frontiers | Research Topics

Systematic reviews of pharmacological and non-pharmacological psychiatric interventions

Edited by
Joe Kossowsky and Mirko Manchia

Published in
Frontiers in Psychiatry

ISSN 1664-8714
ISBN 978-2-8325-2376-6
DOI 10.3389/978-2-8325-2376-6

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Systematic reviews of pharmacological and non-pharmacological psychiatric interventions

Topic editors

Joe Kossowsky — Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, Harvard Medical School, United States

Mirko Manchia — University of Cagliari, Italy

Citation

Kossowsky, J., Manchia, M., eds. (2023). *Systematic reviews of pharmacological and non-pharmacological psychiatric interventions*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-2376-6

Table of contents

frontiers | Frontiers in Psychiatry

TYPE Editorial
PUBLISHED 25 April 2023
DOI 10.3389/fpsyt.2023.1201888

OPEN ACCESS

EDITED AND REVIEWED BY
Wulf Rössler,
Charité University Medicine Berlin, Germany

*CORRESPONDENCE
Mirko Manchia
✉ mirko.manchia@unica.it
Joe Kossowsky
✉ joe.kossowsky@childrens.harvard.edu

RECEIVED 07 April 2023
ACCEPTED 10 April 2023
PUBLISHED 25 April 2023

CITATION
Manchia M and Kossowsky J (2023) Editorial: Systematic reviews of pharmacological and non-pharmacological psychiatric interventions. *Front. Psychiatry* 14:1201888. doi: 10.3389/fpsyt.2023.1201888

Editorial: Systematic reviews of pharmacological and non-pharmacological psychiatric interventions

Mirko Manchia[1,2,3]* and Joe Kossowsky[4,5]*

[1]Section of Psychiatry, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy, [2]Unit of Clinical Psychiatry, University Hospital Agency of Cagliari, Cagliari, Italy, [3]Department of Pharmacology, Dalhousie University, Halifax, NS, Canada, [4]Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA, United States, [5]Department of Anaesthesia, Harvard Medical School, Boston, MA, United States

KEYWORDS

meta-analysis, data synthesis, clinical trials, intervention, severe mental disorders, biostatistics

Editorial on the Research Topic
Systematic reviews of pharmacological and non-pharmacological psychiatric interventions

Systematic reviews aim to search, appraise, and synthesize all relevant empirical evidence related to a specific research question in an unbiased and well-documented fashion. Ideally, they provide readers with a complete interpretation of research results and enable them to critically appraise the literature (1). Given the fast pace of medical research, systematic reviews are becoming increasingly important in providing clear, comprehensive, and reproducible overviews of available evidence and identifying research gaps in the field. Psychiatry has not been an exception in this regard, particularly considering the relatively high rates of patients experiencing inadequate response to treatments (2). Indeed, suboptimal or non-response can manifest during pharmacological as well as non-pharmacological treatments. In this regard, it is of interest that the first conceptualization of the term resistance was developed in the context of psychoanalysis (3). Diverse strategies, such as for instance augmentation, combination therapies, and intensive clinical monitoring can influence substantially treatment outcomes. Thus, qualitative and quantitative data synthesis might guide treatment decision making and effective personalized management of patients affected by mental disorders. In this context, the goal of our Research Topic was to assemble systematic reviews (and when appropriate, meta-analyses) of Pharmacological and Non-Pharmacological Interventions for psychiatric disorders and/or in psychiatric and special populations. The results of these systematic reviews and meta-analyses offered insights on diverse interventions stemming from complementary and alternative medicine to neurocognitive training and behavioral approaches, and from biological treatments to physical exercise. In addition, several relevant outcomes were the object of the studies collected in this Research Topic, including drug adverse effects, violent behavior, agitation, depression, and neurocognitive impairment.

Concerning complementary and alternative treatments, in a systematic review and meta-analysis of 30 RCTS including over 5,000 patients, Rao et al. investigated the efficacy and safety of Traditional Chinese herbal medicine compared to Western Medicine in treating antipsychotic-related constipation. Results indicated that Traditional Chinese herbal medicine was associated with significantly better moderate and marked response rates, as well as remission rates, as compared to Western Medicine. In addition, the adverse effect of rash was significantly less frequent in Traditional Chinese herbal medicine than in Western Medicine. Although authors noted that more high-quality studies are necessary for generalizing findings, results still highlight the safety and efficacy of Traditional Chinese herbal medicine as a treatment for antipsychotic-related constipation in clinical practice. Furthermore, in a systematic review and meta-analysis of 25 studies and 2,213 women, Zhao et al. examined the efficacy of acupuncture for the treatment of perimenopausal depression. Specifically, this study investigated the efficacy of acupuncture independently, and in conjunction with standard care (i.e., antidepressant/hormone replacement therapy), as compared to waitlist control or placebo/sham acupuncture (Zhao et al.). Primary findings suggested that acupuncture outperformed standard care in reducing depressive symptoms, though when used in conjunction with standard care, acupuncture as an adjuvant treatment was more effective in reducing depressive symptoms as compared to either acupuncture alone or standard care alone. The comparative efficacy between acupuncture and placebo/sham acupuncture, however, could not be determined due to a lack of RCTs on this Research Topic. Still, findings indicate the clinical utility of acupuncture as an independent and adjuvant treatment alongside standard care for perimenopausal depression.

Another set of articles examined the efficacy of non-pharmacological interventions in disruptive behaviors such as aggression and violence, neurocognitive impairment and eating disorders. Slamanig et al. conducted a systematic review of 10 non-pharmacological interventions aimed at reducing risk of violence in individuals with schizophrenia spectrum disorders (SSD) in forensic psychiatry settings. These interventions included neurocognitive training, cognitive-behavioral treatment programs, and other interventions, such as an integrative treatment program, among others (Slamanig et al.). Results revealed significant methodological limitations across included studies including small sample sizes, lack of randomization, and lack of control group comparisons; results also indicated no clear trends of effectiveness for such interventions. As such, the authors did not set forth any firm conclusions about the efficacy of non-pharmacological interventions, emphasizing, instead, the need for sufficiently powered RCTs with more reliable operationalizations of "violence" and diagnostic specificity of SSD individuals. Moreover, Stuchlíková and Klírová conducted a mini-review investigating the effects transcranial direct current stimulation (tDCS), which is a non-invasive, low-current neurostimulation method, on the positive, negative, and cognitive symptoms of schizophrenia. This review included 27 randomized controlled parallel-group design studies with 966 patients, and studies were grouped according to their focus on either positive (10 studies), negative (five studies), or cognitive (12 studies) symptoms of schizophrenia. In general, results revealed that tDCS demonstrated efficacy in each symptom domain (Stuchlíková and Klírová). More specifically, six of 10 studies assessing positive symptoms showed improved outcomes, all studies assessing negative symptoms showed improved outcomes, and eight or 12 studies assessing cognitive outcomes showed improved outcomes. Notably, tDCS also emerged as a well-tolerated and safe method of intervention in reviewed studies. The authors concluded that tDCS has clinical promise for addressing wide-ranging symptomatology of schizophrenia. In a systematic review of individuals in forensic settings with acquired brain injuries (ABI), de Geus et al. investigated the efficacy of non-pharmacological interventions, particularly those aimed at supporting the cognitive, emotional, and behavioral changes associated with ABI. In sum, four studies were examined in this review, including two case design studies and two single group experimental designs, with a total of 86 individuals included across the four studies. Results identified the relative efficacy for non-pharmacological interventions for individuals with ABI, including improvements in cognitive functioning, increases in productivity, and decreases in aggression and recidivism (de Geus et al.). Generalized conclusions about non-pharmacological interventions for ABI from this review, however, are tempered by the lack of methodologically rigorous studies conducted thus far on this Research Topic. Finally, Toutain et al. conducted a systematic review of 27 studies aimed at investigating the efficacy of exercise therapy (ET) for individuals with anorexia nervosa in inpatient and outpatient settings. This review examined specifically the effects of four types of ET, including aerobic exercise, resistance exercise, mind-body physical exercise, and combined physical exercise, on anorexia nervosa symptomatology, physical health outcomes, and mental health outcomes. Overall, results indicated that ET had significant, positive effects on outcomes of interest, though specific associations varied by type of ET. That is, results revealed that aerobic and resistance exercise was associated with increased muscle strength and that mind-body physical exercise was associated with improved eating disorder and mental health symptoms. ET that combined different physical exercises was associated with increased weight gain and reduced dysfunctional exercise. Taken together, these studies suggest that ET may be an effective intervention for improved functioning in individuals with anorexia nervosa (Toutain et al.). Authors emphasize, however, that conclusions should be interpreted with caution due to the lack of well-designed RCTs as well as the insufficient details provided about ET interventions, thus limiting reproducibility of findings.

Another two reviews examined the efficacy of pharmacological treatments in substance intoxication and agitation. In their systematic review of 11 RCTs, Amore et al. examined the use of lorazepam for acute agitation in adult patients with mental or behavioral disorders. Overall, findings suggested that lorazepam is an effective treatment of agitation, though some more nuanced results emerged. Specifically, in five studies, the combination of haloperidol and lorazepam was more effective than either medication alone, though lorazepam was not significantly more effective than haloperidol, individually. In another study, olanzapine was more effective than lorazepam. In general, the most frequent side effects that emerged alongside lorazepam treatment were dizziness, sedation, and somnolence, suggesting its relative

safety for clinical use. Moreover, in a review and analysis of 51 case reports, Ordak et al. investigated pharmacotherapy responses for patients presenting with effects of new psychoactive substances. Results revealed that most patients had ingestion of synthetic cathinones or cannabinoids. In terms of pharmacotherapy, most patients (62.7%) were administered benzodiazepines in response to the effects of taking new psychoactive substances, and these were primarily prescribed to reduce patient psychomotor agitation and aggression. In general, the number of medications prescribed to patients increased over time (i.e., length of hospitalization; Ordak et al.). Of note, five case reports indicated a patient fatality, with the majority of these patient deaths due to patient ingestion of synthetic opioids. Taken together, these findings highlight the overall importance of safe management of psychomotor agitation with benzodiazepines for patients taking new psychoactive substances.

The last study by Lin et al. applied software for scientometric visual analysis, investigating trends in research on the topic of GABAergic networks in depression in recent years (i.e., 2004–2020). Results revealed that research in this area has increased significantly overtime, as measured by increasing numbers of publications on GABAergic networks in depression, particularly in the past 5 years (Lin et al.). With respect to clinical and research implications of results from this review, findings highlight the importance of the development of pharmacological interventions that enhance the transmission of GABA for most effective treatment of depression.

In summary, this Research Topic showed that data synthesis is a key component of psychiatric research especially in those areas where treatment options remain suboptimal, engulfed by safety issue, and/or limited by the absence or properly designed trials. The identification of novel treatments through these analytical approaches might promote new lines of clinical and basic research as well as guide clinicians in choosing concomitant treatment options that may increase the rate of response in treated patients.

Author contributions

All authors took part in drafting the article, revising it critically for important intellectual content, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Funding

This paper was partly funded by Fondo Integrativo per la Ricerca (FIR)-2021 granted to MM.

Acknowledgments

The authors wish to thank all contributing authors that have made this Research Topic a reference for the field.

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

References

1. Aromataris E, Pearson A. The systematic review: An overview. *Am J Nurs.* (2014) 114:53–8. doi: 10.1097/01.NAJ.0000444496.24228.2c

2. Howes OD, Thase ME, Pillinger T. Treatment resistance in psychiatry: State of the art and new directions. *Mol Psychiatry.* (2021) 27:58–72. doi: 10.1038/s41380-021-01200-3

3. Sigmund F. A general introduction to psychoanalysis. *J Nerv Mental Dis.* (1920) 52:548–9.

frontiers in Psychiatry

SYSTEMATIC REVIEW
published: 22 February 2021
doi: 10.3389/fpsyt.2021.628965

Treatment of Agitation With Lorazepam in Clinical Practice: A Systematic Review

Mario Amore[1,2], *Mariella D'Andrea*[3] *and Andrea Fagiolini*[4]*

[1] Section of Psychiatry, Department of Neuroscience, Ophthalmology, Genetics and Infant-Maternal Science, University of Genoa, Genoa, Italy, [2] Istituto di Ricovero e Cura a Carattere Scientifico Ospedale Policlinico San Martino, Genoa, Italy, [3] Medical Department, Pfizer Italia, Rome, Italy, [4] Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy

Acute agitation is a frequent occurrence in both inpatient and outpatient psychiatric settings, and the use of medication to calm a patient may be warranted to mitigate the situation. Lorazepam is a benzodiazepine that is widely used for management of acute agitation. Despite its widespread use, there is remarkably little clinical evidence for the benefits of lorazepam in acute agitation. We performed a systematic review with focus on lorazepam, including all randomized clinical trials on lorazepam in mental and behavioral disorders, excluding studies on dementia and pediatric patients and in mixed conditions. A total of 11 studies met inclusion criteria, and all were in patients with mental and behavioral disorders. Most trials generally found improvements across a variety of outcomes related to agitation, although there was some disparity if specific outcomes were considered. In the five studies with haloperidol, the combination of lorazepam and haloperidol was superior to either agent alone, but with no differences between monotherapy with the individual agents. In the study comparing lorazepam to olanzapine, olanzapine was superior to lorazepam, and both were superior to placebo. As expected, the safety of lorazepam among the different studies was consistent with its well-characterized profile with dizziness, sedation, and somnolence being the most common adverse events. Based on this structured review, lorazepam can be considered to be a clinically effective means of treating the acutely agitated patient.

Keywords: lorazepam, agitation, systematic review, benzodiazepine, clinical trial

OPEN ACCESS

Edited by:
Michele Fornaro, New York State Psychiatric Institute (NYSPI), United States

Reviewed by:
Michele De Prisco, Federico II University Hospital, Italy
David Jonathan Castle, The University of Melbourne, Australia

***Correspondence:**
Andrea Fagiolini
andreafagiolini@gmail.com

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: *13 November 2020*
Accepted: *19 January 2021*
Published: *22 February 2021*

Citation:
Amore M, D'Andrea M and Fagiolini A (2021) Treatment of Agitation With Lorazepam in Clinical Practice: A Systematic Review. Front. Psychiatry 12:628965. doi: 10.3389/fpsyt.2021.628965

INTRODUCTION

Agitation in patients with psychiatric conditions is a frequent occurrence and an issue of substantial clinical relevance in psychiatry in emergency settings and in both inpatient and outpatient psychiatric settings (1). Agitation is associated with many psychiatric conditions in addition to substance use and/or intoxication and conditions involving the central nervous system (e.g., Parkinson's disease, Alzheimer's disease, dementia, etc.) and brain trauma (1). The key features generally recognized in patients with agitation include restlessness with excessive or semi-purposeful motor activity, irritability, and augmented responses to internal and external stimuli, together with an unstable clinical course (2). The DSM-5 defines agitation as excessive motor activity associated with a feeling of inner tension, which is frequently accompanied by non-productive, repetitious of behaviors like pacing, fidgeting, wringing of the hands, pulling of clothes, and inability to sit still (3). Progression of agitation can also lead to violence and aggressive behavior (4).

When agitation is severe it can be accompanied by complete lack of behavioral control where the threat of damage to property, assault to others, and self-inflicted injury are of immediate concern (5). In such a clinical condition, the use of medication to calm down the patient may be warranted to mitigate the overall situation through immediate administration of medication, with or without the patient's consent. Given the clinical relevance and impact of agitation, prompt evaluation of causative factors and immediate management are crucial, since this may the healthcare provider to gain control over potentially hazardous behaviors (1). The overarching goal of medication in the management of acute agitation is to rapidly calm the patient without oversedation (6). Assessment of the causes of agitation allow the clinician to choose the most appropriate management strategy. When agitation is due to delirium or another physical condition such as brain trauma, the underlying organic causes should be addressed; if agitation is related to an underlying mental condition such as schizophrenia or bipolar disorder, antipsychotics and/or benzodiazepines are normally considered (7). In fact, intramuscular injections of typical antipsychotics and benzodiazepines, either alone or in combination, have remained the mainstay of treatment for decades, although the use of intramuscular atypical antipsychotics has gained widespread acceptance (5). The intramuscular formulations of atypical antipsychotics indicated for acute agitation include ziprasidone, olanzapine, and aripiprazole (8). Although no direct comparative studies with these intramuscular agents have been carried out, it is generally held that their efficacy is comparable for acute agitation and similar to intramuscular haloperidol (9). While a wide choice of treatments are available, current recommendations on agitation in psychiatry are not univocal.

