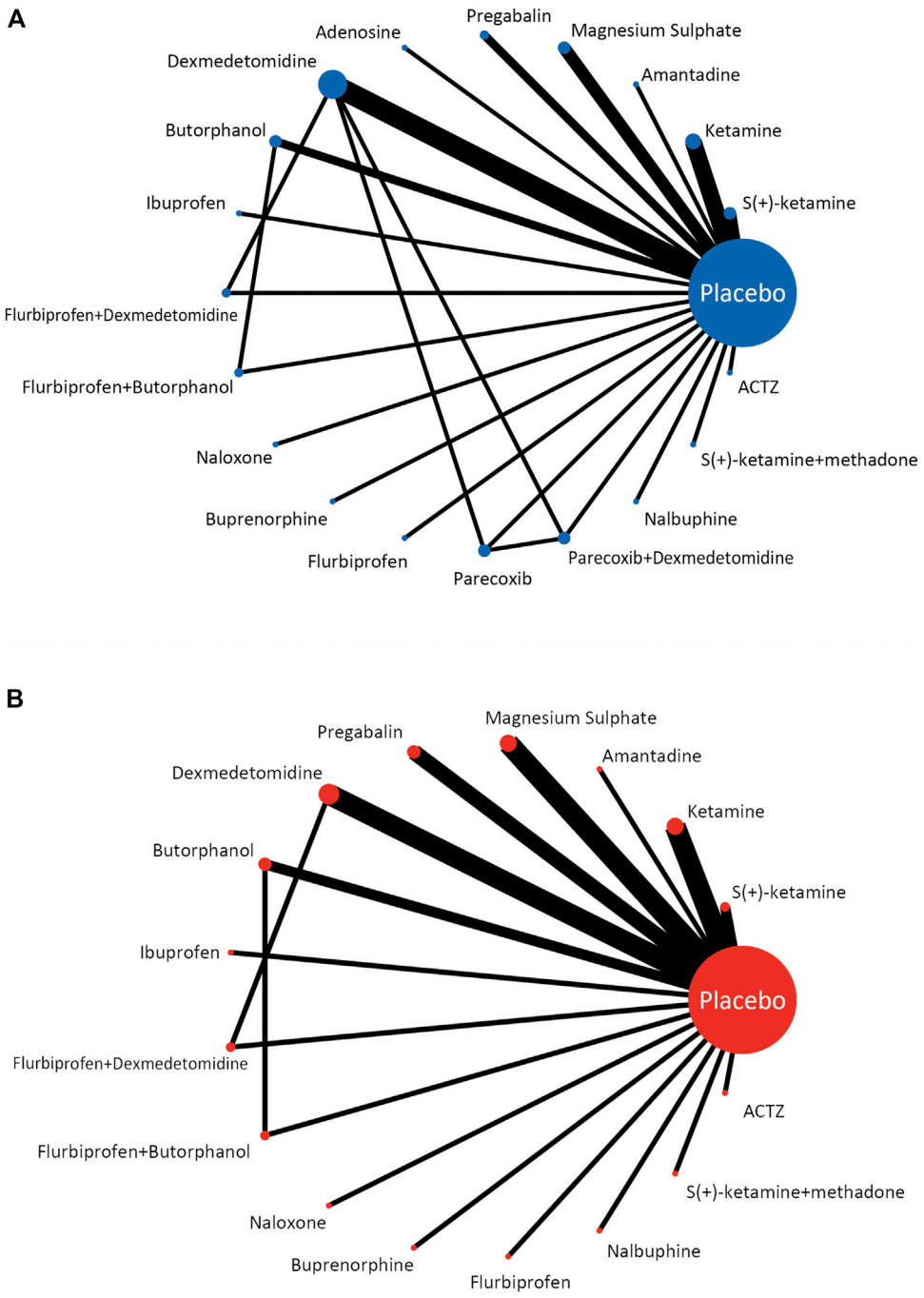

FIGURE 2
Network meta-analysis of eligible comparisons for postoperative pain intensity at rest at 24 h **(A)** and the incidence of PONV **(B)**.

(Supplementary Appendix S4 and Supplementary Figure 4.3.1). When compared with placebo, flurbiprofen plus dexmedetomidine (MD = 43.05, 95% CI: 28.49, 57.60), adenosine (MD = 26.90, 95% CI: 11.98, 41.82), magnesium sulphate (MD = 23.29, 95% CI: 12.27, 34.30) and dexmedetomidine (MD = 11.39, 95% CI: 0.93, 21.84) have a longer time to require first postoperative analgesic (Supplementary Appendix S5 and Supplementary Figure 5.3.2). The league table (Supplementary Appendix S4 and Supplementary Figure 4.3.3) compares the outcome of each intervention to one another. Flurbiprofen plus dexmedetomidine was ranked first in the ranking probability plot (Supplementary Appendix S4 and Supplementary Figure 4.3.4) among 13 interventions with SUCRA value of 98.5.

3.5.4 Incidence of shivering

Nine studies involving nine interventions reported the incidence of shivering (Supplementary Appendix S4 and Supplementary Figure 4.4.1). Dexmedetomidine (OR = 0.16, 95% CI: 0.06, 0.43),

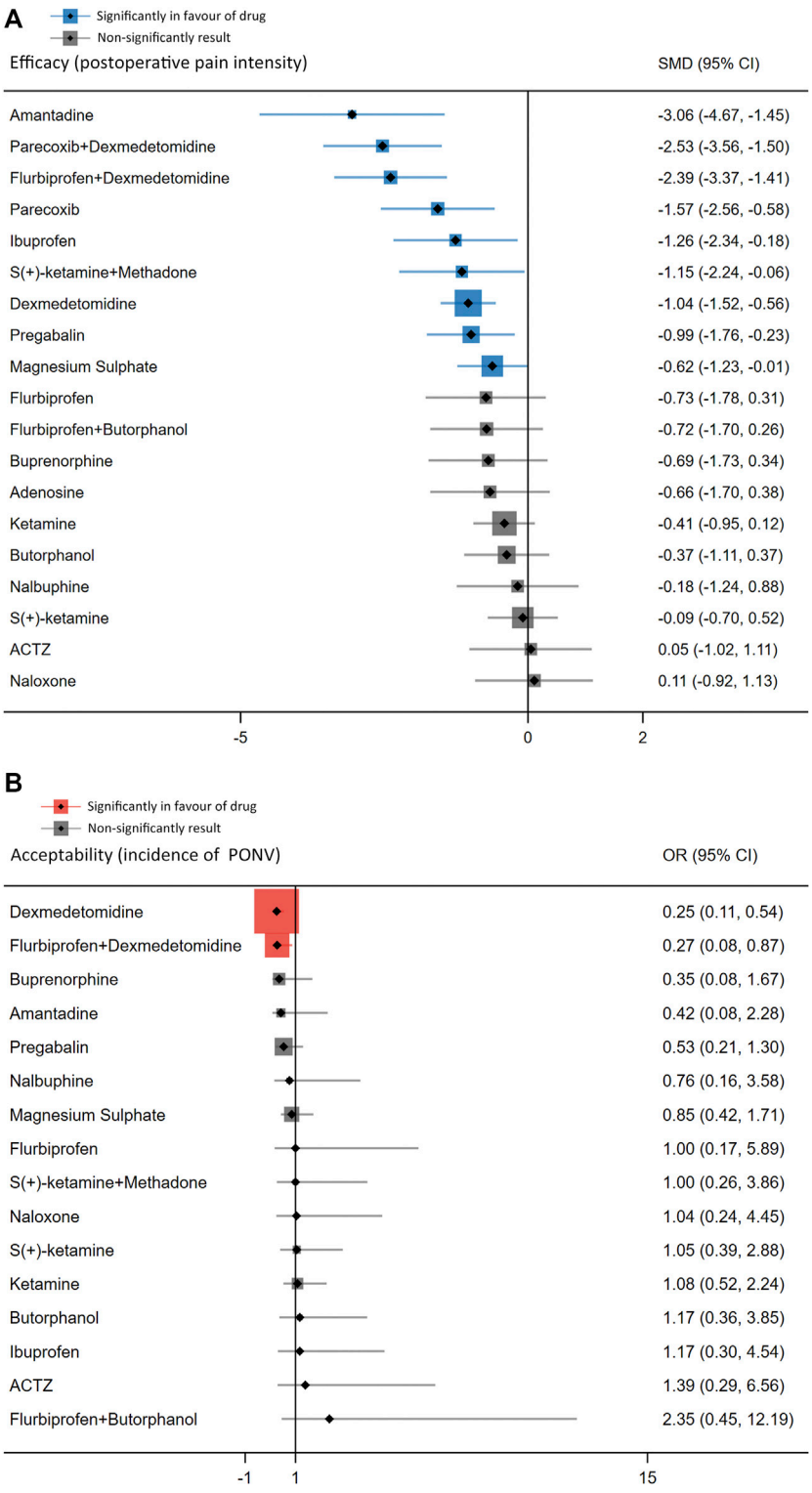

FIGURE 3
Forest plots of network meta-analysis of all trials for postoperative pain intensity at rest at 24 h **(A)** and the incidence of PONV **(B)**.

flurbiprofen plus dexmedetomidine (OR = 0.12, 95% CI: 0.03, 0.49), magnesium sulphate (OR = 0.07, 95% CI: 0.02, 0.36) and S (+) -ketamine (OR = 0.05, 95% CI: 0.00, 0.99) have a lower incidence of shivering than placebo (Supplementary Appendix S4 and Supplementary Figure 4.4.2). The league table (Supplementary Appendix S4 and Supplementary Figure 4.4.3) compares the

Acceptability (incidence of PONV)
Comparison
Efficacy (postoperative pain intensity)