Lorazepam is a widely used benzodiazepine that has been available for more than 40 years (10). Lorazepam is frequently used as the sedative and anxiolytic of choice in inpatient settings due to its rapid (1–3 min) onset of action when administered intravenously, and a relatively good safety profile. Lorazepam is often used for episodes of acute agitation. Despite its widespread use, there is surprisingly scarce clinical evidence for the benefits of lorazepam (and other benzodiazepines) in acute agitation. For example, a recent Cochrane review concluded that the evidence for the use of benzodiazepines is not high, and that the advantage of adding a benzodiazepine to other drugs is not entirely clear, also in light of potential additive adverse effects (11). Others have concluded that a first-generation antipsychotic together with lorazepam or monotherapy with lorazepam or a second-generation antipsychotic are effective therapeutic options for acute agitation (4, 12).

To shed more light in the use of benzodiazepines in managing patients with acute agitation, we performed a systematic review with particular focus on lorazepam. For the purposes of this review, in order to focus on a somewhat homogeneous population, we included all randomized clinical trials on lorazepam in mental and behavioral disorders, excluding studies on dementia and pediatric patients and in mixed conditions such as cancer and AIDS. For the purposes of the present review, attempt was made to distinguish between agitation, violence, or aggressive behavior.

MATERIALS AND METHODS

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (13, 14). In April 2020, we conducted a systematic literature search in the PubMed/Medline database and in the Cochrane Library for papers reporting data on the use of lorazepam in agitated patients. The following search string was used (lorazepam OR Ativan OR Orfidal OR Témesta OR Tolid OR Donix OR Duralozam OR Durazolam OR Idalprem OR Laubeel OR Lorazep OR Lorazepam-Neuraxpharm OR Lorazepam-Ratiopharm OR Novo-Lorazem OR Novolorazem OR Nu-Loraz OR Sedicepan OR Sinestron OR wy-4036 OR wy4036 OR Apo-Lorazepam OR Somagerol OR Temesta) AND (agitation OR aggression OR violence OR delirium OR confusion). The same combination of terms was used in the exploration of the Cochrane Library database. No restrictions on language or type of study were applied, and a meta-analysis was not planned.

Two members of the review team retrieved and evaluated independently the potentially relevant articles, and checked the reference list of all reviews and papers of interest to obtain other pertinent publications. An independent search in Google Scholar was also performed, in order to identify other papers that had been missed. Conference abstracts were evaluated, but none reported sufficient data for inclusion. Unpublished studies were excluded.

No studies were excluded a priori for weakness of design or data quality. Publications identified were included if the following criteria were met: randomized controlled trials (RCT) on lorazepam use, as a single agent or in combination with other drugs, reporting quantitative information on efficacy and/or safety of lorazepam in agitated patients. Studies on both oral and intramuscular lorazepam use were included. On the other hand, publications identified were excluded according to the following criteria: studies not specifically focused on patients with agitation (e.g., studies of patients with alcohol withdrawal syndrome, unless they examined only patients with incipient delirium; studies of mixed psychotic conditions that included also non-agitated patients; etc.); studies not focused on lorazepam (e.g., those that reported use of lorazepam as rescue medication); duplicate publications that did not contain additional data; case-series; case-reports. Studies on agitation associated with agitation/delirium in AIDS, cancer, brain injury, dementia, and alcoholism were excluded, as were those on pediatric patients. Discrepancies between members of the review team were discussed and resolved.

Two members of the review team examined all the publications that had been selected for inclusion, evaluated risk of bias, and abstracted the following information in a standard format: country; study period; study design (RCT or other); number of patients enrolled; underlying condition and study setting; intervention(s) characteristics, including drugs, dose and type of administration (oral, intramuscular, intravenous); efficacy/effectiveness outcomes reported; safety outcomes reported. We extracted results on any available efficacy outcome presented in each publication, such as the proportion

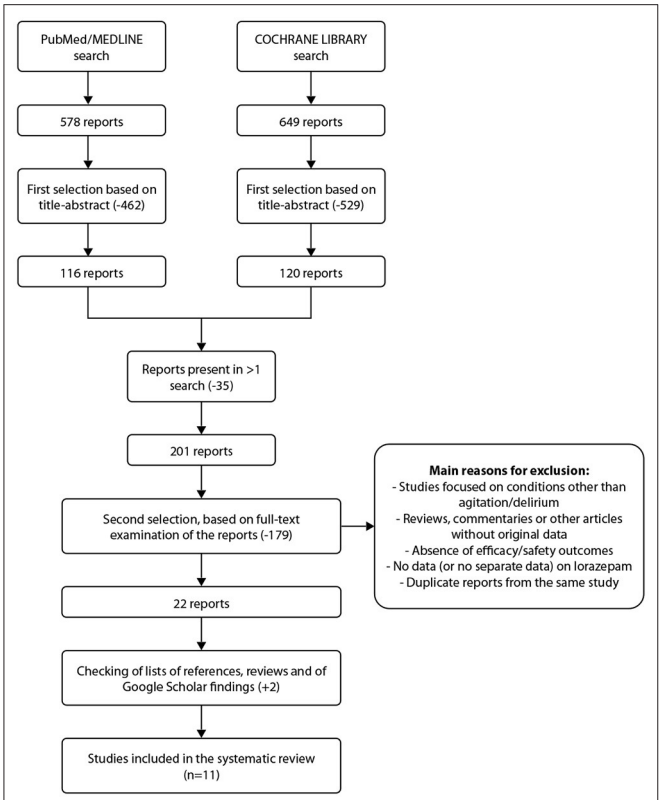


FIGURE 1 | Flowchart for search and selection of studies on lorazepam in agitated patients.

of patients tranquil or asleep at a given timepoint, the Brief Psychiatric Rating Scale (BPRS), the Clinical Global Impression (CGI) score, and the Excited Component of the Positive and Negative Syndrome Scale (PANSS-EC), by reporting data on the percentage of patients achieving the efficacy target or the median/mean score of each outcome in the lorazepam and comparison groups; similarly, we extracted information on several safety outcomes, such as the proportion of any adverse event, of severe adverse events and of extrapyramidal syndrome (EPS) symptoms, in each group. When appropriate and available, findings for the comparison of efficacy and safety between groups (in terms of *p*-values or relative risks) were also abstracted. Differences between data extracted by the members of the review team were further checked on the original articles, and resolved.

RESULTS

Figure 1 shows the process of search and selection of publications for the present systematic review. A total of 578 publications were retrieved from PubMed and 649 from the Cochrane library. Following removal of duplicates, 201 publications remained and were subjected to full text analysis. After final review, based on inclusion criteria, 11 studies were included in the present analysis. The main characteristics of the trials included are shown in **Supplementary Table 1**. Of the 11 trials, 3 studied lorazepam only in combination with other medications, i.e., not as monotherapy, and all were in patients with mental and behavioral disorders. The main efficacy results of randomized controlled trials on lorazepam for treatment of patients with agitation are summarized in **Supplementary Table 2**.

Efficacy

In these 11 studies, a wide variety of outcome measures were used. The most commonly used was CGI or CGI subscales ($n = 7$) followed by the PANNS ($n = 5$). Three studies each used the BPRS, ACES, and VAS agitation.

Haloperidol was the comparator in 5 studies. With the exception of the trial by Salzman et al. (15), in general, significant differences were seen favoring lorazepam over haloperidol, and the combination of lorazepam + haloperidol was superior to lorazepam alone. However, while broadly speaking the differences seen favored lorazepam, the differences were not consistent across trials. For example, Garza-Trevino et al. reported no differences in VAS agitation at 60 min (16), while Bieniek et al. reported significant differences in VAS agitation at 1 h (17). The trial by Battaglia et al. found no differences between groups in CGI at 3 h (18), in contrast to that by Foster et al. who reported significant differences in favor of lorazepam at 1–3 h (19).

The study by Battaglia et al. reported that olanzapine was significantly more effective than placebo considering changes in PANNS-EC at 2 h; the p values for lorazepam vs. placebo were not reported (20). The trial by Alexander et al. compared lorazepam to the combination of haloperidol and promethazine, reporting that the combination was more effective at 2 h than lorazepam with a faster onset of action. Zimbroff et al. compared aripiprazole to lorazepam and placebo, reporting that lorazepam was significantly more effective than placebo for all outcome measures, but with no difference between lorazepam and the antipsychotic (21).

Three studies compared lorazepam in combination with other agents: (i) thiothixene and lorazepam vs. haloperidol and phenobarbital sodium (16); intramuscular (IM) administration of lorazepam and haloperidol vs. oral risperidone + lorazepam (22); IM olanzapine vs. haloperidol + lorazepam (23). Using these combinations, all three studies documented significant efficacy for both study arms, but with no significant differences between groups for any outcome measure.

Supplementary Table 3 reports an evaluation of the quality and of the risk of bias in each study included in this systematic review.

Safety

Supplementary Table 4 summarizes the main findings on the safety of lorazepam and comparators in the treatment of patients with agitation. The safety profile of lorazepam, alone or in combination, was as expected. Dizziness was reported in ≥10% of patients in 3 trials; sedation/somnolence was documented in about 10% of patients in three trials as well.

DISCUSSION

The present systematic review on the use of lorazepam in acute agitation highlights that there is a paucity of randomized

trials. Despite this, most trials generally found improvements across a variety of outcomes related to agitation, even if there was some disparity among different studies when considering specific outcomes. As expected, the safety of lorazepam among the different studies was consistent with its well-characterized profile. Among the studies included in the present analysis, the most frequently used comparators were haloperidol and a second-generation antipsychotic, as monotherapy or in various combinations, which is consistent for the most part with routine practice. The studies were highly heterogeneous, especially regarding treatment arms, doses, and outcome measures, rendering meta-analysis impossible. Indeed, the differences among studies even make overall qualitative evaluation difficult.

In general, in the studies with haloperidol, the combination of lorazepam and haloperidol was superior to either agent alone, with significant differences favoring lorazepam over haloperidol (15–19). In the study comparing lorazepam to olanzapine, olanzapine was superior to lorazepam, and both were superior to placebo (20). In the three studies comparing combinations of agents, interpretation is rendered difficult by the lack of monotherapy groups (16, 22, 23), and so the effects of lorazepam or other comparators cannot be directly interpreted.

Qualitative analysis of the safety profile of lorazepam from the different studies revealed no new safety issues, with dizziness, sedation and somnolence being common among the trials that listed specific adverse events. Haloperidol, but not lorazepam apart from isolated case reports (24), is known to be associated with alterations in QTc (25). This was reported to be of concern for patients with torsade de pointes, but not in the great majority of patients. Case reports with QTc prolongation have also been documented (26), but the event does not seem to be common and QTc prolongation is not reported in the Summary of Prescribing Characteristics. Also, unlike many antipsychotics, routine monitoring of the QT duration by electrocardiography prior to treatment is not recommended for lorazepam (27).

According to the recent expert consensus of treatment of psychomotor agitation, non-pharmacological approaches should be attempted first, with the involvement of the patient in therapeutic decisions as much as possible (1). In the event that these methods are not adequate, pharmacological treatment may be considered in order to rapidly calm an agitated patient. As mentioned, over-sedation should be avoided, and oral medications are preferred. However, in some patients, escalation to IM medication is needed. Rapid onset and the reliability are considered to be the most important factors to consider when choosing a route of administration. Lorazepam is often an anxiolytic of choice, given its rapid onset of action (10).

This systematic review was carried out to evaluate the efficacy and safety of lorazepam for acute agitation and thus better understand its suitability for use in the acute setting. A total of 11 randomized clinical trials were included. Our study has several limitations. First, the heterogeneity of trials from multiple points of view hindered additional analyses. Second, among the studies included, there were little or no available on the clinical implications of rapidity of onset of efficacy, other than the first time point in the respective analysis, or relevant information on use of restraint or seclusion or length of stay. Insightful inter-study comparison of clinical data within the context of this review was further confounded by differences in study design. The trials differed in measures used to assess agitation; many used multiple outcomes measures, and some used only one, with no commonly used measure. Although the scales utilized may be a valid means to measure agitation, the use of differ but outcome measures make comparisons problematic. The degree of agitation among the different studies may also vary. Lastly, it is clear that for inclusion in clinical trials patients have to be unwell enough to warrant invasive intervention, but well enough to give informed consent so that some patients are excluded from inclusion. Based on our analysis, lorazepam seems to be superior to placebo (but not to other treatments) in management of agitation.

The optimal management strategy patients with agitation should begin with quick assessment of possible medical conditions, and non-pharmacological intervention (1). When these methods fail, use of restraint and medications can be considered. The physician must consider the time of onset and risk for adverse events when choosing a medication. The most widely used agents are typical and atypical antipsychotics, benzodiazepines, and combination therapies (5). In a study in Belgium, for example, the preferred medication classes were antipsychotics (59%) and benzodiazepines (41%); among the latter, lorazepam was the preferred drug (28).

Based on this structured review, and despite its limitations, the present analysis reinforces that lorazepam can be considered to be a clinically effective means of treating the acutely agitated patient. However, the choice of drug(s) for rapid tranquilization remains a matter of clinical judgement until additional well-designed studies with larger cohorts of patients are carried out in settings that are more reflective of routine practice.

DATA AVAILABILITY STATEMENT

The original contributions generated for the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

MA, MD'A, and AF contributed equally to the conception, design, and execution of the study, to the drafting and revisions of the manuscript, and read and approved the submitted version. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

Editorial and medical writing support was provided by HPS and was funded by Pfizer. MA and AF received honoraria from Pfizer in connection with the development of this manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.628965/full#supplementary-material

REFERENCES

1. Garriga M, Pacchiarotti I, Kasper S, Zeller SL, Allen MH, Vazquez G, et al. Assessment and management of agitation in psychiatry: expert consensus. *World J Biol Psychiatry.* (2016) 17:86–128. doi: 10.3109/15622975.2015.1132007
2. Lindenmayer JP. The pathophysiology of agitation. *J Clin Psychiatry.* (2000) 61(Suppl. 14):5–10.
3. *American Psychiatric Association*. Available online at: https://www.psychiatry.org/psychiatrists/practice/dsm (accessed Febuary 9, 2021).
4. Zeller SL, Rhoades RW. Systematic reviews of assessment measures and pharmacologic treatments for agitation. *Clin Ther.* (2010) 32:403–25. doi: 10.1016/j.clinthera.2010.03.006
5. Battaglia J. Pharmacological management of acute agitation. *Drugs.* (2005) 65:1207–22. doi: 10.2165/00003495-200565090-00003
6. Zun LS. Evidence-based review of pharmacotherapy for acute agitation. Part 1: Onset of Efficacy. *J Emerg Med.* (2018) 54:364–74. doi: 10.1016/j.jemermed.2017.10.011
7. Amodeo G, Fagiolini A, Sachs G, Erfurth A. Older and newer strategies for the pharmacological management of agitation in patients with bipolar disorder or schizophrenia. *CNS Neurol Disord Drug Targets.* (2017) 16:885–90. doi: 10.2174/1871527316666170919115507
8. Zimbroff DL. Pharmacological control of acute agitation: focus on intramuscular preparations. *CNS Drugs.* (2008) 22:199–212. doi: 10.2165/00023210-200822030-00002
9. Bosanac P, Hollander Y, Castle D. The comparative efficacy of intramuscular antipsychotics for the management of acute agitation. *Austr Psychiatry.* (2013) 21:554–62. doi: 10.1177/1039856213499620
10. Ghiasi N, Bhansali RK, Marwaha R. *Lorazepam*. Treasure Island, FL: StatPearls (2020).
11. Zaman H, Sampson SJ, Beck AL, Sharma T, Clay FJ, Spyridi S, et al. Benzodiazepines for psychosis-induced aggression or agitation. *Cochrane Database Syst Rev.* (2017) 12:CD003079. doi: 10.1002/14651858.CD003079.pub4
12. Hirsch S, Steinert T. The use of rapid tranquilization in aggressive behavior. *Dtsch Arztebl Int.* (2019) 116:445–52. doi: 10.3238/arztebl.2019.0445
13. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ.* (2009) 339:b2700. doi: 10.1136/bmj.b2700
14. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* (2009) 339:b2535. doi: 10.1136/bmj.b2535
15. Salzman C, Solomon D, Miyawaki E, Glassman R, Rood L, Flowers E, et al. Parenteral lorazepam versus parenteral haloperidol for the control of psychotic disruptive behavior. *J Clin Psychiatry.* (1991) 52:177–80.
16. Garza-Trevino ES, Hollister LE, Overall JE, Alexander WF. Efficacy of combinations of intramuscular antipsychotics and sedative-hypnotics for control of psychotic agitation. *Am J Psychiatry.* (1989) 146:1598–601. doi: 10.1176/ajp.146.12.1598
17. Bieniek SA, Ownby RL, Penalver A, Dominguez RA. A double-blind study of lorazepam versus the combination of haloperidol and lorazepam in managing agitation. *Pharmacotherapy.* (1998) 18:57–62. doi: 10.1002/j.1875-9114.1998.tb03827.x
18. Battaglia J, Moss S, Rush J, Kang J, Mendoza R, Leedom L, et al. Haloperidol, lorazepam, or both for psychotic agitation? A multicenter, prospective, double-blind, emergency department study. *Am J Emerg Med.* (1997) 15:335–40. doi: 10.1016/S0735-6757(97)90119-4
19. Foster S, Kessel J, Berman ME, Simpson GM. Efficacy of lorazepam and haloperidol for rapid tranquilization in a psychiatric emergency room setting. *Int Clin Psychopharmacol.* (1997) 12:175–9. doi: 10.1097/00004850-199705000-00009
20. Battaglia J, Lindborg SR, Alaka K, Meehan K, Wright P. Calming versus sedative effects of intramuscular olanzapine in agitated patients. *Am J Emerg Med.* (2003) 21:192–8. doi: 10.1016/S0735-6757(02)42249-8
21. Zimbroff DL, Marcus RN, Manos G, Stock E, McQuade RD, Auby P, et al. Management of acute agitation in patients with bipolar disorder: efficacy and safety of intramuscular aripiprazole. *J Clin Psychopharmacol.* (2007) 27:171–6. doi: 10.1097/JCP.0b13e318033bd5e
22. Currier GW, Chou JC, Feifel D, Bossie CA, Turkoz I, Mahmoud RA, et al. Acute treatment of psychotic agitation: a randomized comparison of oral treatment with risperidone and lorazepam versus intramuscular treatment with haloperidol and lorazepam. *J Clin Psychiatry.* (2004) 65:386–94. doi: 10.4088/JCP.v65n0315
23. Huang CL, Hwang TJ, Chen YH, Huang GH, Hsieh MH, Chen HH, et al. Intramuscular olanzapine versus intramuscular haloperidol plus lorazepam for the treatment of acute schizophrenia with agitation: an open-label, randomized controlled trial. *J Formos Med Assoc.* (2015) 114:438–45. doi: 10.1016/j.jfma.2015.01.018
24. Ziegenbein M, Kropp S. Lorazepam-induced prolongation of the QT interval in a patient with schizoaffective disorder and complete AV block. *Can J Psychiatry.* (2004) 49:414. doi: 10.1177/070674370404900619
25. Harvey AT, Flockhart D, Gorski JC, Greenblatt DJ, Burke M, Werder S, et al. Intramuscular haloperidol or lorazepam and QT intervals in schizophrenia. *J Clin Pharmacol.* (2004) 44:1173–84. doi: 10.1177/0091270004267807
26. Singh TSS, Elahi F, Cheney B. Ketamine-induced QTc interval prolongation. *J Anaesthesiol Clin Pharmacol.* (2017) 33:136–8. doi: 10.4103/0970-9185.173335
27. Warnier MJ, Rutten FH, Souverein PC, de Boer A, Hoes AW, De Bruin ML. Are ECG monitoring recommendations before prescription of QT-prolonging drugs applied in daily practice? The example of haloperidol. *Pharmacoepidemiol Drug Saf.* (2015) 24:701–8. doi: 10.1002/pds.3792
28. Bervoets C, Roelant E, De Fruyt J, Demunter H, Dekeyser B, Vandenbussche L, et al. Prescribing preferences in rapid tranquillisation: a survey in Belgian psychiatrists and emergency physicians. *BMC Res Notes.* (2015) 8:218. doi: 10.1186/s13104-015-1172-2

Conflict of Interest: MA is /has been a consultant and/or a speaker and/or has received research grants from Angelini, FB-Health, Janssen, Lundbeck, Otsuka, Pfizer, Recordati, and Glaxo. AF is/has been a consultant and/or a speaker and/or has received research grants from Allergan, Angelini, Aspen, Boehringer Ingelheim, Daiichi Sankyo Brasil Farmacêutica, Doc Generici, FB-Health, Italfarmaco, Janssen, Lundbeck, Mylan, Otsuka, Pfizer, Recordati, Sanofi Aventis, Sunovion, and Vifor. MD'A is a Pfizer employee.

frontiers in Psychiatry

SYSTEMATIC REVIEW
published: 23 April 2021
doi: 10.3389/fpsyt.2021.669921

Pharmacotherapy of Patients Taking New Psychoactive Substances: A Systematic Review and Analysis of Case Reports

Michal Ordak[1], Aleksandra Zmysłowska[1], Miłosz Bielski[1], Daniel Rybak[1], Maja Tomaszewska[1], Katarzyna Wyszomierska[1], Aleksandra Kmiec[1], Natalia Garlicka[1], Maria Zalewska[1], Michal Zalewski[1], Tadeusz Nasierowski[2], Elzbieta Muszynska[3] and Magdalena Bujalska-Zadrozny[1]*

[1] Department of Pharmacodynamics, Centre for Preclinical, Research and Technology (CePT), Medical University of Warsaw, Warsaw, Poland, [2] Department of Psychiatry, Medical University of Warsaw, Warsaw, Poland, [3] Department of Medical Biology, Medical University of Bialystok, Bialystok, Poland

OPEN ACCESS

Edited by:
Gary T. Hardiman,
Queen's University Belfast,
United Kingdom

Reviewed by:
Fabrizio Schifano,
University of Hertfordshire,
United Kingdom
Amira Guirguis,
Swansea University, United Kingdom

***Correspondence:**
Michal Ordak
mordak@wum.edu.pl
orcid.org/0000-0001-5652-4397

Specialty section:
This article was submitted to Psychopharmacology, a section of the journal Frontiers in Psychiatry

Received: 19 February 2021
Accepted: 31 March 2021
Published: 23 April 2021

Citation:
Ordak M, Zmysłowska A, Bielski M, Rybak D, Tomaszewska M, Wyszomierska K, Kmiec A, Garlicka N, Zalewska M, Zalewski M, Nasierowski T, Muszynska E and Bujalska-Zadrozny M (2021) Pharmacotherapy of Patients Taking New Psychoactive Substances: A Systematic Review and Analysis of Case Reports. Front. Psychiatry 12:669921. doi: 10.3389/fpsyt.2021.669921

Background: In recent years, an increase in the frequency of hospitalizations of patients taking newer and newer psychoactive substances has been observed around the world. Each year, authors publish case reports of patients who consumed previously unknown NPS. Most publications of this type concern the period between 2014 and 2016. However, no publication systematically reviews the pharmacotherapy used in these cases. This study aims to review the case reports of patients taking NPS published between 2010 and 2019, as well as analyzing the pharmacotherapy used.

Methods: We searched the Thomson (Web of Knowledge), PubMed/Medline, Science Direct, Scopus and Google Scholar databases. The search was performed using all possible combinations of the term "case report" describing the use of NPS, also referred to as designer medications, internet medications, research chemicals and herbal highs.

Results: We analyzed 51 case reports on the intake of various types of NPS. Most of them ($p < 0.001$) concerned the use of synthetic cannabinoids (41.2%) and cathinones (31.4%). The pharmacotherapy applied primarily ($p < 0.001$) consisted of administering benzodiazepines to patients (62.7%), most of whom took only this group of medications (25.5%), followed by groups receiving benzodiazepines combined with neuroleptics (15.7%) and muscle relaxants (11.8%). Opioids were administered primarily to patients taking synthetic opioids ($p < 0.001$). Of the 5 cases of deaths from NPS reported in the literature, three relate specifically to the synthetic opioid MT-45. The later the time period, the more medications patients were administered ($p = 0.02$).

Conclusion: In the pharmacotherapy for NPS poisoning, one should focus primarily on combating psychomotor agitation.

Keywords: new psychoactive drugs, case report, psychopharmacology, pharmacotherapy, substances abuse

INTRODUCTION

In recent years, there has been a sharp increase in the frequency of hospital admissions of patients who take new psychoactive substances (NPS). The problem of NPSs has been observed in many countries around the world, where the substances are also known as "legal highs," "designer drugs," "herbal highs," "spice," or "research chemicals" (1).

A few thousand NPS were preliminarily identified in the "NPS.Finder®", which is four times bigger number than the figure suggested by European and international drug agencies. Pharmacodynamics and pharmacokinetics of NPS are not fully understood due to their constantly evolving chemical composition (2).

In clinical practice, it is often difficult to determine the appropriate diagnostic methods and standards of treatment and management in emergencies caused by NPS. As we lack simple, specific tests to detect NPSs in patients' bodily fluids or tissues, there is, regrettably, no specific method of treatment for NPS poisoning. Another problem is the fact that patients combine NPSs with other psychoactive substances, which also often blurs the clinical picture (1, 3).

In the literature, there is no review describing previously published scientific papers on the pharmacotherapy of patients receiving various types of NPSs. The division was made into three time periods: until up to 2013, from 2014 to 2015, and from 2016 to 2019. This is due to the fact that the first publications appeared in the first of these periods, in which the authors included case reports of patients who had taken NPSs. Between 2014 and 2015, articles described the treatment used for many of the newer NPSs which had appeared on the market. Based on the 2014 data from the European Drug Report of the European Monitoring Center for Drugs and Drug Addiction (EMCDDA), a record 101 new psychoactive substances were detected in Europe (4). In 2016, the European Monitoring Center for Drugs and Drug Addiction (EMCDDA) drew attention to the constantly emerging new substances and the changing patterns of drug use. According to the 2016 EMCDDA report, the analysis highlighted the need to consider a number of more complex aspects of the problem in European drug strategy, including NPSs, compared to the previous time period (5).

Because the literature on the subject covers case reports, an additional goal was to conduct a review and analysis of these reported cases.

Abbreviations: AB-PINACA, N-[1-(aminocarbonyl)-2-methylpropyl]-1-pentyl-1H-indazole-3-carboxamide; ADHD, Attention deficit hyperactivity disorder; AOT, opioid agonists; 5-APB, 5-(2-aminopropyl)benzofuran; AM2201, (1-(5-fluoropentyl)-3-(1-naphthoyl)indole); AM-694, (1-(5-fluoropentyl)-3-(2-iodobenzoyl)indole); AM-2233, 1-[(N-methylpiperidin-2-yl)methyl]-3-(2-iodobenzoyl)indole; BB-22, 1-(cyclohexylmethyl)-1H-indole-3-carboxylic acid 8-quinolinyl ester); 25B-NBOMe, novel N-2-methoxybenzyl-phenethylamine; CPK, creatine phosphokinase; DOC, 2,5-dimethoxy-4-chloroamphetamine; DSM, Diagnostic and Statistical Manual of Mental Disorders; EMCDDA, European Monitoring Centre for Drugs and Drug Addiction; EDDP, (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine); 5FADP-PINACA, N-[1-(aminocarbonyl)-2,2-dimethylpropyl]-1-(5-fluoropentyl)-1H-indazole-3-carboxamide; 5F-PB-22, (quinolin-8-yl 1-(5-fluoropentyl)-1H-indole-3-carboxylate); 3-FPM, 3- uorophenmetrazine; HAT, Heroin-assisted Therapy; 3-HO-PCP, 3-Hydroxyphencyclidine; ICU, intensive care unit; ILE, lipid emulsion therapy; JWH018, naphthalen-1-yl-(1-pentylindol-3-yl) methanone; JWH-073, naphthalen-1-yl-(1-butylindol-3-yl) methanone; JWH-122, (4-Methyl-1-naphthalenyl)(1-pentyl-1H-indol-3-yl)-methanone; K2, synthetic cannabinoid (Spice); MDMA, 3,4-Methylenedioxymethamphetamine; MDMB-CHIMICA, N-[[1-(cyclohexylmethyl)-1H-indol-3-yl]carbonyl]-3-methyl-L-valine, methyl ester; MDMB-PINACA, 2-{[1-(5- uoropentyl)-1H-indazole-3-carbonyl]amino}-3,3-dimethylbutanoate; MDPV, methylenedioxypyrovalerone; 3-MeO-PCP, 3-Methoxyphencyclidine; 3-MMC, 3-Methylmethcathinone; 4-MMC, 4-methylmethcathinone; MT-45, 1-cyclohexyl-4-(1,2-diphenylethyl) piperazine; NPS, new psychoactive substances; NWS, neonatal withdrawal syndrome, PASS, Postural Assessment Scale for Stroke; PB22, (1-pentyl-8-quinolinyl ester-1H-indole-3-carboxylic acid); PCP, phencyclidine; PVCs, premature ventricular contractions; PVP, alpha-pyrrolidinovalerophenone; THC, tetrahydrocannabinol; U-47700, 3,4-dichloro-N-((1S,2S)-2-(dimethylamino)cyclohexyl)-N-methylbenzamide; VES, ventricular extrasystoles.

MATERIALS AND METHODS

International databases, including Thomson (Web of Knowledge), PubMed/Medline, Science Direct, Scopus and Google Scholar were searched for case reports on the use of various types of new psychoactive substances (NPS) published between 2010 and 2019. The variables used in the analysis included: year of publication, age, gender, NPS taken, clinical symptoms, pharmacological treatment applied and deaths. The search was performed using all possible combinations of the term "case report" describing the use of NPS, also referred to as designer medications, internet medications, research chemicals, and herbal highs. Additionally, when searching the databases, the abbreviations and full names of NPS were entered, such as MT-45 [1-cyclohexyl-4- (1,2-diphenylethyl) piperazine] and mephedrone [4-methyl methcathinone (4-MMC)].

Pharmacotherapy of Patients Taking NPSs

2010–2013

Synthetic Cathinones

Synthetic analogs of drugs such as methamphetamine and cocaine were legally sold as "bath salts" between 2010 and 2013. Synthetic cathinones are β-ketophenethylamines, which are structurally similar to amphetamines and are therefore abused. Cathinone, and to a lesser extent its metabolite—cathine—are responsible for the amphetamine-like euphoric effects, which are achieved by chewing the leaves and twigs of the khat plant (Catha edulis). Many psychoactive substances, including mephedrone, methylenedioxypyrovalerone (MDPV), methylone, butylone, and naphirone, have been identified in the newer products, so-called bath salts. Cathinone, mephedrone, methcathinone, and methylone have been shown to strongly inhibit the reuptake of dopamine, serotonin, and noradrenaline. These substances also increase the presynaptic release of the same monoamines, but to a lesser extent (6, 7). The literature offers limited data on the pharmacokinetics and pharmacodynamics of synthetic cathinones in humans.

Penders and Gestring (8) describe the case of three people who consumed bath salts. The patients suffered from hallucinations, were hyperactive and aggressive, and had insomnia. Two of them were treated with risperidone orally at a dosage of 0.5 mg twice

daily. One of the men was given 1 mg of haloperidol. After 2–3 days of therapy, the symptoms of paranoia subsided (8).