SKET	0.97 (0.28,3.37)	2.49 (0.35,17.72)	1.25 (0.35,4.37)	2.00 (0.51,7.83)	—	4.29 (1.18,15.56)	0.90 (0.19,4.24)	0.90 (0.17,4.90)	3.90 (0.83,18.33)	0.45 (0.07,3.09)	1.01 (0.17,5.93)	2.97 (0.47,18.82)	1.05 (0.14,8.09)	—	—	1.39 (0.22,8.78)	1.05 (0.20,5.68)	0.76 (0.12,4.82)	1.05 (0.39,2.88)
0.32 (-0.49,1.13)	KET	2.56 (0.41,16.03)	1.28 (0.47,3.51)	2.06 (0.64,6.56)	—	4.40 (1.50,12.88)	0.92 (0.23,3.72)	0.93 (0.20,4.33)	4.01 (1.01,15.86)	0.46 (0.08,2.79)	1.04 (0.20,5.28)	3.05 (0.55,16.87)	1.08 (0.16,7.35)	—	—	1.42 (0.26,7.87)	1.08 (0.23,5.02)	0.78 (0.14,4.32)	1.08 (0.52,2.24)
2.97 (1.25,4.69)	2.65 (0.95,4.34)	AMA	0.50 (0.08,3.10)	0.80 (0.12,5.45)	—	1.72 (0.27,11.08)	0.36 (0.05,2.84)	0.36 (0.04,3.16)	1.57 (0.20,12.18)	0.18 (0.02,1.90)	0.41 (0.04,3.77)	1.19 (0.12,11.76)	0.42 (0.04,4.89)	—	—	0.56 (0.06,5.49)	0.42 (0.05,3.67)	0.30 (0.03,3.01)	0.42 (0.08,2.28)
0.53 (-0.33,1.39)	0.21 (-0.60,1.02)	-2.44 (-4.16,-0.72)	MAG	1.61 (0.51,5.04)	—	3.44 (1.20,9.88)	0.72 (0.18,2.88)	0.73 (0.16,3.35)	3.14 (0.80,12.23)	0.36 (0.06,2.16)	0.81 (0.16,4.09)	2.39 (0.44,13.06)	0.85 (0.13,5.70)	—	—	1.11 (0.20,6.10)	0.85 (0.18,3.88)	0.61 (0.11,3.35)	0.85 (0.42,1.71)
0.90 (-0.08,1.88)	0.58 (-0.35,1.52)	-2.06 (-3.84,-0.28)	0.37 (-0.61,1.35)	PRE	—	2.14 (0.65,7.11)	0.45 (0.10,2.00)	0.45 (0.09,2.31)	1.95 (0.45,8.53)	0.22 (0.03,1.47)	0.51 (0.09,2.80)	1.48 (0.25,8.91)	0.53 (0.07,3.85)	—	—	0.69 (0.12,4.16)	0.53 (0.10,2.67)	0.38 (0.06,2.28)	0.53 (0.21,1.30)
0.57 (-0.64,1.77)	0.25 (-0.92,1.41)	-2.40 (-4.31,-0.49)	0.04 (-1.17,1.24)	-0.34 (-1.63,0.95)	ADE	—	—	—	—	—	—	—	—	—	—	—	—	—	—
0.95 (0.17,1.72)	0.62 (-0.09,1.34)	-2.02 (-3.70,-0.35)	0.42 (-0.36,1.19)	0.04 (-0.86,0.95)	0.38 (-0.76,1.52)	DEX	0.21 (0.05,0.87)	0.21 (0.04,1.01)	0.91 (0.27,3.06)	0.10 (0.02,0.65)	0.24 (0.05,1.24)	0.69 (0.12,3.94)	0.25 (0.04,1.71)	—	—	0.32 (0.06,1.84)	0.25 (0.05,1.18)	0.18 (0.03,1.01)	0.25 (0.11,0.54)
0.28 (-0.69,1.24)	-0.04 (-0.96,0.87)	-2.69 (-4.46,-0.92)	-0.25 (-1.21,0.71)	-0.63 (-1.69,0.44)	-0.29 (-1.57,0.99)	-0.67 (-1.55,0.21)	BUT	1.00 (0.17,6.12)	4.34 (0.82,23.00)	0.50 (0.10,2.60)	1.13 (0.17,7.37)	3.30 (0.47,23.28)	1.17 (0.14,9.91)	—	—	1.54 (0.22,10.87)	1.17 (0.19,7.09)	0.84 (0.12,5.96)	1.17 (0.36,3.85)
1.17 (-0.07,2.41)	0.85 (-0.35,2.05)	-1.80 (-3.73,0.13)	0.64 (-0.60,1.88)	0.27 (-1.06,1.59)	0.60 (-0.89,2.10)	0.22 (-0.95,1.40)	0.89 (-0.42,2.20)	IBU	4.32 (0.72,25.95)	0.50 (0.06,4.21)	1.12 (0.15,8.21)	3.29 (0.42,25.82)	1.17 (0.12,10.90)	—	—	1.54 (0.20,12.05)	1.17 (0.17,7.93)	0.84 (0.11,6.61)	1.17 (0.30,4.54)
2.30 (1.15,3.45)	1.98 (0.86,3.09)	-0.67 (-2.55,1.21)	1.77 (0.62,2.92)	1.40 (0.15,2.64)	1.73 (0.31,3.16)	1.35 (0.39,2.32)	2.02 (0.80,3.25)	1.13 (-0.32,2.58)	FLU+DEX	0.12 (0.02,0.87)	0.26 (0.04,1.67)	0.76 (0.11,5.29)	0.27 (0.03,2.25)	—	—	0.36 (0.05,2.47)	0.27 (0.05,1.61)	0.19 (0.03,1.36)	0.27 (0.08,0.87)
0.63 (-0.53,1.78)	0.31 (-0.81,1.42)	-2.34 (-4.22,-0.46)	0.10 (-1.05,1.25)	-0.27 (-1.52,0.97)	0.06 (-1.36,1.49)	-0.32 (-1.41,0.77)	0.35 (-0.62,1.33)	-0.54 (-1.99,0.92)	-1.67 (-3.05,-0.29)	FLU+BUT	2.26 (0.25,20.30)	6.61 (0.69,63.44)	2.35 (0.21,26.39)	—	—	3.09 (0.32,29.61)	2.35 (0.28,19.75)	1.69 (0.18,16.25)	2.35 (0.45,12.19)
-0.20 (-1.39,1.00)	-0.52 (-1.68,0.64)	-3.17 (-5.07,-1.26)	-0.73 (-1.92,0.47)	-1.10 (-2.38,0.18)	-0.76 (-2.23,0.70)	-1.14 (-2.28,-0.01)	-0.47 (-1.74,0.79)	-1.37 (-2.85,0.12)	-2.50 (-3.92,-1.08)	-0.83 (-2.25,0.59)	NALO	2.93 (0.35,24.52)	1.04 (0.11,10.30)	—	—	1.37 (0.16,11.45)	1.04 (0.14,7.57)	0.75 (0.09,6.28)	1.04 (0.24,4.45)
0.60 (-0.60,1.80)	0.28 (-0.88,1.44)	-2.36 (-4.27,-0.46)	0.07 (-1.13,1.27)	-0.30 (-1.59,0.99)	0.04 (-1.43,1.50)	-0.34 (-1.48,0.80)	0.33 (-0.94,1.60)	-0.57 (-2.06,0.93)	-1.70 (-3.12,-0.27)	-0.03 (-1.45,1.40)	0.80 (-0.66,2.26)	BUP	0.35 (0.03,3.73)	—	—	0.47 (0.05,4.17)	0.35 (0.05,2.77)	0.26 (0.03,2.29)	0.35 (0.08,1.67)
0.64 (-0.57,1.86)	0.32 (-0.86,1.50)	-2.32 (-4.24,-0.41)	0.11 (-1.10,1.33)	-0.26 (-1.56,1.04)	0.08 (-1.40,1.55)	-0.30 (-1.45,0.85)	0.37 (-0.92,1.65)	-0.53 (-2.03,0.98)	-1.66 (-3.09,-0.22)	0.01 (-1.42,1.45)	0.84 (-0.63,2.31)	0.04 (-1.43,1.51)	FLU	—	—	1.32 (0.12,13.86)	1.00 (0.11,9.29)	0.72 (0.07,7.60)	1.00 (0.17,5.89)
1.48 (0.31,2.65)	1.16 (0.03,2.29)	-1.49 (-3.38,0.40)	0.95 (-0.21,2.12)	0.58 (-0.68,1.83)	0.91 (-0.52,2.35)	0.53 (-0.45,1.52)	1.20 (-0.04,2.44)	0.31 (-1.15,1.78)	-0.82 (-2.16,0.52)	0.85 (-0.54,2.25)	1.68 (0.25,3.11)	0.88 (-0.55,2.31)	0.84 (-0.61,2.28)	PAR	—	—	—	—	—
2.44 (1.24,3.64)	2.12 (0.95,3.28)	-0.53 (-2.44,1.38)	1.91 (0.71,3.11)	1.53 (0.25,2.82)	1.87 (0.41,3.34)	1.49 (0.47,2.51)	2.16 (0.89,3.43)	1.27 (-0.22,2.76)	0.14 (-1.23,1.51)	1.81 (0.39,3.23)	2.64 (1.18,4.09)	1.83 (0.37,3.29)	1.79 (0.32,3.27)	0.96 (-0.14,2.06)	PAR+DEX	—	—	—	—
0.09 (-1.14,1.31)	-0.23 (-1.42,0.96)	-2.88 (-4.80,-0.95)	-0.44 (-1.67,0.78)	-0.81 (-2.12,0.50)	-0.48 (-1.96,1.01)	-0.86 (-2.02,0.31)	-0.19 (-1.48,1.11)	-1.08 (-2.59,0.43)	-2.21 (-3.65,-0.77)	-0.54 (-1.98,0.90)	0.29 (-1.19,1.77)	-0.51 (-1.99,0.97)	-0.55 (-2.05,0.94)	-1.39 (-2.84,0.06)	-2.35 (-3.83,-0.87)	NALB	0.76 (0.10,5.93)	0.55 (0.06,4.90)	0.76 (0.16,3.58)
1.06 (-0.19,2.30)	0.74 (-0.48,1.95)	-1.91 (-3.85,0.03)	0.53 (-0.72,1.77)	0.15 (-1.18,1.48)	0.49 (-1.01,1.99)	0.11 (-1.08,1.30)	0.78 (-0.54,2.10)	-0.11 (-1.64,1.42)	-1.24 (-2.70,0.22)	0.43 (-1.04,1.89)	1.25 (-0.24,2.75)	0.45 (-1.05,1.95)	0.41 (-1.10,1.92)	-0.42 (-1.90,1.05)	-1.38 (-2.88,0.12)	0.97 (-0.55,2.49)	SKET+MET	0.72 (0.09,5.64)	1.00 (0.26,3.86)
-0.14 (-1.36,1.09)	-0.46 (-1.65,0.73)	-3.10 (-5.03,-1.18)	-0.67 (-1.89,0.56)	-1.04 (-2.35,0.27)	-0.70 (-2.19,0.78)	-1.08 (-2.25,0.09)	-0.41 (-1.71,0.88)	-1.31 (-2.82,0.21)	-2.44 (-3.88,-0.99)	-0.77 (-2.21,0.68)	0.06 (-1.42,1.54)	-0.74 (-2.22,0.74)	-0.78 (-2.27,0.71)	-1.62 (-3.07,-0.16)	-2.57 (-4.06,-1.09)	-0.23 (-1.73,1.28)	-1.19 (-2.72,0.33)	ACTZ	1.39 (0.29,6.56)
-0.09 (-0.70,0.52)	-0.41 (-0.95,0.12)	-3.06 (-4.67,-1.45)	-0.62 (-1.23,-0.01)	-0.99 (-1.76,-0.23)	-0.66 (-1.70,0.38)	-1.04 (-1.52,-0.56)	-0.37 (-1.11,0.37)	-1.26 (-2.34,-0.18)	-2.39 (-3.37,-1.41)	-0.72 (-1.70,0.26)	0.11 (-0.92,1.13)	-0.69 (-1.73,0.34)	-0.73 (-1.78,0.31)	-1.57 (-2.56,-0.58)	-2.53 (-3.56,-1.50)	-0.18 (-1.24,0.88)	-1.15 (-2.24,-0.06)	0.05 (-1.02,1.11)	PLA

FIGURE 4
League table of head-to-head comparisons for postoperative pain intensity at rest at 24 h and the incidence of PONV of all pharmacological interventions and placebo. PLA = placebo. SKET = S (+)-ketamine. KET = ketamine. AMA = amantadine. MAG = magnesium sulphate. PRE = pregabalin. ADE = adenosine. DEX = dexmedetomidine. BUT = butorphanol. IBU = ibuprofen. FLU + DEX = flurbiprofen + dexmedetomidine. FLU + BUT = flurbiprofen + butorphanol. NALO = naloxone. BUP = buprenorphine. FLU = flurbiprofen. PAR = parecoxib. PAR + DEX = parecoxib + dexmedetomidine. NALB = nalbuphine. SKET + MET = S (+)-ketamine + methadone.

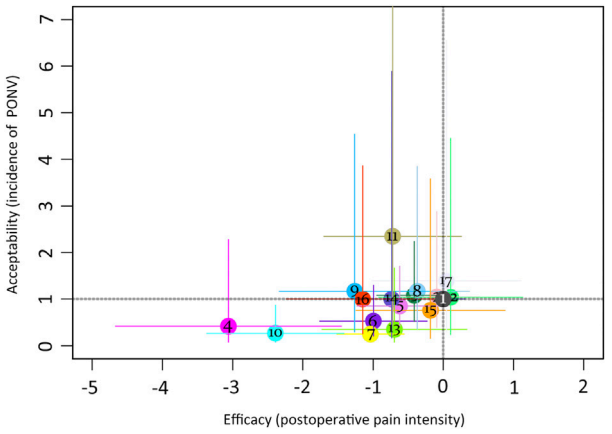

FIGURE 5
Two-dimensional graphs for postoperative pain intensity at rest at 24 h and the incidence of PONV. 1 = placebo; 2 = S (+)-ketamine; 3 = ketamine; 4 = amantadine; 5 = magnesium sulphate; 6 = pregabalin; 7 = dexmedetomidine; 8 = butorphanol; 9 = ibuprofen; 10 = flurbiprofen + dexmedetomidine; 11 = flurbiprofen + butorphanol; 12 = naloxone; 13 = buprenorphine; 14 = flurbiprofen; 15 = nalbuphine; 16 = S (+)-ketamine + methadone; 17 = ACTZ.

outcomes of each intervention to one another. S (+) -ketamine was ranked highest in the ranking probability plot (Supplementary Appendix S4 and Supplementary Figure 4.4.4) among nine interventions with SUCRA value of 82.0.

4 Discussion

Because of the morbidity concealment, complex pathogenesis, and treatment uncertainty of OIH, the best strategy is to avoid it. This is the first systematic review and network meta-analysis to compare various pharmacological interventions and investigate the best strategy for preventing the increase in postoperative pain caused by OIH in adults following general anesthesia. The following aspects of the 20 treatments were compared and analyzed: pain intensity, opioid-related adverse effects, pain threshold, time first to rescue analgesia, and morphine consumption. We identified that no such perfect drug performs best in all indicators. This emphasizes the significance of individualized treatment selection and a multimodal approach.

Our findings reveal that amantadine, magnesium sulphate, pregabalin, dexmedetomidine, ibuprofen, flurbiprofen plus dexmedetomidine, parecoxib, parecoxib plus dexmedetomidine and S (+)-ketamine plus methadone all have the potential to prevent the increase in postoperative pain intensity, with amantadine appearing to be the best option among the 20 interventions studies. Although the mechanisms underlying OIH are not fully understood. Preclinical models implicate the glutaminergic system and pathological NMDA receptor activation in the development of central sensitization (Mao et al., 1994; Mao et al., 2002; Zhao et al., 2012). Amantadine, magnesium sulphate, methadone, and S (+)-ketamine are known to be the NMDA receptor's antagonists, where its primary effects are thought to

occur. Wu L et al. found that perioperative administration of NMDA receptor antagonists effectively reduced postoperative pain intensity and morphine consumption (Wu et al., 2015), without evident psychological effects. However, our findings suggest that amantadine may be the best option when either ketamine or S (+)-ketamine fails to show significant superiority in preventing the rise of postoperative pain intensity. A possible explanation for this discrepancy is that Wu L et al.'s conclusion requires extraordinary caution in interpretation due to high heterogeneity even after subgroup analysis. The studies involved were small (only 14 studies included 3 drugs which directly act on NMDA receptors), with possible overestimation of the risk of Type II statistical error. However, the effect of an intervention may be influenced to varying degrees by other factors in NMDA. Therefore, we suggest that future studies should consider confirming the findings of our meta-analysis.

Ibuprofen, flurbiprofen, and parecoxib are NSAIDs that have potent anti-inflammatory, analgesic, and antipyretic activities and are used globally. One of their primary mechanisms of action is the inhibition of cyclo-oxygenase (COX), an enzyme involved in the biosynthesis of prostaglandins and thromboxane (Bacchi et al., 2012). Prostaglandins have been demonstrated to modulate nociceptive processing (Baba et al., 2001) and stimulate the release of the excitatory amino acid glutamate in the dorsal horns of the spinal cord (O'Rielly Darren and Loomis Christopher, 2006). Moreover, COX constitutively expressed in the spinal cord and is activated in response to peripheral stimuli that cause pain, primarily through the involvement of NMDA and substance P signaling (Yaksh and Malmberg, 1993). As such, NSAIDs have been demonstrated to inhibit the heightened sensitivity to pain triggered by the activation of spinal NMDA and substance P receptors (Malmberg and Yaksh, 1992; Yaksh and Malmberg, 1993). Clinical studies or meta-analyses about the effect of COX inhibitors on OIH are still lacking, even though it has been proved in animal models (Li et al., 2018; Peng et al., 2019) and human volunteers (Koppert et al., 2004; Lenz et al., 2011).

It has been indicated that opioid-induced pronociceptive effects are caused by central and peripheral nervous system sensitization, similar to the mechanism of hyperalgesia associated with nerve injury (Mao et al., 1995). Pregabalin is a 3-substituted analogue of γ-aminobutyric acid used to treat neuropathic pain (Guay, 2005) with the side effects of dizziness and drowsiness. It has a similar structure and mechanism of action to gabapentin but has fewer side effects (Ben-Menachem, 2004). Pregabalin binds strongly to the α2δ-1 subunit of voltage-gated calcium channels. This binding impairs channel trafficking and reduces the release of various neurotransmitters, including glutamate, noradrenaline, and substance P (Bannister et al., 2011). These effects result in interactions with spino-bulbo-spinal loop-comprising projection neurons in the superficial dorsal horn and brainstem, leading to facilitation of 5-hydroxytryptamine3 receptor-mediated effects in pain modulation. It has been indicated that pregabalin reduce hyperalgesia and allodynia in human volunteers (Chizh et al., 2007) and rat models (Field et al., 1999). However, A J Lederer et al. reviewed the effects of pregabalin on OIH and concluded that, despite strong support by theoretical considerations, the recommendation as a clinical use still lacks clinical evidence (Lederer et al., 2011). Stoicia et al. reached a similar conclusion, stating that applying gabapentin in mitigating OIH still requires support from large-scale standardized patient studies (Stoicea et al., 2015).

Dexmedetomidine is a potent and highly selective α-2 adrenoceptor agonist with sympatholytic, sedative, amnestic, and analgesic properties (Khan et al., 1999). Its anti-hyperalgesia effects are closely associated with NMDA receptors. Animal studies reveal that dexmedetomidine modulates spinal cord NMDA receptor activation by suppressing tyrosine phosphorylation of NR2B in the superficial spinal cord, which was found to be upregulated during remifentanil-induced hyperalgesia (Zheng et al., 2012). Furthermore, another study has provided evidence supporting the prevention of OIH by dexmedetomidine through the regulation of spinal NMDA receptors, as well as the levels of protein kinase C (PKC) and calcium/calmodulin-dependent protein kinase II (CaMKII), both of which are involved in neuronal signaling (Yuan et al., 2017). Similarly, its anti-hyperalgesia effect in clinical practice requires further investigation.

The findings of the present meta-analysis also revealed that dexmedetomidine and flurbiprofen plus dexmedetomidine are interventions associated with a lower PONV incidence compared to placebo. It is worth noting that flurbiprofen alone has no superior effect. This appears to imply that dexmedetomidine plays a significant role in preventing PONV, consistent with previous studies (Le Bot et al., 2015; Jin et al., 2017; Grape et al., 2019). Jin S et al. (Jin et al., 2017) investigated the effect of dexmedetomidine on PONV in patients undergoing general anesthesia. They identified that dexmedetomidine (irrespective of administration mode) had a significantly lower incidence of PONV than placebo. It was thought that this additional antiemetic effect of α2 agonists might be explained by inhibiting catecholamines by parasympathetic tone, even though the biological basis remains unknown. Alternatively, dexmedetomidine may reduce intraoperative anesthetics and opioids, which have been considered risk factors for PONV (Gan et al., 2020).