Antonowicz et al. (6) describe the case of a 27-year-old girl and her 32-year-old boyfriend who were brought to a hospital after reporting to the police that they were under attack. Police officers found them barricaded in the bedroom, claiming that there was a corpse in the hallway and that they had been killed. Upon reaching the emergency room, they had tachycardia, were scared, and were perspiring profusely. Blood and urine counts were normal. They were transferred to a psychiatric ward where they were monitored. The woman was given 0.5 mg of risperidone; the man was not administered any antipsychotic drugs during his hospital stay. The patients admitted that they had been consuming an illegally obtained drug, Suboxone. Then they started taking a product called "Powdered Rush." They were ingesting it by inhalation for 5–6 days before being admitted to the hospital. The substance ingested by the couple contained MDPV and was marketed as "bath salts" (6).

Mangewala et al. (9) cite the case of a 15-year-old boy with no prior psychiatric history. He reported to the emergency room complaining of agitation and psychotic symptoms. The patient had reportedly smoked marijuana laced with bath salts. Soon afterwards, the patient became paranoid and barricaded himself in his father's house. The police were called to forcibly enter the house and the patient was taken to the emergency room. The patient's agitation continued to worsen and laboratory tests revealed an elevated level of creatine phosphokinase (CPK). The urine toxicology report was negative. The patient was treated in a hospital intensive care unit (ICU) where he continued to exhibit psychotic and agitated behavior, at one point attacking a staff member. He returned home a few days later once his health had stabilized, although at home he was still showing signs of paranoia. When the patient presented again with symptoms of paranoia a month later, his father took him back to the hospital, where he was referred for psychiatric hospitalization. During the first interview, during which he was non-verbal, the patient was diagnosed with periods of extreme psychomotor impairment. In another situation, he seemed confused, and kept repeating questions to himself. He made paranoid statements such as, "Don't let them take me!" and "How do I get out of this?" The patient reported that nothing around him was real. He claimed that his father had been replaced by an impostor, and that his sister had been hurt by unknown parties. During the interview, he was able to admit that some part of his paranoia was not real. He reported fear but denied any thoughts, intentions, or plans that were suicidal or homicidal in nature. The patient's family was also interviewed and denied that the patient had any history of psychiatric problems or similar behavior. In addition, they reported no history of head injuries or epileptic seizures and no family history of psychiatric illness. However, they declared that the patient had used marijuana in the past without any negative side effects. As mentioned earlier, the patient stated that, to his belief, he was smoking marijuana mixed with "bath salts." While hospitalized, the patient was treated with a combination of 5 mg of olanzapine once daily and 0.5 mg of lorazepam twice daily. The dose of olanzapine was increased to 7.5 mg per day, which combined with the lorazepam reduced the symptoms of psychosis and agitation. He began to interact with his peers. The symptoms of paranoia resolved within 3 days of treatment and the patient was discharged with a prescription for 7.5 mg of olanzapine once daily, 0.5 mg of lorazepam twice daily, and outpatient follow-up. He had no recurrence of symptoms during the 8-week follow-up period. He denied continued use of the substance. No further adjustments in dosage were required (9).

Lenz et al. (10) report the story of a 22-year-old man who found himself in the Emergency Department (ED) after ingesting 1 g of a substance which he called Cristalius the previous night. Mephedrone and a synthetic cathinone derivatives were presumed as the main ingredients.

That morning, after running three miles to start his intense physical exercise, he felt dizzy and light-headed. He was transported to his military aid station and had a brief syncopal episode on the way. He woke up at the aid station confused and belligerent, and therefore had to be handcuffed. Eventually, he calmed down enough to be taken to the hospital, but had a tachycardia of up to 173 beats per minute during the transport. After arriving at the ED, he was given 2 mg of lorazepam for sedation. He remained confused. His heart rate slowly returned to normal, and within 3 h it had dropped to 100 beats per minute with a blood pressure of 129/50 mmHg. He was aware of people, his surroundings, and the time and was less anxious, though he complained of fatigue. The clinically significant laboratory results at that time were a creatine kinase level of 668 U/l (norm: 25–200), a creatinine level of 1.35 mg/dl (norm: 0.66–1.25), and a troponin level of 0.516 ng/ml (norm: 0.0–0.034). One week prior to his admission to the hospital, the patient's urine screening test was positive for amphetamines. He claimed it was because he had borrowed Adderall from a friend, but tested negative for the drug while hospitalized. Intravenous hydration was also initiated; his creatinine levels dropped to 0.97 and his creatine kinase levels rose to 1544. The patient, however, remained asymptomatic with no muscle pain. He only confessed to using marijuana in high school and denied taking any other illegal substances before using Cristalius twice. He denied any past or current symptoms of mood disorders or post-traumatic stress. He refused a positive drug test on his ward and stated that he consumed his last alcoholic drink 6–7 months earlier. At the time of discharge, the patient was stable and asymptomatic (10).

Nervous system stimulants, including methamphetamine and cocaine, are responsible for permanent changes in the dopaminergic reward system in the brain. This causes persistent dysphoria after drug withdrawal (11). There are also psychoactive substances that produce a psychotic syndrome similar to schizophrenia. Usually, these symptoms disappear with treatment, but a few cases of persistent hallucinations have been reported after stopping amphetamine use. Electroshock has been shown to alleviate these types of hallucinations. Synthetic cathinones, which are also stimulants, cause similar symptoms as the above-mentioned products. The case of a patient who was abusing MDPV for several months has been described. He suffered from persistent symptoms of psychosis, visual hallucinations, suspicion, and social withdrawal. After unsuccessful attempts at antipsychotic treatment, electroconvulsive therapy was performed (12).

Penders et al. (12) report the case of a 26-year-old woman who suffered from severe hallucinations and social withdrawal. These symptoms had appeared 8 months earlier, after she had taken bath salts, and persisted even after the substance was no longer being consumed. The patient had been using these substances for 13 months before being admitted to the hospital, but the first hallucinations began 5 months later. There were no serious mental disorders in her family medical history. No improvement was observed under prior treatment with haloperidol and risperidone; minimal improvement was noted only after the administration of 120 mg of lurasidone nightly. The patient was also prescribed 40 mg of citalopram and 300 mg of trazodone for sleep. Before commencing a modified bilateral electroconvulsive therapy, the patient was subjected to general anesthesia consisting of intravenous injection of 100 mg of methohexital and 100 mg of succinylcholine. The Somatic Thymatron IV device was used at the short heart rate setting, the stimulus being 15% (75.6 milicouloms or 15 J). The initial dosage of 120 mg of lurasidone was still being administered at nighttime. After two treatments with a seizure time of 31 and 44 s, the patient reported a reduction in visual hallucinations. Lurasidone was then discontinued. After two more treatments with a seizure time of 19 and 25 s, the hallucinations decreased again. The patient noticed an improvement in mood and a reduction in social anxiety, after which she was discharged from the hospital. Eight months after the end of treatment, the woman continued to experience occasional hallucinations, fewer psychotic symptoms with improved social functions, and a complete disappearance of the previous suspicions. This was the first case to be described in which the symptoms of depression and hallucinations persisted after cessation of synthetic cathinone use (bath salts). In this case, the patient's condition did not improve on antipsychotics and antidepressants. A significant yet incomplete improvement was achieved after a short cycle of four standard electroconvulsive therapy sessions. During the abuse of stimulants, including synthetic cathinones, the level of dopamine changes. Some evidence suggests that generalized seizures lead to the release of monoamines, which confirms the beneficial effects of electroconvulsive shock therapy in schizophrenia. Electroshock therapy and antipsychotics have also been shown to work synergistically. Electroconvulsive therapy may be beneficial in patients with persistent psychotic symptoms following drug abuse, including synthetic cathinones (12).

Another patient with depressive disorders due to cathinone dependence was prescribed bupropion with a gradual increase in dosage to 450 mg per day, which along with the therapy sessions, helped to end these symptoms (13).

Lev-Ran et al. (13) present the case of a 23-year-old man. As a child, he was diagnosed with ADHD and was treated with methylphenidate for 3 years. Two years before the event in question, he started having depressive states and suicidal thoughts. During this time, he occasionally used cannabis and MDMA. Then he started taking cathinone daily. He claims that he was initially euphoric after consuming the substance, but within a few weeks the level of euphoria it caused decreased despite higher dosages. He gradually increased the daily intake, and swallowed up to 15 capsules (200 mg/capsule) per day. He worked during this time and was not intoxicated during working hours. His regimen of use was to consume cathinone continuously after returning home in the afternoon until late at night, when he fell asleep exhausted. He reported regular effects of withdrawal-like dysphoria and agitation during working hours that resolved after returning home and consuming cathinone. After a few months, the effect of cathinone weakened and he began to inhale the contents of the capsules. In the following year, his cathinone use increased and his level of functioning gradually worsened. He reported a severe, constant dysphoric mood that would improve for a very short time after consuming cathinone. He took cathinone almost exclusively when he was alone and gradually withdrew from social activities. Eventually, he underwent a psychiatric evaluation. His symptoms and complaints met the DSM-IV criteria for substance (amphetamine) addiction and major depression. After the initial evaluation, the patient agreed to weekly treatment sessions and was prescribed bupropion, with the dose gradually increasing to 300 mg/day. At the end of the meeting, the patient rated his motivation to stop cathinone treatment as "five out of ten" and confidence in abstaining from cathinone as "one in ten." After 4 weeks of bupropion treatment, he reported a partial improvement in his mood as well as a significant reduction in cathinone cravings. He also reported reducing the frequency of cathinone use to twice a week and decreasing the amount to 5–10 capsules each time. At that time, he rated his confidence level of abstaining from cathinone as "five out of ten" and decided to return to ingesting (instead of inhaling) cathinone as part of a harm reduction strategy. The bupropion was increased to 450 mg/day and the weekly therapy continued for an additional 4 weeks. At the end of this period, the patient reported complete cathinone abstinence and markedly improved mood, and rated his confidence level in cathinone abstention as "nine out of ten." He continued to abstain from cathinone and since remained in remission from depression for 12 months (13).

Garrett et al. (14) write about a 22-year-old man who presented to the ED. During the examination, the patient suffered from tachycardia and was sweating profusely. His pupils were dilated and he had a tremor at rest. The patient was unable to stand on his own. He had no drug allergies that he was aware of. He was taking fluoxetine (40 mg) and olanzapine (10 mg). He was also administered zopiclone at night. The patient had suffered from depression, mania, and self-harm for 2 years. Two bags were found on his person: a plastic bag labeled "Vegetable Food" and a brown paper bag labeled "Red Doves." The patient admitted to taking approximately 40 capsules from these bag within a 4-h span; the main substance ingested was mephedrone. Adequate treatment of his serotonin syndrome (general supportive measures, IV fluids, and oral diazepam) led to the neurological symptoms resolving and the patient being discharged after 15 h (14).

Kasick et al. (15) report the case of a 38-year-old white male with no prior history of psychosis who claimed to have seen snakes and was acting oddly. He was given 2 mg of naloxone twice at the scene, but no improvement was observed. After 45 min of verbal de-escalation by the doctors, the patient was confined to an emergency bed and taken to an external hospital. While in

the ED, he had tachycardia (the ECG revealed a pulse of 144, sporadic premature ventricular contractions (PVCs), and a QTc of 430 ms) and his temperature was 38.2°C. He was restrained on the bed, but he did not want to be covered with a blanket for fear of being bitten by "scorpions." The patient had ingested bath salts packaged under the name "Arctic Blast" (a street name for synthetic cathinone) twice in the previous 2 days. He remained agitated in the emergency room and received 3 mg of intravenous lorazepam over 4 h with 2 L of IV fluids. Laboratory assays showed elevated levels of hemoglobin and hematocrit, consistent with his history of polycythemia. The white blood cell and platelet counts were normal. His first urine drug test was ostensibly only positive for phencyclidine (PCP); his serum ethanol level was zero. He remained very agitated and oversensitive and was given 4 mg of intravenous lorazepam on account of his attempts to leave the hospital. He was anxious and paranoid: he believed that people were stealing his possessions. He fought physically with security guards. Owing to his physical aggression, he was given a total of 6 mg of intravenous lorazepam and 5 mg of haloperidol. His creatine kinase (CK) level was elevated, at 1,468 IU/L. He was given IV fluids at 200 ml/ hour for 24 h. The additional drug screening done 9 h after the initial screening was positive for benzodiazepines, but negative for PCP or other substances. As time went on, the patient became calmer, but still had difficulties with awareness, orientation, cognitive speed, and attention. The next morning, 35 h after the patient's first exposure to emergency services, he remained alert and irritable, but his awareness had improved significantly. The patient clearly described how he had bought the "bath salts" from the local "head shop" and how he had drunk about half a spoonful of the bath salts in a carbonated cola drink twice in the 2 days prior to admission. He still vehemently denied ever using phencyclidine, although he did describe a more distant history of alcohol and cannabis use. He denied any history of psychosis or previous psychiatric treatment. His vital signs and increased CK levels returned to normal. Over the next 24 h, the patient showed a lasting improvement in attention, awareness, focus, concentration, and speed of thought. He had no residual psychotic symptoms and behaved normally on further cognitive screening. The next day, he was discharged (15).

Benzer et al. (16) report the case of a 36-year-old man with a history of alcohol and drug abuse who was admitted to hospital because of severe agitation and paranoia. The patient's girlfriend reported that the patient had been sober for ∼20 months until he lost his job. Three days prior to admission, the patient began drinking alcohol and taking bath salts intranasally after sleepless nights. The night before taking the psychoactive substance, agitation, and auditory and visual hallucinations occurred; as a consequence, the patient believed that people were trying to harm him. On the morning of admission, shortly after taking more bath salts, he ran outside without any clothes on, shouting that someone was trying to strangle him. His girlfriend called the police, who found the patient running naked in the street. When the paramedics arrived, they found him being restrained by police officers, belligerent and confused, with illogical, paranoid, and rambling speech. His pulse was 157 beats per minute, with limited radial pulses, and his respiratory rate was 24 breaths per minute. His pupils were 5 mm in diameter. The patient was transported to the emergency room. On the way, he suddenly fell silent, and the paramedics suspected a seizure. They tried to administer midazolam but the patient removed the intravenous catheter. After arriving at the hospital, it was impossible to communicate with the patient. His history was obtained from his girlfriend. He had a history of depression and alcohol and drug abuse (including heroin, cocaine, and prescription opiates). His only medication was fluoxetine, which he reportedly had not taken for 2 weeks. During the examination, the patient was agitated, flailing his arms and legs, jerking his head, and making loud, incomprehensible sounds. He was unable to cooperate during the investigation and had to be restrained by several security officers. His pupils were equal and reactive to light; his gaze was focused upwards with slow, horizontal movements of the eyes. The patient's speech was quick and mostly incomprehensible, but he mentioned attacking and being attacked by animals, humans, and monsters. The rest of the examination proceeded normally. The patient was immobilized and administered intravenous midazolam followed by lorazepam, but his condition did not improve. Then, etomidate and rocuronium were administered, the trachea was intubated, and mechanical ventilation was begun, followed by sedation with propofol. A urinary catheter and an esophagus tube were inserted. In the next stage, fomepizole, sodium thiosulfate, sodium bicarbonate, saline solution, and potassium chloride were administered intravenously, after which he was admitted to the ICU and his condition improved (16).

Synthetic Cannabinoids

Synthetic cannabinoids first appeared in Europe in the mid-2000s and have been increasingly popular ever since. They are available on the Internet and in drug stores specializing in illegal drug accessories. These products contain several chemicals, including JWH018 and JWH-073 (naphthoylindoles), which have a similar mechanism to THC but appear to cause additional symptoms. "Spice" products contain several ingredients that are potent agonists of the cannabinoid receptors (17). Spice was initially the name of one of the popular brands, then became a generic term for other synthetic cannabinoid products, such as Black Mamba, Funky Monkey, K2, Popeye, Demon Smoke, Purple Haze, Dank, Hawaiian Harvest, and Vanilla Sky (18).