The treatment risk/benefit ratio is an important consideration in clinical decision-making. Our findings revealed that, while there is the best option in every index, dexmedetomidine is the only pharmacological intervention that outperformed placebo in all indicators. In addition, the multifaceted benefit of dexmedetomidine in improving the quality of emergence from anesthesia (Aouad et al., 2019), reducing postoperative delirium incidence (Duan et al., 2018), enhancing recovery after surgery (Kaye et al., 2020) and providing organ-protective effects (Bao and Tang, 2020) has already been fully demonstrated and widely accepted. Despite the side effects of hypotension and bradycardia, it is difficult to deny that dexmedetomidine is an attractive anesthetic adjuvant (Weerink et al., 2017).

This network meta-analysis had several possible limitations. First, because multiple interventions were included in the analysis, several had data from only one study, resulting in a relatively small sample size, which could have led to possible bias and overestimation of the treatment effect. Second, some non-pharmacological interventions, such as gradual withdrawal of remifentanil (Comelon et al., 2016), opioid rotation (Mercadante

and Arcuri, 2005) and combination with a regional nerve block (Rivat et al., 2013), were not included in the comparison. Third, it is important to acknowledge that despite conducting comprehensive literature research prior to designing the retrieval strategy and considering commonly used drugs in clinical anesthesia, there is a possibility that our study may have omitted other drugs that have been investigated for their effects on OIH. Finally, there was variation in gender, opioid dosage, timing, administration regimens, surgery duration, and anesthesia maintenance. These disparities limit the amount of data pooled in a meta-analysis, posing significant challenges in interpreting and applying the results.

Overall, this systematic review and network meta-analysis provides the most comprehensive summary of the comparative effect of various pharmacological interventions on improving the intensity of postoperative pain caused by OIH.

5 Conclusion

In summary, a meta-analysis of eligible RCTs identified that amantadine was the best at preventing an increase in postoperative pain and non-inferior to placebo in the incidence of PONV. In contrast, dexmedetomidine was the only intervention superior to placebo in all indicators.

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.

Author contributions

W-JX and WL proposed and designed the study. Y-CL, J-SH, C-FF, and H-FC provided experimental research. W-JX and Y-CL participated in data analysis. W-JX and J-SH wrote and revised the manuscript. All authors contributed to the article and approved the submitted version.

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.2023.1199794/full#supplementary-material

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The impact of medication belief on adherence to infliximab in patients with Crohn's disease

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Objective: Crohn's disease (CD) is an incurable chronic disease that requires long-term treatment. As an anti-tumor necrosis factor (TNF) agent, Infliximab (IFX) is widely used in the treatment of Crohn's disease, while the adherence is not high. The purpose of this study was to investigate the adherence to IFX among CD patients in China and evaluate the association between medication belief and IFX adherence.

Methods: Demographic data, clinical information and patients' medication beliefs were collected using an online questionnaire and reviewing electronic medical records (EMRs). The Beliefs about Medicines Questionnaire (BMQ)-specific was used to assess medication beliefs which contains the BMQ-specific concern score and the BMQ-specific necessity score. An evaluation of adherence factors was conducted using univariate and multidimensional logistic regression analyses.

Results: In all, 166 CD patients responded the online questionnaire among which 77 (46.39%) patients had high adherence. The BMQ-specific concern score in patients in low adherence was 30.00 and in high adherence patients was 27.50, and patients with lower BMQ-specific concern score had higher adherence (p = 0.013). The multiple regression analysis showed that the BMQ-specific concern score (OR = 0.940, 95% CI: 0.888–0.996) significantly affected the IFX adherence in CD patients. Otherwise, gender, marital status, time spent on the way (including the waiting time in infusion center) and accommodation to the center were also the influencing factors of adherence.

Conclusion: The IFX adherence to CD in China was not high. Medicine concerns may be predictive factor of adherence. Education, the duration of IFX therapy and experience of adverse effects were not significantly associated with IFX adherence. By enhancing knowledge and relieving medicine concerns, we may increase patients' adherence to IFX.

KEYWORDS

adherence, medication belief, Crohn's disease, infliximab, China

Introduction

Crohn's disease (CD) is a type of inflammatory bowel disease (IBD), which primarily affects the digestive system (Loftus, 2004). It is an incurable chronic disease that requires long-term treatment. Anti-inflammatory and immunosuppressive medications have become the standard of treatment for CD (Agrawal et al., 2020). Besides, biological agents have been

widely used in the recent years and have greatly improved the remission rate in CD patients who were refractory to traditional medicine (Mastronardi et al., 2019). Anti-tumor necrosis factor (TNF) agents such as infliximab (IFX) is the most used biological agent, and has diminished hospitalizations and surgeries related to CD significantly (Lichtenstein et al., 2005).

Medication adherence is an important determinant of outcomes in patients with chronic diseases. The definition of adherence to medication is the degree to which a person's behavior of taking medication, following a diet, and/or implementing lifestyle changes corresponds with their healthcare provider's recommendations (Chew et al., 2020). Several reports have shown that 30%–50% of patients with chronic diseases have low medication adherence (Tamura et al., 2020) and a large meta-analysis examining medication adherence in IBD reported variable adherence rates, ranging from 7% to 72% (Jackson et al., 2010). Non-adherence to infliximab treatment increases the risk of treatment failure and developing immunogenicity to anti-TNF agents, which contributes to increasing healthcare cost (Kane and Shaya, 2008; Kane et al., 2009; Van Assche et al., 2010). Study showed that compared with adherent patients, the all-cause medical expenses and CD related medical expenses of non-adherent patients were 81% and 94% higher, respectively (Kane et al., 2009). A systematic review revealed that pooled adherence was 70.7% in infliximab-treated patients in IBD (11). Furthermore, females, smokers, and patients accompanied by psychiatric comorbidities are at increased risk of nonadherence (Fidder et al., 2013; Lopez et al., 2013). However, to our best knowledge, no study on adherence to infliximab among CD patients has been performed in China. A rapid increase in IBD has been observed in China over the past decade. It is expected that 1.5 million people in China will suffer from IBD by 2025 (Kaplan, 2015). IFX is the first anti-tumor necrosis factor agents approved for the treatment of CD patients in China. Therefore, it is necessary to investigate IFX adherence in China.

Among the predictors of medication adherence, the most significant one is medication belief (Mitzel and Vanable, 2020). Medication belief refers to an individual's view of medication., which not only includes the cognitive responses to medication, but also includes the views on the harmfulness of the medication and maintenance therapy. Several studies have reported the significant correlation between medication adherence and medication belief (Horne et al., 2013; Chapman et al., 2014). To date, the study of medication belief has mainly focused on chronic disease, such as high blood pressure (Suarez-Arguello et al., 2022), ischemic stroke (Chen et al., 2019), diabetes (Mohammadi et al., 2018) and so on. A meta-analysis showed that if the patient has a higher belief in the necessity of taking medicine and a lower belief in the concern of harmfulness, the patient will show better adherence (Adem et al., 2021). In recent years, our research teams have focused on the medication adherence in IBD patients, we found medication belief is associated with improved adherence to exclusive enteral nutrition in patients with CD patients (Li et al., 2021). However, adherence to IFX among Chinese CD patients and its association with medication belief remain unclear.

In this study, we assessed adherence to IFX among patients with CD in China and evaluated the relationship between medication belief and IFX adherence.