The effects of using synthetic cannabinoids vary from patient to patient, and include drowsiness, agitation, and odd behavior. Similar symptoms can present after marijuana use. Patients have reported somnolence, agitation, or paranoia. Other symptoms include tachycardia, warm and dry skin, and dilated pupils. These symptoms may suggest an anticholinergic or sympathomimetic effect. Lactic acidosis and leukocytosis have occurred, which may be due to agitation, respiratory failure, or possible seizure activity (18).

Data in the literature on patients who have overdosed on synthetic cannabinoids known as "Spice" show that lorazepam is effective at a dose of 4 mg to inhibit uncontrolled movement (19).

Simmons et al. (17) describe the case of a 25-year-old man who was admitted to the hospital due to two episodes which lasted several minutes. His blood pressure was 109/47 mmHg, his pulse was 122 beats per minute, his temperature was 37.3°C, and his

glucose level was normal. The patient spontaneously moved his limbs to protect his airways and opened his eyes, but he did not respond to stimuli. His pupils were dilated with a slow reaction and intermittent esotropia. His skin was dry and warm. The electrocardiogram showed sinus tachycardia with a right bundle branch block pattern. No drugs were found in the urine and no alcohol was detected in the blood. The man did not use any drugs or alcohol, but 45 min before the episode he smoked a product called "Spice" for the first time. Laboratory analysis of his urine for synthetic cannabinoids was positive for JWH-018 metabolites and negative for JWH-073. After rehydration, the lactate level was 1.2 mmol/L. The patient was administered 4 mg of lorazepam and saline intravenously. After 3 h of observation, the patient's condition improved and the tachycardia resolved (17).

Kasick et al. (15) cite the case of a 36-year-old woman who was abusing illegal substances: synthetic cannabinoid preparations with the trade name "Black Mamba Spice." The patient suffered from depression and migraine. She had a generalized tonic–clonic seizure that progressed into an epileptic seizure. The convulsions continued until she was re-intubated at the ED because she had been inadvertently intubated with an endotracheal tube in the esophagus. She was given lorazepam, etomidate, vecuronium, propofol, levetiracetam, and phenytoin. Laboratory tests for alcohol, THC, opiates, amphetamines, and cocaine were negative. The WBC count was 1,2400/μl (abnormal), though the level normalized within 48 h. The patient did not have an elevated temperature and had a normal chest X-ray; an MRI of the brain without contrast was normal. The EEG was mildly encephalopathic, with no focal features or epileptiform discharges. The woman was extubated 12 h after admission. She admitted that she had smoked Black Mamba Spice for the first time before the seizure. There were no more seizures during her stay in the hospital. As part of the follow-up interview after 6 months, the woman did not report any further episodes and did not smoke the preparation called "Spice" again (15).

In order to inhibit excitation, haloperidol—an antagonist of the dopamine receptors—is also administered. Simmons et al. (17) describe the case of a 21-year-old man who was hospitalized after collapsing on the floor in a store. He presented with repetitive back and forth movements and was unable to speak, but was able to obey verbal commands. The emergency services transported him to the emergency department in an oxygen mask. After being admitted, his blood pressure was 204/103 mmHg, his pulse was 48 beats per minute, respiratory rate 8 breaths/min, and temperature 37.8°C. He had no signs of injury. His skin was warm and dry. Initial laboratory testing showed abnormal leukocyte counts and elevated levels of lactate, glucose, and creatine kinase. A urine drug test and blood alcohol level were negative. Due to the hypoventilation and impaired consciousness, the patient was intubated. Laboratory analysis revealed JWH-018 and JWH-073 synthetic cannabinoid metabolites. The doctors administered 5 mg of haloperidol to sedate him. The next day he was extubated. The leukocytosis, elevated lactate levels, and elevated creatine kinase levels resolved after the administration of intravenous fluids. The man confessed to taking a drug called "Spice," which likely caused the change in his behavior. He was discharged from the hospital after 24 h (17).

According to the literature on the subject, patients are also given ondansetron (a 5-HT3 antagonist) and promethazine (a histamine receptor antagonist) to control vomiting. Hopkins et al. (20) described a case of a 30-year-old man who presented to the ED with persistent abdominal pain, nausea, and vomiting. His symptoms also did not improve after oral ondansetron, which he had been prescribed at another emergency room just 3 days earlier. He told the story of countless visits to hospitals and clinics over the past few years, mostly at local emergency rooms, some of which resulted in hospital admissions and others in outpatient gastroenterologist consultations. The patient reported that in the previous 2 years he had had "more abdominal CT scans than he could remember," several abdominal ultrasound scans, and two endoscopic procedures. He also believed that he had severe cramping abdominal pain associated with persistent nausea and vomiting which did not resolve after treatment and recurred every few weeks. His symptoms would last for two or 3 days then slowly subside, often after several visits to the ED for intravenous hydration and antiemetic therapy. In fact, the patient stated that his only real relief was taking hot showers, which meant he bathed several times a day. Further interview revealed that he had been using marijuana since the age of 13 and had smoked several times a day for the past few years, but had stopped using marijuana 6 months earlier. Interestingly, he reported that he had been convicted of growing and possessing marijuana 6 months earlier and was forced to submit weekly urine samples for screening as part of his release. He quickly identified the product with the trade name "Synthetic Sweat" as an ideal substitute because it had similar psychotropic effects but could not be detected by his court-ordered drug testing. Once he was convinced that he could smoke NPSs with impunity, he quickly returned to his daily smoking habits and in the month before the situation in question, he often smoked synthetic cannabinoids every hour, and even woke up several times during the night to smoke. The patient provided a sample of "Synthetic Sweat" which contained a packet of dried herbs that he had purchased from a local grocery store. He reported that he had previously experimented with several brands of synthetic marijuana, including "K2" and "Spice," which were also available for sale at the same location. However, for the 2 months prior to this episode, he had only been using the "Scooby Snacks" brand. With the use of mass spectrometry and gas chromatography, the herbal mixture was found to contain the following synthetic cannabinoids: JWH-018, JWH-073, JWH-122, AM2201, and AM-694. The patient's urine sample collected at the ED was negative for THC metabolites. It is worth noting that an analysis of his urine by liquid chromatography and mass spectrometry revealed synthetic cannabinoids similar to the herbal mixture which he brought: JWH-018, JWH-073 and AM-2201. His condition improved thanks to IV fluids and intravenous ondansetron. The patient was discharged with a prescription for promethazine suppositories. Three months later, the man was abstaining from marijuana and synthetic cannabinoid products. He reported that it took 2 weeks of sobriety before his symptoms completely subsided. It is noteworthy that the patient reported that after the symptoms had resolved, he no longer required multiple baths and showers

every day, his hygiene habits normalized, and his quality of life improved considerably (20).

2014–2015

Synthetic Cathinones

Adamowicz et al. (21) describe the diazepam and midazolam treatment of a 20-year-old man with a history of addiction to psychoactive substances. The patient consumed substances that he purchased online, which he combined with 250 ml of 40% alcohol. A few minutes after consumption, he developed severe psychomotor agitation, as a result of which an ambulance was called. The patient was given 10 mg of diazepam and 5 mg of midazolam on site. On admission to the hospital, the man was conscious, cardiovascularly and respiratorily stable, severely agitated, and non-verbal. The patient screamed and fought; he was uncooperative and a threat to his own health. He presented with convulsions and an elevated temperature. His electrocardiogram showed a sinus rhythm. After 2 h, he suffered from cardiac arrest; intubation, ventilation, defibrillation, and cardiac massage were performed and adrenaline and atropine were administered, but this did not have much effect. Death occurred <4 h after the consumption of the psychoactive substance. Postmortem blood tests showed that the young man was intoxicated with 3-MMC, 5-APB, and ethyl alcohol (21).

Midazolam was also used in a case described by Hall et al. (22), in which a 21-year-old man who had snorted "bath salts" (research showed that the product was a mixture of synthetic cathinones) was described by police officers as having "superhuman strength" and being seemingly immune to pain. He was sweating heavily, making growling noises, and hallucinating. Help was called and paramedics immediately administered 10 mg of midazolam intramuscularly. The patient was immobilized and transported to the emergency room. The patient's condition normalized after sedation and intravenous rehydration with saline solution (22). Propofol was cited as an alternative to benzodiazepines in studies done from 2010 to 2013, but more recent research has also demonstrated the effectiveness of dexmedetomidine (23).

Pichini et al. (24) in their article, report the case of a male infant who, 20 h after delivery, began to display increased irritability, high-pitched crying, increased muscle tone of the limbs and increased tendon reflexes. The mother confessed to smoking mephedrone daily during her pregnancy. The newborn was diagnosed with neonatal withdrawal syndrome (NWS). The following treatment was applied: phenobarbital once as an intramuscular bolus at a dosage of 20 mg/kg, and then 10 mg/kg per day orally. The dose was gradually reduced over the following days as the Finnegan score (the neonatal withdrawal symptom score) was above eight. After 12 days of phenobarbital treatment, the symptoms improved. HPLC analysis showed the presence of methadone, its metabolite EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine) and 4-MMC (4-methylmethcathinone; mephedrone) in the blood of the newborn. After 15 days, he was discharged from the hospital (24).

Pierluigi et al. (25) describe a case illustrating the use of risperidone in a 28-year-old man in 2014. The patient was admitted to the clinic due to symptoms suggestive of a depressive episode that had occurred within the previous 4 weeks. When he was hospitalized, his assessment of reality was not marked by hallucinations or delusions. The patient complained of a general "lack of energy." He was medicated with antipsychotics and antidepressants, i.e., risperidone (4 mg/day), venlafaxine (75 mg/day), biperide (4 mg/day), and delorazepam (2 mg/day). During the course of therapy, the patient explained that most of the experimental substance use in his life had taken place over several years, but in the last 8 months prior to admission to the ward, his frequency of taking the psychoactive substance Alpha-PVP (synthetic cathinone) had increased. At the same time, he experienced a worsening of his depression symptoms until the last episode, in which he experienced visual hallucinations, leading to a referral for treatment. The stay in the ward lasted 40 days, during which he participated in a rehabilitation program including individual (every 2 weeks) and group (two or three times a day) psychotherapy sessions as well as psychopharmacological assessment and psychomotor rehabilitation. A significant change in his health status occurred after administration of bupropion (150 mg/day). This drug helped reduce the depressive symptoms caused by the consumption of the psychoactive substance (25). This antidepressant was chosen because of its chemical structure. Bupropion, a substituted cathinone, α-aminocetone, is a dopamine and norepinephrine reuptake inhibitor and an antagonist of the nicotinic acetylcholine receptor. It has also been shown to modulate the levels of certain cytokines associated with inflammatory diseases. Numerous studies have also been conducted to investigate the effectiveness of bupropion in smoking cessation therapy (26).

Oppek et al. (27), however, describe a case of a 29-year-old woman with a history of polysubstance addiction who used significant amounts of bupropion (up to 2.4 g) intravenously to intoxicate herself. Although it is widely believed that bupropion is not addictive, this situation shows us that people prone to addiction can consume it in very large doses daily. Based on this case, Oppek and other authors conclude that administration of bupropion in subjects prone to addiction should be carried out with caution, as its possible impact raises doubts (27).

Literature from 2014 to 2015 contains guidelines—for the first time—on how to counteract serotoninergic syndrome. Apart from intensive cooling of the body and the benzodiazepines mentioned in the studies done from 2010 to 2013, 5-HT2A receptor antagonists should be administered, i.e., cyproheptadine or chlorpromazine (28).

Synthetic Cannabinoids

Research carried out from 2014 to 2015 shows that the same treatments were used as in previous years, i.e., benzodiazepines, most often lorazepam, to reduce seizures, agitation, and anxiety (29, 30).

Schep et al. (31) presents a case study of diazepam treatment of synthetic cannabinoids benzodiazepine poisoning. A 23-year-old man smoked a joint containing synthetic cannabinoids (trade name K2) for recreational purposes at home. After 6 h, he was suffering from tonic-clonic seizures with urinary incontinence and damage to his tongue. After 3 h, he took another, smaller dose

of the psychoactive substance. Vomiting started: he presented to the hospital with nausea, dry mouth and persistent vomiting. On admission, tests showed no neurological or cardiac aberrations. The patient was discharged, and after 3 h (4 h after taking the substance) he had a second seizure episode. The patient returned to the hospital. He received an intravenous infusion of saline (1,500 ml) and oral diazepam. The man was discharged home. In a later study using the LC-MS (liquid chromatography/mass spectroscopy) method, numerous synthetic cannabinoids were detected in the patient's body, i.e., BB-22, AM2233, PB-22, 5F-PB-22, and JWH-122 (31).

Orsini et al. (32) also mention the use of such benzodiazepines as midazolam in the case of a 41-year-old man who smoked a recreational drug under the trade name "K2" (a mixture of synthetic cannabinoids). After ingestion, the patient had acute hypoxic/hypercapnic respiratory failure caused by acute heart failure. In order to achieve sedation, propofol, fentanyl and midazolam were administered. Intravenous antimicrobial therapy consisting of piperacillin/tazobactam (3.375 g every 6 h) was also used. He was extubated on the 11th day of his stay in the Intensive Care Unit (32).

In order to resolve hallucinations, in previous years patients have been given antipsychotic drugs as mentioned, i.e., haloperidol, olanzapine, and quetiapine (33).

One example is the 27-year-old man described by Green and Kinzie (34). He was admitted to the hospital because he was experiencing hallucinations after smoking a cigarette with synthetic marijuana. The patient received a single dose of 10 g olanzapine to treat psychosis. The therapy was successful and the patient was discharged home (34).

If it is necessary to perform intubation in a patient with synthetic cannabinoids poisoning, and to remember to use non-depolarizing neuromuscular blockers, such as rocuronium (29).

In 2015, the idea appeared of using intravenous lipid emulsion therapy (ILE) in patients who show symptoms of acute synthetic cannabinoids poisoning. It was the only symptomatic treatment of bradycardia in these situations.

Clinical cases of men aged 15, 17, and 19 who took a preparation containing synthetic cannabinoids under the trade name "Bonzai," in which the ILE therapy was applied (20% lipid in the emulsion) was described by Aksel et al. (35). The first male presented with bradycardia and hypotension. An ILE bolus of 1.25 ml/kg was administered followed by an infusion of 0.50 ml/kg per minute over 60 min. Apart from ILE, no other medications were administered. After the infusion, the bradycardia resolved within 5 min. After a 24-h follow-up period, the patient was discharged home. Another patient presented with ventricular extrasystoles (VES). The patient was treated with intravenous bolus of ILE at a dose of 1.5 ml/kg, followed by an infusion of 0.25 ml/kg per minute over 60 min. On the fifth minute of the ILE infusion, it was observed that the VES rate decreased and the patient's general condition also improved. The patient was discharged after 24-h observation. In the third patient, the EKG showed sinus bradycardia. The ILE infusion therapy was used again, first as a 1.5 ml/kg bolus, then an infusion of 0.25 ml/kg per minute for 60 min. Bradycardia gradually began to resolve and completely resolved after the infusion was finished. The patient was discharged after 24-h observation (35).

Synthetic Opioids

In the case of opioid analogs, a similar therapy can be applied as for substances from this group that have been known for years, i.e., substitution treatment. Studies show that such treatment does not markedly affect the prevention or treatment of addiction itself. However, it controls the desire to consume drugs and the amount of side effects caused. The therapy consists in prescribing controlled amounts of longer-acting, but less euphoric, opioids. Currently, methadone is the most commonly used synthetic opioid for this purpose. It is effective in relieving the symptoms of opioid withdrawal and reducing the negative effects of illegal drug use. Individual variability in clinical responses to methadone and dosage requirements depends on several factors, including age, diet, metabolism, protein binding, drugs, genetic variants, and other substances taken (36).

Suboxone has been approved for use in Canada since 2007 and contains a combination of buprenorphine and naloxone in a 4:1 ratio. When used sublingually, only buprenorphine shows partial agonist effect, as naloxone cannot be sufficiently absorbed in this form. When administered parenterally, naloxone causes a withdrawal effect in addicted patients. Therefore, the role of this combination is to ultimately alleviate withdrawal symptoms while at the same time stopping intravenous drug use. The effects of Suboxone are less potent than of full opioid agonists, but it causes less physical dependence than other full agonists. It also has weaker dysphoric effects than methadone, which encourages patients to continue treatment. It also has a threshold effect, meaning that its effectiveness remains constant above a certain dose, thus helping to limit abuse (37).

Helander et al. (38) report cases of intoxication in three young men caused mainly by MT-45 (synthetic opioid). In all cases, the presence of other psychoactive substances was found. Treatment with different doses of naloxone was also applied in all three men. Each of the cases ended in the patient's death (38).

The literature from 2015 also describes the management of an overdose of a synthetic opioid, namely desomorphine, for which supportive care is the main treatment option. Naloxone is useful in treating both acute opioid intoxication and overdose. Symptoms of aggression and psychosis can be treated with sedatives (benzodiazepines, propofol) and antipsychotics [haloperidol or less common drugs such as quetiapine or ziprasidone (39).

Another substance used in substitution therapy is naltrexone, which blocks the euphoric effects of opioids. The initially used oral drug turned out to be ineffective after years, and therefore long-acting injections and subcutaneous implants began to be introduced to the market. However, Naltrexone reduces tolerance to opioids, which increases the risk of overdose if the patient returns to the addiction. According to observations conducted between 2000 and 2003 during the follow-up year, the percentage of deaths associated with the use of naltrexone as a treatment for opioid dependence was up to seven times higher than that of methadone. A fairly new and controversial approach is Heroin-assisted Therapy (HAT). It involves administering injections with

a controlled amount of diacetylmorphine, the active ingredient in heroin. However, studies show that HAT therapy turns out to be more effective than methadone treatment in terms of reducing consumption and increasing the intervals between the consumed doses of the substitute (40).

The 2C Family of Drugs

Tang et al. (41) describe two clinical cases of intoxication with NBOMe: a synthetic hallucinogen considered to be a derivative of the substituted phenylethylamine of the 2C-I family. The first patient, a 17-year-old man, was admitted to the hospital emergency department with symptoms of confusion, agitation and mild consciousness impairment. Immediately after admission, he developed convulsions and a sympathomimetic syndrome with high blood pressure, tachycardia, sweating, hyperthermia, and dilated pupils. A muscle relaxant was used and intubation was performed. To counteract acute sympathomimetic toxicity, the patient required high doses of intravenous fluids and high titrate doses of intravenous diazepam (17.5 mg in total). The patient's condition was controlled by infusions of midazolam (the maximum rate of 0.28 mg/kg/h) and of rucuronium (0.7 mg/kg/h). Cyproheptadine was given prophylactically as an antidote for possible serotonin syndrome. The patient regained full consciousness 12 h after admission to hospital, was discharged after 5 days, and fully recovered. The second patient was a 31-year-old Chinese citizen with a history of addiction who was admitted to a hospital emergency department with sympathomimetic symptoms: signs of agitation, hypertension, dilated pupils, hyperthermia, intense sweating, and moderate consciousness impairment. The patient developed rhabdomyolysis, decreased liver functions and impaired kidney function. The results returned to baseline after the treatment was applied. The patient was treated with intravenous fluids, intravenous lorazepam as a 2 mg bolus every 5 min, until his sympathomimetic symptoms subsided (12 mg in total). His body was cooled with bags of ice. He was given sodium bicarbonate to alkalize the urine. Despite the doctors' recommendations, he left the hospital at his own request after 3 days of hospitalization (41).

Amphetamine-Type Stimulants

Serotonin syndrome can be a side effect of taking amphetamine-type stimulants. Its mild form usually resolves spontaneously or requires only maintenance treatment, while in more severe cases, hospitalization is required. As a rule, agitation and tremors are eliminated with benzodiazepines. In a moderate case of serotonin syndrome, the development of excessively high temperature should be prevented, and in more severe cases, 5-HT2A receptor antagonists, e.g., cyproheptadine and chlopromazine, are used. Sedation and intubation are essential for critically ill patients (42).

Sedation and intubation were used in a patient who took an amphetamine derivative: 2,5-dimethoxy-4-chloroamphetamine (DOC), described by Burish et al. (43). An 18-year-old man presented with hallucinations and agitation which progressed to an epileptic seizure. The patient received 2.5 mg intranasal midazolam which stopped the seizures only briefly. The second administration of the same dosage had no effect. The patient received 2 mg of lorazepam which improved his tonic head movement. The patient was sedated and paralyzed with propofol and rucuronium for intubation. Sedation with propofol at 20 μg/min was continued, and in the next hour the drip was increased to 100 μg/min. As rhythmic toe twitching was observed, he received an additional 9 mg of lorazepam, 20 mg/kg fosphenytoin and 7 mg/h midazolam to the drip. At a later stage of treatment, the drip of midazolam was continued and the drip of propofol was weaned off. Leukocytosis and rhabdomyolysis improved with supportive care, especially with antiepileptic drugs and intravenous fluids. On the second day of his hospital stay, the patient was extubated and developed amnesia. His memory improved on the third day, although his reaction time was still slower (43).

Symptoms of amphetamine psychosis caused by chronic use of this type of substances resolve after the administration of antipsychotic drugs. The new generation olanzapine is of particular importance here due to the increased safety of use. However, these measures do not guarantee that psychosis will not recur (39).

Anderson et al. (44) presents a case of the treatment of schizophrenia relapse induced by the consumption of ethylphenidate and benzocaine. A 30-year-old man took a substance labeled as "el blanco" containing these two substances in liquid form: he mixed the powder with a cola drink. He had a relapse of schizophrenia. The patient's treatment was based on the use of clonazepam 0.5 mg four times a day, as well as haloperidol and lorazepam for acute behavioral and agitation disorders. In antipsychotic treatment, olanzapine was used at a dose of 10 mg twice daily, which was then changed to pipothiazine palmitate 50 mg every 4 weeks. Treatment with clozapine was initiated as his recovery was considered incomplete with previous treatment regimens. The patient responded well to clozapine (44).

A Vaccine for Drug Addiction

There are also very unusual methods of treating addictions in the literature that could be used for NPSs available on the market.

The idea was to covalently link addiction-inducing substances to immunoproteins via binding molecules. Scientists believe that the drug molecule itself is too small to trigger the immune response, but such a combination could trigger the production of antibodies that detect the molecule and seek to eliminate it from the body, which would significantly reduce its effects on the central nervous system. Such vaccines against morphine, nicotine, and cocaine have even entered the stage of clinical trials (45).

2016–2019

Synthetic Cathinones

According to the literature, it is still very difficult to define a universal method of treating intoxication with cathinones due to the large differences in action and the immense number of NPS's. As there is no specific treatment plan, therapy is symptomatic and supportive. Taking into account the similarity of cathinones to other stimulants, it is recommended to take similar steps in reducing the side effects. When cathinone-induced delirium is suspected, clinicians focus on controlling agitation and complications such as metabolic acidosis. If serotonin

syndrome occurs, benzodiazepines and/or cyproheptadine are recommended, just like in the studies published from 2014 to 2015.

As it follows from the publications released between 2010 and 2015, benzodiazepines are still administered orally or intravenously, e.g., diazepam (0.1–0.3 mg/kg body weight), in the case of over-excitation, hyperthermia, aggression, hallucinations or bradycardia and hypertension. Occasionally, higher doses of the drug can be used to achieve and/or maintain a sedative effect. Heart attacks and arrhythmias should be excluded with the use of electrocardiogram (12). Therapy aimed at controlling aggression and agitation still relies on the intranasal or intramuscular administration of midazolam or the intramuscular administration of lorazepam, which can also prevent seizures. As reported in previous years, if there are contraindications to the use of benzodiazepines (e.g., alcohol consumption), administration of propofol or antipsychotics (haloperidol, olanzapine, ziprasidone) should be considered, which may additionally prevent seizures and dysrhythmia. Furthermore, the literature shows that olanzapine is effective in controlling attacks of aggression. Clinicians do not recommend the use of antipsychotics for acute psychosis, owing to the reduction of the seizure threshold and the risk of extrapyramidal symptoms. As medical data show, there are currently no effective pharmacological treatments for synthetic cathinone addiction and withdrawal syndrome. For patients who regularly take synthetic cathinones, symptomatic treatment should be combined with psychotherapy and behavioral therapy (46–48).

Synthetic Cannabinoids

The data published in the medical reports show that there is still no specific antidote to intoxication with synthetic cannabinoids. Treatment is symptomatic and supportive. As mentioned earlier, between 2014 and 2015 research on the use of naltrexone in addiction therapy was initiated. It is still continued and, according to the latest literature, there are reports of positive preliminary results of studies with baclofen and naltrexone in the treatment of withdrawal syndrome (49). The chief supportive clinical procedures include intravenous administration of rehydration fluids, potassium, oxygen, and intubation and mechanical ventilation.

In their case series, Hill et al. (50) report a clinical case of a 57-year-old man who fell after consuming four to six cans of high-proof beer and smoking a preparation called "Old spice." At the time of admission to the hospital, he was severely hypothermic (31°C), with a pulse of 89/min and systolic blood pressure at 50 mmHg. His condition quickly improved after the administration of intravenous fluids. Blood tests showed mild acidosis and increased lactate levels. The presence of MDMB-CHMICA, 5FADB-PINACA, and AB-PINACA was detected in the patient's serum. The patient was discharged from the hospital 8 h after admission, at his request, against the doctors' recommendations (50).

As in previous years, also more recent literature reports indicate that in the case of central nervous system side effects, such as psychosis, hallucinations or agitation, it is recommended to administer benzodiazepines. Research demonstrates that midazolam is the fastest-acting of all benzodiazepines and antipsychotics. Clonazepam is recommended for the treatment of permanent visual impairment caused by synthetic cannabinoids. Coppola et al. (51) report the case of an 18-year-old man whose hallucinations and visual disturbances completely resolved only a few years after consuming a synthetic cannabinoid. The patient ingested the JWH-122 drug. Symptoms of a synthetic drug poisoning were similar to natural cannabinoids poisoning, with the exception of tachycardia and visual disorders. Acute intoxication symptoms disappeared within 3 h. Over the following days, the patient experienced hallucinations again, saw colorful, geometric forms, and presented with dissociative symptoms. The man was given 6 mg of clonazepam daily, which reduced the frequency and severity of his symptoms. For the next 3 years, the patient occasionally experienced some side effects of acute intoxication, which completely resolved 4 years after the consumption of JWH-122 (51).

With regard to antipsychotics, it should be remembered that, according to the literature, they can prolong the QT interval and interfere with the body's ability to cool itself. Clinical studies indicate that the occasional use of an antipsychotic such as haloperidol controls agitation and psychosis when high doses of benzodiazepines are administered. In addition, the combination of haloperidol and benzodiazepines helps to effectively soothe the patient (52, 53).

Bonaccorso et al. (54) describe the case of a 32-year-old woman with diagnosed schizoaffective disorder, whose condition was stabilized after administering 30 mg of aripiprazole daily and 800 mg of lithium carbonate nightly. The urine toxicology test was negative. After 4 weeks, the patient's condition deteriorated significantly: she displayed a delusional mood and complex delusions of grandeur and persecution. She became physically and verbally aggressive and developed sexual disinhibition, and a repeat urine toxicity test was positive for THC and synthetic cannabinoids. An intensive pharmacological treatment plan was implemented with the administration of 10 mg of haloperidol and 8 mg of clonazepam daily. The patient remained in poor condition for 72 h. After 10 days, the urine drug test was consistently positive for synthetic cannabinoids, confirming the suspicion that the patient had been using drugs in the ward. After the suspension of her permit and more stringent searches, the woman's condition improved significantly. Another case concerned a 20-year-old man who was diagnosed with the first psychotic episode after taking a multi-component substance. The patient was given 50 mg haloperidol decanoate and 10 mg haloperidol per night. He developed over-excitation, sexual disinhibition, over-aggression, and severe thinking disorders and the urine drug test was positive for synthetic cannabinoids. The patient was therefore treated with 9.75 mg of aripiprazole three times a day and 6 mg clonazepam daily in divided doses. Within 72 h, his condition improved (54).

Patients with symptoms of poisoning are also often given antiemetics such as diphenhydramine or Ondansetron. The use of antidepressants has also been observed. If neuromuscular transmission disorders occur, antiepileptic and anticonvulsant drugs are administered, i.e., Levetiracetam, phenytoin, and valproic acid. Sometimes hypnotics (hydroxyzine, etomidate,

zopicon) and anesthetics (vecuronium, lidocaine) as well as pressure-lowering drugs (nitroglycerin, metoprolol, and clonidine) or sympathomimetics such as adrenaline, noradrenaline or phenylephrine are used (55).

In their case study, Hill et al. present the case of a 23-year-old man with a history of recreational drug consumption, including synthetic cannabinoids, marijuana and diazepam. The patient was additionally taking prescription quetiapine. At the time of admission, he exhibited abnormal behavior: hallucinations, instability, sweating, agitation, aggression, insomnia, and a tendency for self-harm (hitting the head against a wall). He was very aggressive in the hospital and refused to cooperate. He had fever, tachycardia, dilated pupils and mild metabolic acidosis. He received 3 mg of lorazepam intravenously. Afterwards, he was intubated and mechanically ventilated. The urine test was positive for benzodiazepines only. In order to maintain normal blood pressure, the patient was given phenylephrine followed by noradrenaline. The day after admission, he was extubated and disconnected from mechanical ventilation. The patient remained confused and aggressive for several consecutive days; he required high doses of benzodiazepines and haloperidol. He was discharged from the hospital after 9 days elapsed from admission. He confirmed the ingestion of a substance called "Vertex." MDMB-CHMICA and methiopropamine were found in his serum (50).

The Psychoactive Surveillance Consortium and Analysis Network is a network of academic emergency medical services, toxicologists, and pharmacologists that collects clinical data paired with biological samples to identify and improve treatment methods for NPS poisoning. Brandehoff et al. (56) provide data on eight reported use cases of "Black Mamba." The authors describe cases of intoxication in four women and four men with a median age of 28, who experienced acute symptoms such as agitation, delirium, chest pain, and heart rhythm disturbances visible in the electrocardiogram. One patient with a prior seizure also experienced a tonic-clonic seizure. Almost all patients had high blood pressure, only two of them developed tachycardia and two patients also developed hypokalemia. The patients received diazepam or lorazepam for sedation. One patient was also given haloperidol and diphenhydramine in addition to lorazepam. In four of the subjects, the agitation subsided. Some patients also received ondansetron for nausea. A 25-year-old woman in whose serum no other drugs such as cocaine or methamphetamine were found, developed severe agitation and aggression. Her blood pressure was 140,106 mmHg and she also developed tachycardia. The woman was administered 2 mg of lorazepam, 5 mg of haloperidol and 50 mg of diphenhydramine. The patient was discharged after 10 h of observation in the emergency department. Another case was a 23-year-old woman who complained of chest pain. An electrocardiogram showed T wave inversion, nausea and diarrhea. Her blood pressure was 148/100 mmHg. The patient received 15 mg of ketorolac, 4 mg of ondansentron and 1 g of acetaminophen, as well as 30 ml of simethicone and 15 ml of 2% viscous lidocaine. Having been observed for 9 h in the emergency department, she was discharged home. A 27-year-old man who was taking marijuana concurrently with a synthetic cannabinoid complained of bilateral palpitations, numbness in his hands and vomiting; his blood pressure was 155/85 mmHg. The patient was administered 1 mg of lorazepam twice, as well as 1l mg of saline solution. He was discharged from the hospital after 3 h (56).