Methods

Patient population and design

The study was conducted at the Second Affiliated Hospital, Zhejiang University School of Medicine (SAHZU) from November 15 to 28 December 2021. All CD patients treated with infliximab were retrospectively identified in the electronic medical records (EMRs) from the SAHZU Crohn's and Colitis Center. The inclusion criteria were as follows: patients with a confirmed diagnosis of CD; were treated with infliximab for at least 12 weeks; were informed consent. In our study, the infliximab was dissolved in saline and infused by intravenous infusion. IV infusion doses were at least 5 mg/kg. The same dose was given at 2 weeks, 6 weeks and every 8 weeks after the first administration. Infliximab regimen may be adjusted by the IBD specialists if the disease changes during the treatment. Nobody had a history of neurological or psychiatric conditions. As shown in Figure 1, we created an online questionnaire which was evaluated and modified by IBD experts and feedback from IBD patients after filling in. At the same time, healthy people were invited to complete the questionnaire and gave opinions on the readability of the questionnaire. And then we used the WeChat-based Questionnaire Star application generating a Quick Response code (OR code). Patients scanned the code and filled in the questionnaire. In addition, clinical information was gathered by reviewing EMRs and telephone follow-up. A total of 267 patients responded this online questionnaire, out of which 101 (37.83%) respondents had to be excluded: 10 patients had no prior history of infliximab treatment, 81 patients' the medication history of infliximab were less than 1 year 10 patients had more than 50% missing data through EMRs and telephone follow-up were excluded.

Clinical data collection

Three parts of data collection were conducted: Demographic data, clinical information and patients' medication beliefs. These data were considered possible influencing factors on the results regarding non-adherence to infliximab treatment from previous studies (Lopez et al., 2013; van der Have et al., 2016; Govani et al., 2018). All the patients' demographic data, including sex, age, marital status, education level, employment status, monthly income, smoking status and health insurance.

The clinical information was divided into two parts, disease related data and infliximab treatment data. Including disease duration, disease localization (was evaluated by Montreal classification), disease activity (was measured through Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), albumin and fecal calprotectin), family history, surgical history, concomitant therapy and complications. Infliximab treatment data including duration of infliximab, adverse effects and the convenience of medical care, for example, "What is your primary mode of transportation to the infusion center you visit most often? The total time (including waiting time) you spent to the infusion center? How far are you from your most frequent infusion center? What is the total cost of transportation to and from the infusion center you visit most often? If accommodation is required for the visit, what is the total approximate cost of accommodation?"

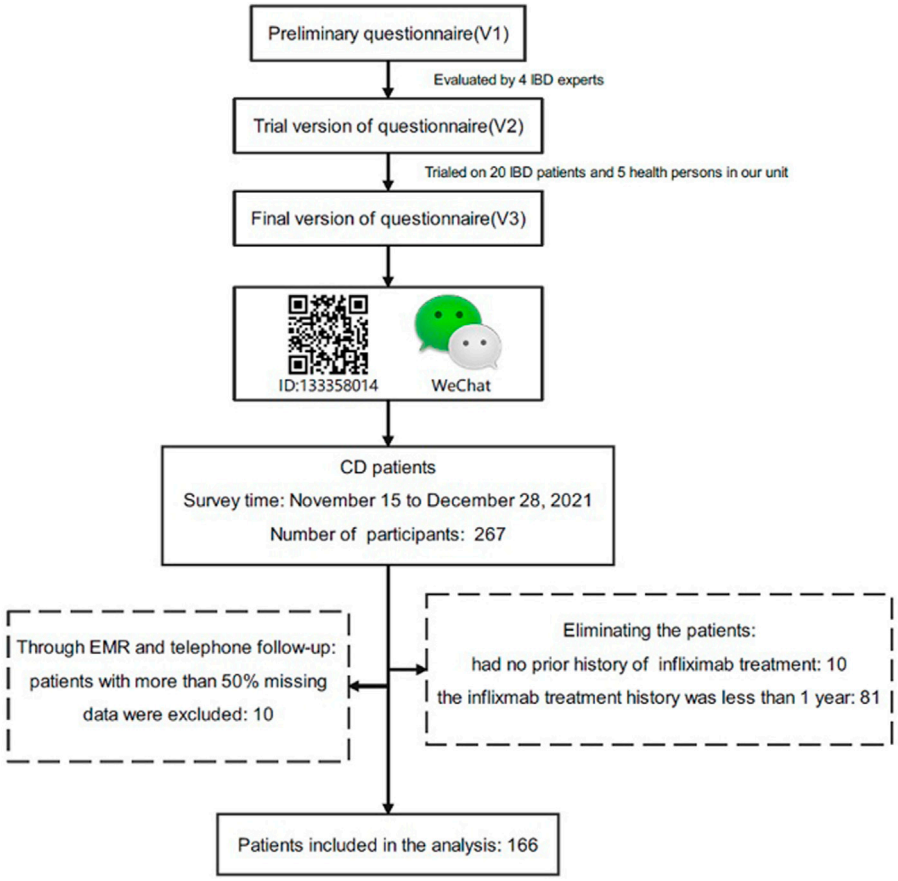

FIGURE 1
Flow chart of the study. The questionnaire was evaluated and modified by IBD experts and was produced by Wenjuanxing. We sent the questionnaire to the WeChat group for patient management and 267 patients responded, out of which 101 respondents were excluded.

The Beliefs about Medicines Questionnaire (BMQ)-specific was used to assess medication beliefs (Horne et al., 1999). It has 10 items, 5 items on medication necessity, and 5 items on medication concern. A 5-point Likert scale was used for each item, ranging from 1 (strongly disagree) to 5 (strongly agree). The questionnaire has a score range of 5–25; higher scores indicate stronger levels of treatment beliefs. A patient's overall belief about infliximab treatment can be derived by subtracting the average 5 item medication concerns scale score from their average 5 item medication necessity scale score, with a range of −20 to 20. Based on median scores, patients were categorized into High-BMQ and Low-BMQ.

Adherence measures

Adherence was judged by comparing the theoretical infusion times with the actual infusion times in recent 1 year, which was referred to the definition of modified medication possession radio (mMPR) (Steiner TDK et al., 1988). Participants who adhered to their treatment plan at 90% or more were considered high adherence; those who adhered at less than 90% were considered low adherence (Ramos et al., 2022). If the infusion time was advanced or delayed for more than 1 week, it was considered as low adherence.

Statistical analysis

All statistical analyses were performed using SPSS software (version 26.0, IBM Corp). Continuous variables were presented as means±standard deviations (SD) or means with interquartile range (IQR), and categorical variables were expressed as percentages. Student's t-test and Chi-square test were used for statistical analysis of the data. Multivariate logistic regression analyses were performed to assess whether the individual variables were related to the adherence to Infliximab. In our analysis, $p < 0.05$ was considered significant. A multiple regression analysis was conducted with the adherence as the dependent variable. Factors with $p < 0.2$ in univariate analysis were included in multivariate analysis (using a forward-LR stepwise regression procedure).

Ethical considerations

This study was reviewed and approved by the medical ethics committee of the Second Affiliated Hospital, Zhejiang University School of Medicine (No. 2021 0901).

TABLE 1 Baseline characteristics of respondents (n = 166).