The literature also shows that regardless of whether the patient has experienced psychosis before, the use of atypical antipsychotics, such as ziprasidone, olanzapine or zuclopenthixol, may be effective. Bonaccorso et al. (54) describe the use of zuclopenthixol in the pharmacotherapy of a 39-year-old man with a long history of bipolar disorder and abuse of many psychoactive substances (alcohol, cocaine, MDMA, marijuana and legal highs). During his admission at Highgate Mental Health Center, the patient was highly agitated and aggressive. The urine drug toxicity was negative. He was administered 400 mg of Ablify Depot, but the drug showed little therapeutic efficacy. The man was diagnosed with a manic episode of bipolar disorder. Therapy with Ablify was discontinued, zuclopenthixol was started and the medications previously taken by the patient were continued. During the patient's 3-week stay at the center, urine drug testing was positive for synthetic cannabinoids, benzodiazepines and THC, and the patient showed poor compliance with treatment. After his permit was suspended, the urine drug test was negative 1 week later and the episodes of aggressive behavior resolved. Therapy with 300 mg of zuclopenthixol weekly and 1,200 mg of sodium valproate was satisfactory (54).

The side effects of the medications administered may be more pronounced in patients who already suffer from psychosis, agitation or anxiety. The emerging akathisia, which is one of the side effects of these drugs, may increase the already existing anxiety and may be confused with the stimulation resulting from the use of synthetic cannabinoids, which may lead to incorrect pharmacotherapy. The literature on the subject draws attention to the fact that first-generation antipsychotics administered with or without anticholinergics, or with benzodiazepines, are superior to benzodiazepine monotherapy in patients with acute psychotic symptoms such as delusions, hallucinations and agitation (57). Sweet et al. (58) report a case of a 47-year-old man who ingested a synthetic cannabinoid "King Kong," and then was brought by the police to the emergency department with high fever, tachycardia, accelerated breathing and blood pressure of 153/103 mm Hg. The man was agitated, had delusions and hallucinations. He was given 1 olanzapine tablet orally, but it was not possible to calm him down, he was still aggressive toward the medical staff. For this reason, the patient was given 10 mg of haloperidol intramuscularly together with 2 mg of lorazepam and 50 mg of diphenhydramine. The next day he was calm and able to take part in a medical interview. He admitted that he had smoked King Kong before and was involuntarily hospitalized each time (58).

Bonaccorso et al. (54) report the case of a 28-year-old man with a 4-year-long psychosis with frequent relapses, who was treated with risperidone at a dosage of 37.5 mg every 2 weeks + olanzapine 10 mg daily + pregabalin 100 mg daily. After the patient was transferred to the intensive care unit (PICU), previous treatment was continued. The patient's condition was stable and the drug test was negative. One week after the patient's

transfer, his condition deteriorated: he developed persecutory delusions and became verbally and physically aggressive. After the patient was transferred, a repeated toxicology test was positive for synthetic cannabinoids. The olanzapine dosage was increased to 20 mg and clonazepam to 8 mg, which improved the patient's condition within 24 h (54).

As for the circulatory system, in the case of chest pain, specialists recommend excluding myocardial ischemia and arrhythmias using an electrocardiogram. As indicated in the literature, bradycardia may require external cardiac stimulation or administration of atropine. Medical data indicate that tachycardia should be treated with benzodiazepines and intravenous fluids (59). For cardiac ischemia, administration of antiplatelet drugs such as clopidogrel, aspirin or nitroglycerin is recommended (60).

There is clinical evidence that an overdose of synthetic cannabinoids can directly or indirectly lead to death. A systematic review from 2016 found that out of 4,000 cases, at least 26 were fatal, and death was associated with the consumption of synthetic cannabinoids (12). Due to the short duration of the effects of these substances, hospitalization usually lasts several hours (42, 50).

In reports from 2017, we can find an example of a multicenter cohort study focused on the analysis of patients who take synthetic cannabinoids. The study was based on cases from the ToxIC Case Registry. This register is kept by specialists in their field and therefore it should be assumed that it constitutes a reliable database. The study in question covers 353 cases of synthetic cannabinoids poisoning. The median age among patients was 25, most of whom— 84%—were men. As many as 61% of the patients were referred to the emergency room, 15% were admitted to the hospital room, and 24% to the ICU (61).

According to the study, the most common symptoms of SC poisoning in patients are:

- agitation, delirium and psychosis in 41% of patients
- coma or depression of the central nervous system in 24.1% of patients
- epileptic seizures in 17% of patients.
- tachycardia as 12.5% of patients had a heart rate above 140 beats per minute
- hallucinations in 7.1% of patients
- bradycardia as 5.7% of patients had a heart rate below 50 beats per minute.

Moreover, symptoms such as hypotension, hyperthermia, rhabdomyolysis and kidney damage occurred. As far as pharmacological treatment is concerned, the most frequently used drug therapy was benzodiazepines (37%), followed by antipsychotics (10%). About 9% of patients were medicated with both benzodiazepines and antipsychotics. Naloxone was administered in 3.4% of cases, while 2.5% of subjects received anticonvulsant treatment and 2.3% received neuromuscular blockers and mechanical ventilation. Only three out of 15 severely hypotensive patients required vasopressors. One patient died (61).

There is also data on the possibility of treating cannabis dependence with the use of preparations containing tetrahydrocannabinol, gabapentin or N-acetylcysteine, but there are no studies confirming their effectiveness in the treatment of addiction to synthetic cannabinoids (57).

Synthetic Opioids

It is generally recognized that the real antidote only exists for cases of opioid poisoning. The literature clearly indicates that in opioid poisoning, the most important course of action is to inhibit respiratory depression with the μ-naloxone opioid receptor antagonist (62).

Due to the ease of overdose and the very fast action of the opioid, data also suggest that appropriate treatment procedures should be implemented as soon as possible. If an overdose is suspected, treatment should be initiated when the respiratory rate is <12 per minute and the oxygen saturation is <90%. Initially, oxygen should be given together with mechanical ventilation (if necessary): these procedures are designed to open the airway. The next step is the administration of an opioid antagonist to reverse respiratory failure (36). Naloxone can be administered by any route: intravenous, intramuscular, intranasal, subcutaneous, intratracheal, inhalation, and sublingual. Orally administered naloxone undergoes first-pass metabolism, which is associated with its low bioavailability, therefore the parenteral route is chosen much more often. Naloxone administered intravenously works as early as after 30 s. Intranasal administration is also gaining more and more favor, due to the ease of application and the reduced risk of needle stick injuries to medical personnel. There is no specific dosage recommended for respiratory depression. The dosage used depends on the type of opioid overdose, the patient's weight and the substance amount taken, and it may be necessary to administer naloxone several times at intervals (53). According to the literature, the initial dose for children is 0.1 mg/kg (35). In the case of out-of-hospital administration, it is assumed that 400 μg of naloxone should be intravenously injected initially and constantly continued at a dose of 400 μg every 2–3 min, until vital functions are restored or the dosage should be stepped up to 2 × 0.8 mg. The maximum allowable dose of naloxone in this situation is 2 mg. When administered in the hospital, intravenous starting dose is 400 μg, if there is no response within 60 s, then 800 μg. If there is still no response, another 800 μg dose should be given after 60 s. If there is still no effect, a final dose of 2 mg is administered (in exceptional cases, in the absence of a satisfactory effect, a dose of 4 mg is used (42).

Wilde et al. report a case of a 25-year-old male after intranasal intake of cyclopropylfentanyl in 2019. The man snorted a preparation that was supposed to contain fentanyl. Ten minutes later, he developed nausea, sweating and shortness of breath, followed by coma and respiratory failure. On arrival, the rescuers gave the patient oxygen and 0.4 mg of naloxone. Another dose of 0.4 mg of naloxone was required to restore respiratory function. Upon admission to the hospital, the patient was in a coma, with severely constricted pupils and a respiratory rate of 14/min. and additionally, hypothermia (34.9°C) was noted. The patient was observed in the intensive care unit and oxygen was administered intranasally. Within 12 consecutive hours, he experienced episodes of apnea with oxygen desaturation. After

1 day under observation, he was discharged from the hospital. Immunoassays showed positive results for cocaine, cannabinoids, LSD and cyclopropylfentanyl consumption (63).

According to the data from the Chicago Emergency Department, during the deadly wave of fentanyl abuse between 2005 and 2006, the standard dose of 0.4 mg naloxone was effective in only 15% of cases, and the mean dose of naloxone required to save lives was 3.36 mg. Initial therapy should be targeted at restoring respiratory function, but should not be focused on the patient regaining consciousness. The length of hospitalization in an opioid overdose is still under discussion. It is assumed that the patient should be observed for at least 2 h after respiratory function is restored and consciousness is regained since the duration of action of naloxone is between 30 and 120 min. After this time, re-administration of the drug may be required if large amounts of the narcotic substance have been ingested (64).

In the case of MT-45 poisoning, traditional doses of naloxone are also used. In a group of five people who were intoxicated with U-47700 and MT-45, two subjects did not require naloxone, one person improved after administering a dose of 0.4 mg, two cases required 2 mg, and in one person had to have two doses of 2 mg administered (52). However, administration of naloxone in the event of intoxication with synthetic opioids is not always recommended.

Domanski et al. (65) describe a clinical case of a 26-year-old man and a 24-year-old woman who, according to clinical findings, consumed alcohol and alprazolam in combination with a powder that was supposed to be synthetic cocaine, but turned out to be a new U-47700 opioid. Three hours after intake, the man was found unconscious with severe breathing problems, cyanosis and oxygen saturation at the level of 50%. At first he was intubated and placed in an orthopedic collar. He was given ketamine, lorazepam and rocuronium during intubation. The doctors decided not to administer naloxone because according to available information he had ingested alcohol concomitantly with alprazolam. The patient had pinpoint pupils, heart rate of 125 beats/min, blood pressure of 150/63 mmHg, and 14 bpm. Initially, oxygen saturation was 84%, but as a result of artificial ventilation, it quickly increased to 100%. Laboratory tests showed mild acute kidney injury (creatinine 1.5 mmol/L) and elevated lactate 4.4 mmol/L, which were stabilized after intravenous fluid administration. The ECG revealed a sinus tachycardia of 125 bpm with normal intervals and non-specific ST segment changes. The patient was referred to the intensive care unit, where he was given propofol. He was discharged from the hospital on his request after 3 days of hospitalization (65).

As in previous years, the literature data on patients who overdosed on the U-47700 synthetic opioid indicate the effectiveness of 5 mg diazepam, potassium and leveticeram administered in patients with a depressive mental state. In the case of an overly agitated patient with chest pain, it is advisable to administer saline, 25 mg of diazepam, 15 mg of ketorlac, lisinopril, and 5/325 mg of hydrocodone. Two mg of lorazepam, 5 mg of haloperidol, and 50 mg of diphenhydramine were given to a patient showing agitation and aggressive behavior (66).

According to the case reports, constipation in such patients can be treated with pantoprazole. For withdrawal symptoms, diazepam, pyritamide, clonidine, clomethiazole, and pipamperon are used (67).

The most common therapy is treatment with opioid agonists (AOT). As it was done from 2014 to 2015, methadone and buprenforine are the most commonly used drugs (36, 53).

The 2C Family of Drugs

There is no doubt in the literature that, as with other NPS, there is no specific antidote against NBOMEs. As in the reports from 2014 to 2015, in order sedate the patient, reduce aggression, tremors and convulsions, clinicians recommend benzodiazepines, especially lorazepam or midazolam administered intravenously. Sometimes catecholamines (e.g., noradrenaline, dopamine) are prescribed to control bradycardia. As indicated in the published studies, antiarrhythmic drugs (B-blockers, amiodarone) should be administered in the case of supraventricular tachycardia, paired with antipyretic drugs or mechanical cooling if hyperthermia occurs. Blood transfusions may be required in patients with hematological disorders. Furthermore, in the event of rhabdomyolysis, which can lead to serious complications, the literature indicates that skeletal muscles relaxants (e.g., midazolam, rocuronium) are used and fluids are administered at the same time to maintain the urine flow at 200–300 ml/h. Moreover, urine should be alkalized to prevent hyperkalemia and hypocalcaemia and the deposition of myoglobin in the renal ducts (68).

Zygowiec et al. (69) report a case of a 27-year-old man with symptoms of 25C-NBOMe poisoning. The man was brought to the emergency department by the police due to his aggressive behavior. The patient's initial blood pressure was 139/90 mmHg, his heart rate was 146 bpm, and his respiration rate was 28 bpm. He was given 2 liters of 0.9% saline via an intravenous solution. The case was consulted with specialists from the Michigan Poison Control Center. They recommended intravenous fluids, cardiopulmonary monitoring, and administration of benzodiazepines as needed. The patient was initially administered 2 mg of lorazepam and 5 mg of haloperidol lactate. The next day, the man escaped from the hospital, but after about 3 weeks, he returned to the emergency department with symptoms of intoxication with 25I-NBOMe. Upon admission to the ward, the patient was very agitated, his heart rate was 120 beats per minute, his blood pressure was 153/119 mm Hg, and his respiratory rate was 22 breaths/min. The patient was intravenously treated with 4 mg of lorazepam and 1 L of 0.9% saline. The dosage of benzodiazepines was gradually increased. Within 4.5 h, he received a total of 34 mg of lorazepam. Despite high doses of lorazepam, the patient's vital signs remained stable and he did not require airway support. He was admitted to hospital for further psychiatric monitoring and evaluation. The psychiatrist recommended that he be transferred to an addiction center. The patient, however, refused and requested to be discharged from hospital 48 h after admission (69).

PCP—Phencyclidine Derivatives

According to the literature, due to the lack of specific treatment methods, the treatment of PCP poisoning is symptomatic.

Some of the patients require intensive care. As the reports show, the main treatment regimens include administration of benzodiazepines (midazolam) and of intravenous fluid (NaCl solution). Berar et al. (70) describe a case of a 17-year-old male who ingested 3-McO-PCP. The man with a history of drug consumption was admitted to the hospital with severe agitation and altered states of consciousness. Afterwards, the patient experienced nystagmus with dysarthria. His systolic/diastolic pressure was 158/131 mmHg, his HR was 100 beats/min, and his oxygen saturation was 99%. Laboratory tests showed hyperlactatemia (2.6 mmol/L), elevated creatine kinase levels (CK 290IU/L) and respiratory acidosis. Due to hypertonia, the patient was given 1 mg of midazolam and 1500 ml of saline solution. He was referred to the intensive care unit, where, in order to control anxiety and agitation, he received antipsychotic drugs: loxapine and cyamemazine. Additionally, the intravenous administration of electrolytes 3,000 ml/24h was continued. Within 24 h, neurological disorders, blood pressure and heart rate returned to baseline. The following day, the patient only experienced the effects of moderate sedation. The interview showed that the man consumed about 200 mg of a substance called 3-MeO-PCP. He was referred to a psychiatric hospital, from which he was discharged after a few days. One week later he was hospitalized again after ingesting 50 mg of the same substance. On admission to the hospital, his vital signs were as follows: blood pressure 150/104 mmHg, HR 105 bpm, SpO2 96%. Mild psychomotor disorders and dysarthria were observed. The patient was discharged from the hospital after 12-h observation (70).

Zidkova et al. (71) report two cases of 3-methoxyphencyclidine poisoning. A 37-year-old man was admitted to the emergency department 2 h after consuming the drug with alcohol. The patient presented with symptoms such as high blood pressure (170/100 mm) and tachycardia (120/min). He also developed psychosis, altered neurological function, and increased muscle tone. The patient underwent gastric lavage, was given activated charcoal, macrogol and prokinetic drugs: metoclopramide and synostigmine. The patient developed hypophosphatemia (0.55 mmol/L), but the kidney and liver function was normal. Within hours, he regained full consciousness, and showed no neurological or hemodynamic symptoms. He reported complete amnesia from the period of intoxication. Having been observed for 24 h in the emergency department, the patient was discharged home (71).