Characteristics		n (%)
Age[a]	32.00 (25.00,39.00)	
Duration of disease (years)[a]	4.00 (2.00,6.00)	
Gender	Female	51 (30.7)
	Male	115 (69.3)
Marital status	Non-Married	59 (35.5)
	Married	107 (64.5)
Education [b]	Low	53 (31.9)
	Intermediate	91 (54.8)
	High	22 (13.3)
Employment	No	59 (35.5)
	Yes	107 (64.5)
Family income(monthly)	<¥5000	35 (21.1)
	¥5001-¥10000	48 (28.9)
	¥10001-¥20000	49 (29.5)
	>¥20001	34 (20.5)
Smoking	Negative	135 (81.3)
	Active	31 (18.7)
Commercial insurance	No	124 (74.7)
	Yes	42 (25.3)
Montreal Classification	L1 (ileal localization)	63 (37.9)
	L2 (colonic localization)	7 (4.2)
	L3 (ileocolonic localization)	93 (56.0)
	L4a (from mouth to treitz ligament)	13 (7.8)
	L4b (from treitz ligament to distal 1/3 ileum)	65 (39.2)
	B1 (non-stricturing,non-penetrating behavior)	84 (50.6)
	B2 (stricturing behavior)	51 (30.7)
	B3 (penetrating behavior)	31 (18.8)
	p (perineal disease)	84 (50.6)
IBD-related surgery [c]	No	83 (50.0)
	Yes	83 (50.0)
Combined medication	Amino salicylates	35 (21.1)
	Glucocorticoid	2 (1.2)
	Oral immunosuppressants	72 (43.4)
	Enteral nutrition	89 (20.5)
Adverse effects of infliximab [d]	Never	105 (63.3)
	Have suffered or are currently suffering	61 (36.7)
Duration of infliximab[a]	3.00 (2.00,4.00)	
CRP(g/L)[a]	11.93 (0.90–15.63)	

(Continued on following page)

TABLE 1 (*Continued*) **Baseline characteristics of respondents (n = 166).**

Characteristics	n (%)
ESR(mm/h)[a]	14.51 (3.75–21.00)
ALB(g/L)[a]	40.81 (37.76–45.43)
Fecal calprotectin(μg/g)[a]	1,001.03 (280.80–1800.00)

[a]Presented as median(P_{25},P_{75}).
[b]Low level included junior high school education and below, intermediate level included senior high or technical secondary school and college education, and high level included bachelor or graduated education and above.
[c]It was defined as any intestinal or perianal surgical procedure performed for underlying IBD.
[d]Adverse effects of infliximab: such as chest tightness, rash, difficulty breathing, pneumonia, tuberculosis and so on.

Results

Patient inclusion and baseline characteristics

A total of 166 CD patients responded this online questionnaire. Of them, the median age was 32 years old, 115 (69.3%) patients were male, 107 (64.5%) had married; approximately 54.8% of the patients attained intermediate level of education (senior high or technical secondary school and college education); the median duration of disease was 4 years. In terms of adverse effects of infliximab, 61 (36.7%) had suffered or were currently suffering adverse effects (such as chest tightness, rash, difficulty breathing, pneumonia, tuberculosis and so on); The duration of infliximab use was from 2–4 years with a median of 3 years. Other characteristics were listed in Table 1.

Associations between participants' characteristics and adherence to infliximab

Only 77 (46.39%) patients had high adherence, while the other 89 (53.61%) had low adherence. A univariate analysis of clinical and demographic characteristics was conducted to explore the factors associated with adherence to infliximab. Patients with female gender, married status, and experience of adverse effects showed lower adherence. Also, the shorter time patients spent to the infusion ($p < 0.001$) and the lower cost of accommodation to the infusion center ($p = 0.002$), the higher adherence they reported (Table 2).

Influence of medication belief on adherence to infliximab

The BMQ-specific concern score, BMQ-specific necessity score and BMQ-specific score were showed in Table 3. The BMQ-specific concern score in patients with low adherence was higher than high adherence patients (30.00 vs. 27.50, $p = 0.013$). The BMQ-specific score in patients in low adherence was 00.00 and in high adherence patients was 5.00. Patients were divided into the high-BMQ group (BMQ-Specific score >0) and low-BMQ group (BMQ- Specific score ≤0). More patients with a high BMQ score had high adherence to IFX compared to those with a low BMQ score ($p < 0.001$).

The multiple regression analysis showed that the BMQ-specific concern score (OR = 0.940,95%CI:0.888–0.996) significantly affected the IFX adherence in CD patients. Other factors affecting adherence included gender (OR = 0.454,95%CI: 0.210–0.981), marital status (OR = 0.454,95%CI:0.210–0.981), time spent on the way (OR = 0.139,95%CI:0.041–0.474), accommodation to the center (OR = 0.479,95%CI:0.234–0.982). The result was presented in Figure 2.

Discussion

CD is a chronic disease in which required long-term pharmacotherapy and one of the key elements of medication efficacy is adherence. A patient's adherence is measured by his or her ability to follow medical advice, such as taking medications and changing his or her lifestyle. Non-adherence of IBD may lead to treatment failure, increased hospitalization rate and treatment costs. However, the adherence to IFX therapy in Chinese CD patients was rarely reported. In our study we investigated adherence to IFX among CD patients and the factors associated with IFX adherence. We found almost more than half of IFX-treated CD patients were low adherent in China, which was varied crossed studies (Kitney JMT et al., 2009; Carter et al., 2011). For example, Carter et al. (2011) showed that the IFX adherent rate in CD patients was 57.1% (Carter et al., 2011); In pediatric IBD patients, Kitney's study showed that the adherent rate for IFX use was 79.8% (Kitney JMT et al., 2009). Reasons for the differences in adherence could be attributable to differences in the methods of assessing medication adherence. In our study, high adherence was defined as an MPR higher than 90%, which applied a more exacting criterion by defining high adherence higher than 80% Carter et al. (2011). Participant adherence data relied on self-reported which may over-estimate. In addition, there may be differences in these results between countries with different health systems containing social and economic barriers that prevent medication adherence (Hu et al., 2020).

In our study, we found that adherence is influenced by gender, marital status, convenience (such as the total time patient spent to the infusion center every time and the total cost of accommodation to the infusion center every time). Compared to non-married patients, married patients had a higher adherence. There may be a greater level of socioeconomic status in married patients, as well as less emotional burden (Zhao et al., 2019). They could obtain emotional and financial support from their spouses or children (Feng et al., 2020). To ensure adherence and efficacy of treatment, the role of convenience may become even more significant (Centonze et al., 2021). IFX is administered intravenously. In China, patients need go to integrative hospital with a professional

TABLE 2 Predictive Factors for Adherence to infliximab (Univariate Analysis).

Characteristics classification		Low adherence	High adherence	*p*-value
Age		30.00 (25.00,36.50)	33.00 (26.00,42.50)	0.143
Duration of disease		4.00 (2.50,6.00)	4.00 (2.00,6.00)	0.715
Gender	Female	21 (41.2)	30 (58.8)	0.032
	Male	68 (59.1)	47 (40.9)	
Marital status	Non-Married	40 (67.8)	19 (32.2)	0.007
	Married	49 (45.8)	58 (54.2)	
Education [a]	Low	32 (60.4)	21 (39.6)	0.297
	Intermediate	48 (52.7)	43 (47.3)	
	High	9 (40.9)	13 (59.1)	
Employment	No	31 (52.5)	28 (47.5)	0.837
	Yes	58 (54.2)	49 (45.8)	
Family income(monthly)	≤¥10000	43 (51.8)	40 (48.2)	0.641
	>¥10000	46 (55.4)	37 (44.6)	
Smoking	Negative	70 (51.9)	65 (48.1)	0.342
	Active	19 (61.3)	12 (38.7)	
Commercial insurance	No	66 (53.2)	58 (46.8)	0.863
	Yes	23 (54.8)	19 (45.2)	
IBD-related surgery [b]	No	45 (54.2)	38 (45.8)	0.876
	Yes	44 (53.0)	39 (47.0)	
Adverse effects of infliximab [c]	Never	47 (44.8)	58 (55.2)	0.003
	Have suffered or are currently suffering	42 (68.9)	19 (31.1)	
Duration of infliximab		3.00 (2.00,4.00)	3.00 (2.00,4.00)	0.711
The total time patient spent to the infusion center every time				<0.001
Short time spent (<12 h)		64 (46.7)	73 (53.3)	
Long time spent (≥12 h)		25 (86.2)	4 (13.8)	
The distance from home to infusion center				0.372
Short distance (<10 km)		19 (47.5)	21 (52.5)	
Long distance (≥10 km)		70 (55.6)	56 (44.4)	
The total cost of transportation to and from the infusion center every time				0.334
Low transportation costs (<¥500)		84 (52.8)	75 (47.2)	
High transportation costs (≥¥500)		5 (71.4)	2 (28.6)	
The total cost of accommodation to the infusion center every time				0.002
Low accommodation (<¥100)		39 (42.9)	52 (57.1)	
High accommodation (≥¥100)		50 (66.7)	25 (33.3)	

[a]Low level included junior high school education and below, intermediate level included senior high or technical secondary school and college education, and high level included bachelor or graduated education and above.

[b]It was defined as any intestinal or perianal surgical procedure performed for underlying IBD.

[c]Adverse effects of infliximab: such as chest tightness, rash, difficulty breathing, pneumonia, tuberculosis and so on.

infusion department to receive IFX therapy. We found that the longer time the patient spent to the infusion center (including waiting time), the poorer medicine adherence they were, and the same is true for cost of accommodation There was higher adherence in the shorter time spent (<12 h) and lower accommodation cost (<¥100) in our study. One possible explanation was that their

TABLE 3 Influence of medication belief on adherence to infliximab.

Characteristics classification		Low adherence	High adherence	*p*-value
BMQ-specific concern		30.00 (25.00,33.75)	27.50 (20.00,32.50)	0.013
BMQ-specific necessity		32.50 (27.50,37.50)	32.50 (27.50,35.00)	0.723
BMQ-Specific		0.00 (0.00,6.25)	5.00 (0.00,10.00)	0.023
BMQ-Specific	Low-BMQ[a]	61 (71.8%)	24 (28.2%)	<0.001
	High-BMQ[b]	28 (34.6%)	53 (65.4%)	

[a]Low-BMQ: the BMQ-Specific score ≤0 was defined as low-BMQ.
[b]High-BMQ: the BMQ-Specific score>0 was defined as high-BMQ.

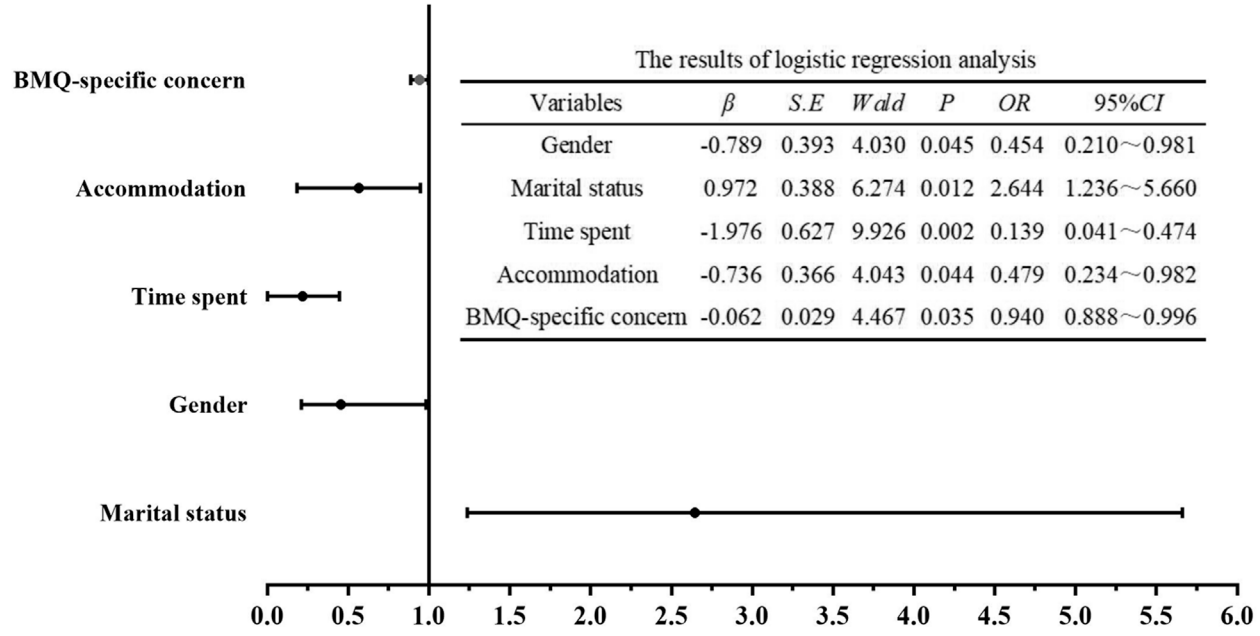

FIGURE 2
Multi-factor logistic regression models for medication adherence in IFX. The multiple regression analysis showed five variables, including BMQ-specific concern score, gender, marital status, time spent on the way and accommodation to the center were the main factors affecting the IFX adherence in CD patients.

treatment process was burdened by the time and cost they had to spend on IFX infusion.

In this study, we found that BMQ-specific concern but not BMQ-specific necessity was significant associated factor for adherence. IFX is a chimeric monoclonal antibody against tumor necrosis factor alpha (TNF-α), and there are side effects associated with IFX treatment. The common side effects of IFX are serious infection, malignancies, infusion-related reaction and so on. Opportunistic infections are a major safety concern in patients with IBD, especially as IFX therapy becomes more widespread (Park et al., 2020). The most common opportunistic infection of IFX therapy is tuberculosis (TB) by destroying the granuloma integrity and increasing the reactivation of latent TB infection (Ford and Peyrin-Biroulet, 2013). Similarly, it can stimulate hepatitis B virus (HBV) resulting viral reactivation (Li et al., 2017b). In China, the prevalence of smear-positive tuberculosis, which approximates 59/100,000, is one of the highest in the world (Li et al., 2017a). And also infection with HBV is most prevalent in China (Dai et al., 2019). Therefore, the patient's concern is truly a major clinical problem. We can improve adherence by relieving patients' medication concerns. Clinicians should adequately explain to the patients the side effects of IFX, especially about opportunistic infections. There must be a balance between therapy and adverse effects. Screening the latent TB and HBV infection before and during IFX therapy for latent TB and HBV infection can ensure the safety of medications. Nurse can also play a critical role in helping patients to understand and take medication properly by bridging the gap between them and their practitioners (Jamison et al., 2017). They could help patients to improve their knowledge about IBD and understand the mode of action of IFX, and thus to improve the self-management abilities, self-health-promoting behaviors, and medical adherence. In addition, in order to ensure the safety of patients during medication administration, it is crucial to set up or update guidelines, to create a conducive

environment, and to trained nurses on how to administer medications safely.

To our knowledge, this is the first study exploring the influence of medication belief on adherence to IFX in CD patients in China, and analyzing the adherence-influencing factors. Our findings reflected significant impacts of medicine concerns on IFX therapy adherence. There are also a few limitations in this study. Firstly, the study recruited patients from a single tertiary medical center, which may have led to selection bias. Secondly, our study only investigated the samples from CD patients, nevertheless, definitive studies should be conducted in patients with ulcerative colitis. Thirdly, previous studies have found psychosocial factors would affect adherence, such as anxiety and depression (Dolovich et al., 2021). In our study, these factors were not considered.

Conclusion

In conclusion, the IFX adherence in Chinese CD patients was calling for improvement. Gender, marital status, convenience, medicine concerns may be predictive factors of adherence. Enhancing knowledge and relieving medicine concerns in CD patients may increase the treatment adherence on IFX.

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 the medical ethics committee of the Second Affiliated Hospital, Zhejiang University School of Medicine (No. 2021 0901). 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

SL: data curation and software. SH and ZN: investigation. ML and CY: methodology and supervision. SL and YM: writing–original draft. ML and HS: writing–review and editing. All authors contributed to the article and approved the submitted version.

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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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