Dunlop et al. (72) describe a clinical case of a 56-year-old male who ingested 3-OH-PCP and hexene. A patient with a history of a heart attack and one stent in a coronary artery was regularly taking clopidogrel, simvastatin, atenolol, and lansoprazole. He was found at home. When the paramedics arrived, he was drowsy, sweaty, and hot, his pupils were rigid and insensitive. His vital signs were as follows: RR 40 breaths/min, body temperature 39.9°C. In an interview, he admitted that he had ingested a substance called hexene. He was hallucinating and sweating. Within 4 h, the patient was administered intravenously 4.3 l of infusion fluids in crystalline form, which had previously been cooled to 2–6°C. Additionally, the patient received 7.5 mg of diazepam intravenously within 2 h. His body temperature dropped to 37.7°C after 1 h of treatment. On the second day of hospitalization, the patient's clinical condition improved. His history showed that he had been using N-ethylhexedrone by nasal insufflation and rectal injection for 3 months. He admitted that he developed a psychological addiction to it. The night before admission to the hospital, he took 100 mg of hexene, but did not experience any negative effects. In the morning he felt as if he had an upper respiratory tract infection, so he took a cough syrup of unknown composition and about 10 mg of 3-OH-PCP. He did not remember what happened until the second day of his stay in the hospital. The patient developed rhabdomyolysis with moderately severe kidney damage. He was discharged from the hospital after 25 h (72).

Additionally, it has been proven that in the case of phencyclidine derivatives poisoning, flumazenil and naloxone do not show effective action. There are reports in the literature about the beneficial effects of Noopept, but they have not yet been scientifically proven. Hemodialysis and peritoneal dialysis seem to be ineffective in PCP poisoning (70, 72).

Designer Benzodiazepines

Designer benzodiazepines are a group of substances whose pharmacotherapy case reports have only recently appeared in the literature. The most common therapeutic steps include intravenous fluid administration, naloxone, oxygen, other benzodiazepines, and flumazenil. Additionally, intubation, mechanical ventilation and administration of antiemetics are sometimes used. In most cases, there is a reduction in side effects and treatment is found to be effective. Many patients end up in intensive care units, and some of them are referred to psychiatric centers. Deaths are very rare. The mean hospitalization time and the mean duration of drug-related adverse events are <24 h. In extreme cases, the effects may last up to 1 month. Flumazenil is a commonly reported benzodiazepine antidote in studies. It is an antagonist of benzodiazepine receptors. It shows weak internal action on GABA-a receptors. According to the literature, it is used to reverse sedation and to prevent respiratory depression caused by benzodiazepine consumption (73, 74).

Gummin et al. (75) report a fatal clinical case of a 24-year-old man who ingested flubromazolam. The man was found unconscious with a half empty drug wrapper. He was intubated en route to the hospital. The medical interview showed schizophrenia and abuse of alcohol and other substances. Additionally, the patient was taking medications such as risperidone, alprazolam, zolpidem, popranolol, atomoxetine, disulfiram, lithium, and clozapine. Benzodiazepine immunoassays were positive. On day six, the patient developed fever (38.6°C) and was treated with meropenem and fluconazole. On day 12, he was transferred to a specialist hospital. On day 15, tracheostomy and percutaneous endoscopic gastrostomy were performed. Additionally, leviracetam was included in the treatment. The patient received scopolamine combined with albuterol and ipratropium by nebulization. On day 19 the patient was insensitive to pain stimuli and his pupils were dilated and non-reactive. On day 20, as a result of non-response to treatment and deterioration of his condition, flumazenil was administered, but without the expected improvement. On the 21st day, he was

transported to a hospice, where on the 30th day he died. Autopsy revealed that the cause of death was a complication of drug overdose (75).

Statistical Analysis

The statistical analysis was carried out using the IBM SPSS Statistics 25 package. The chi-square test was used to analyze whether the compared groups of people were equinumerous and to check whether there was a statistically significant relationship between the nominal variables. Logistic regression was applied to determine whether consumption of the most frequently used NPS was a statistically significant predictor of the occurrence of characteristic clinical symptoms and death. Spearman's correlation was used to analyze whether there was a statistically significant relationship between the publication year for the case reports and the total number of NPS used.

RESULTS

Clinical Characteristics

The study included 51 NPS case reports written between 2010 and 2019 (**Table 1**).

Most case reports were published in 2014 (**Figure 1**).

Men and people aged 21 to 30 were the most numerous groups. Synthetic cannabinoids and cathinones were the most commonly consumed NPS. Moreover, 62.7% of the patients described took benzodiazepines and most of them received only this group of medications, followed by those who were administered benzodiazepines combined with neuroleptics and benzodiazepines combined with muscle relaxants. The most common clinical symptoms were nervousness and confusion (**Table 2**).

The results of the logistic regression analysis concerning the occurrence of the most common clinical symptoms associated with the use of NPS, such as tachycardia, nervousness, hallucinations, seizures and disorientation are presented below. Of the individual NPS, synthetic cathinones and cannabinoids ($n > 10$ patients) were included in the analysis. Taking synthetic cathinones and, to a slightly greater extent, cannabinoids evokes nervousness in patients. It is also noteworthy that synthetic cathinones, unlike synthetic cannabinoids, have a statistically significant influence on the occurrence of confusion in patients (**Table 3**). Other NPS were not included in the analysis as they were characterized by a low number.

NPS and Applied Treatment

Figure 2 shows the medications used in patients taking the most common NPS, that is, synthetic cathinones, cannabinoids, and opioids.

Individuals who were administered the remaining medications listed in **Table 1** used mainly synthetic cathinones or cannabinoids. As for amphetamine-like stimulants, one person received benzodiazepines with opioids. One person who took phencyclidine derivatives was given benzodiazepines with antipsychotics. Moreover, benzodiazepines with muscle relaxants were prescribed to patients taking various types of NPS.

NPS-Related Fatalities

Five of the 51 patients died. They were all men. Three of them had taken the piperazine derivative MT-45. Each of them combined MT-45 with other psychoactive substances. In the case of the first patient, this was phencyclidine and 3-methoxyphencyclidine. The second patient combined MT-45 with benzofurans, flubromazepam, pyrazolam, and alpha-pyrrolidinepentiophenone. The third man combined MT-45 with 3-methylmethcathinone and pyrazolam. Subsequent deaths in the group of patients studied concerned one patient taking 3-methylmethcathinone, 5- (2-Aminopropyl)benzofuran and alcohol, as well as one person after they consumed flubromazolam, a psychoactive substance from the designer benzodiazepines group.

In the group of patients taking MT-45, loss of consciousness, low oxygen saturation and visual impairment occurred. Psychomotor agitation, increased heart rate, convulsions and elevated temperature were observed in the patient taking 3-MMC. Death resulted when a patient took an overdose of flubromazolam. In addition to fever, the patient suffered from brain damage due to hypoxia.

It is noteworthy that three of the five patients taking MT-45 with other psychoactive substances received the opioid drug naloxone. In the patient taking 3-MMC with 5-APB and ethanol, the treatment consisted of administering diazepam, midazolam, adrenaline, and atropine. For the patient taking flubrazolam, the applied treatment consisted of administering flumazenil, as well as other medications such as meropenem, fluconazole (without improvement) and, from the 15th day of hospitalization, levitracetam and scopolamine with albuterol/ipratropium bromide.

Due to the growing problem of polypharmacotherapy in medical patients in recent years, it was decided to additionally investigate this problem in the group of 51 patients taking NPS. In this study, a statistically significant relationship was observed between the year of the published case reports on NPS intake and the total number of medications used. The later the time period, the more medications the patients were administered, $r = -0.32$; $p = 0.02$ (Odds ratio = 3.12; 95% CI 0.92–10.58). The significant relationship between the years of research and the number of drugs taken, i.e., higher than 2 is the confirmation of the obtained result, Vcramer = 0.42; $p = 0.003$.

The number of NPS taken in total does not show a statistically significant relationship with the study period, $r = 0.09$; $p = 0.53$. With each passing time period (**Figure 3**), the median number of medications taken by the studied group of patients increased by one.

The result obtained is confirmed by the statistically significant relationship between the type of substance taken and the total number of medications prescribed (**Table 4**). With the emergence of newer and newer psychoactive substances, or in other words, as time went on, patients took more medications.

DISCUSSION

Clinical Characteristics

Of the analyzed cases, the largest groups included men and people aged 21 to 30. This is confirmed by scientific data

TABLE 1 | Case reports on the use of various types of new psychoactive substances (NPS) published between 2010 and 2019.

References	New psychoactive substance	Sex	Age	The effect associated with the intake of NPS	Treatment method	The effect of pharmacotherapy
(14)	Mephedrone	Male	22	Tachycardia, diaphoresis, hypertonia, hyperreflexia, clonus	Intravenous fluids, diazepam	Fifteen hours after admission, he was discharged from hospital after his neurological symptoms subsided.
(76)	"Spice"	7 men	13-27	Confusion, convulsions, daze, nervousness	Benzodiazepines	–
(8)	"Bath salt" Mephedrone	Male	–	Hyperactivity, insomnia, anger, anxiety, hallucinations	Risperidone 0.5 mg	After 2 days of therapy, the symptoms of paranoia subsided and the patient was discharged home after 5 days.
(8)	"Bath salt" Mephedrone	Female	–	Anorexia, anxiety, insomnia, hallucinations	Risperidone 0.5 mg	After 3 days of therapy, anxiety and behavioural withdrawal subsided. After 2 months, the patient complained about memory loss when taking mephedrone.
(8)	"Bath salt" Mephedrone	Male	–	Hyperactivity, insomnia, visual and auditory hallucinations	Haloperidol 1 mg	After 3 days, the patient no longer suffered from hallucinations and hyperactivity. The patient's friend pointed to his memory distortion when taking mephedrone.
(6)	MDPV "Powdered rush"	Female	27	Tachycardia, diaphoresis, anxiety, psychosis	Risperidone 0.5 mg	The patient's condition stabilised the next day after taking the medicine.
(17)	"Spice" (JWH-018)	Male	25	Dilated pupils, uncontrolled movements, no reaction to external stimuli, tachycardia	Lorazepam 4 mg	Three hours after taking the medicine, tachycardia subsided and the patient's condition improved.
(17)	JWH-018, JWH-073 "Spice"	Male	21	Confusion, uncontrolled movements of the lower extremities, high blood pressure, low heart rate, respiratory disorders; the patient was intubated	Haloperidol 5 mg	The next morning, the patient was extubated, 24 h after admission he was discharged from the hospital.
(18)	"Funky monkey Spice"	Male	24	Erectile dysfunction, tonic-clonic seizure with urinary incontinence; abnormalities were found during magnetic resonance imagining (MRI)	Hydrocodone	Thirteen days after taking the medicine, the MRI examination was performed again, all abnormalities resolved.
(18)	"Black mamba Spice"	Female	36	Epileptic seizure, intubated	Lorazepam, etomidate, vekuronium, propofol, levetiracetam, phenytoin	Twelve hours after taking the medicines, the patient was extubated, no further seizures.
(77)	"Spice" THC, JWH-018, JWH-073	Female	22	Confusion, anxiety, tremor, palpitations	–	The patient was calmed down and observed for an hour, then released home.
(77)	"Spice" THC, JWH-018, JWH-073	Female	20	Confusion, anxiety, increased pulse	–	The patient refused to undergo laboratory tests. She left the hospital in good condition.
(15)	"Bath salt" Mephedrone	Male	32	Tachycardia, hallucinations, premature ventricular contractions	Lorazepam 6 mg haloperidol 5 mg	The patient gradually became calmer, but he still had impaired consciousness and orientation. Thirty-five hours after taking EMS, the patient was still irritable, but his mental condition improved significantly. Over the next 24 h, the patient's condition improved, he was discharged from the hospital after all symptoms disappeared.

(Continued)

TABLE 1 | Continued

References	New psychoactive substance	Sex	Age	The effect associated with the intake of NPS	Treatment method	The effect of pharmacotherapy
(15)	"Bath salt" Mephedrone	Male	26	Auditory hallucinations, a sense of detachment from reality, paranoia, suicidal thoughts	Lorazepam 5 mg risperidol 2 × 0.5 mg	Ninety-six hours after taking the medicines, he was discharged from the hospital. The patient was conscious, hallucinations subsided.
(76)	K2	Male	17	Aggression, convulsions, drowsiness, daze	Naloxone 2 mg	–
(13)	Cathinone	Male	23	Depression	Bupropion, a dose gradually increased to 450 mg daily	After 4 weeks of using bupropion at a dose of 300 mg/day, the patient reported a partial improvement in mood and a decrease in thirst for cathinones. He used bupropionin at a dose of 450 mg/day for the next 4 weeks, after which the patient reported complete abstinence and a significant improvement in mood.
(12)	"Bath salt"	Female	26	Suspiciousness, hallucinations, social withdrawal	Haloperidol and risperidol (no improvement) 120 mg of lurasidone overnight (minimal improvement) 40 mg of citalopram 300 mg of trazodon overnight Electroconvulsive treatment was also used.	After electroconvulsive treatment, the number of hallucinations decreased, mood improved and social anxiety decreased. After 8 months of treatment, the patient occasionally had hallucinations, but she no longer suffered from mood disorders.
(10)	Mephedrone, MDPV, benzocaine, caffeine, lidocaine, procaine ("Cristallus")	Male	22	Tachycardia, daze, aggression, significant increase in troponin, creatine kinase and creatinine levels	Lorazepam 2 mg	The levels of troponin and creatinine decreased, the level of creatinine kinase increased, but the patient did not complain of muscle pain.
(16)	"Bath salts"	Male	36	Paranoia, anxiety, hallucinations, chaotic speech, aggression, dilated pupils, flushed skin, diaphoresis, high pressure, uncontrolled movements (waving, jerking), fast heart rate	Midazolam, lorazepam, etomidate, rocuronium, sodium thiosulfate	No improvement after midazolam and lorazepam. The patient was intubated and received etomidate and rocuronium. Poisoning with cyanide or poisonous alcohol was suspected, and sodium thiosulfate and fomepizole were administered for this purpose.
(20)	JWH-018, JWH-073, AM-2201	Male	30	Abdominal pain, nausea, vomiting	Ondansetron, promethazine	After receiving fluids and ondasetron, the patient's condition improved. He was discharged from the hospital, but only after 2 weeks of sobriety did all symptoms disappear.
(9)	"Bath salts"	Male	15	Stimulation, psychotic symptoms, paranoia (the patient barricaded himself at home), periods of psychomotor impairment	Olanzapine 5 mg daily, then increased to 7.5 mg lorazepam 0.5 mg twice daily	Symptoms of paranoia subsided after 3 days. After returning home, the patient took 7.5 mg of olanzapine daily and 0.5 mg of lorazepam twice daily.
(24)	Mephedrone EDDP	Male	Newborn baby	Nervousness and irritability, high scream, increased muscular tension in the extremities, increased tendon reflexes	Phenobarbital 20 mg/kg once intramuscularly, then 10 mg/kg daily orally	After 12 days of phenobarbital treatment, the symptoms improved. The infant was discharged after 15 days weighing 2,566 g and being in good condition.
(41)	25B-NBOMe 25C-NBOMe	Male	17	High blood pressure, tachycardia, diaphoresis, hyperthermia, dilated pupils	Diazepam (by titration, total 17.5 mg) midazolam (infusion 0.28 mg/kg/h) rocuronium (infusion 0.7 mg/kg/h) cyproheptadine	The patient regained consciousness 12 h after admission to hospital and was discharged after 5 days, fully recovered.

(Continued)

TABLE 1 | Continued

References	New psychoactive substance	Sex	Age	The effect associated with the intake of NPS	Treatment method	The effect of pharmacotherapy
(41)	25B-NBOMe 25C-NBOMe	Male	31	High blood pressure, tachycardia, diaphoresis, hyperthermia, dilated pupils, rhabdomyolysis	Lorazepam intravenously 2 mg every 5 min (total 12 mg) sodium bicarbonate	Despite the doctors' recommendations, the patient left the hospital after 3 days of hospitalisation on request.
(21)	3-MMC (3-methylcathinone) 5-APB Ethanol	Male	20	Psychomotor agitation, accelerated heart rate, convulsions, increased temperature, cardiac arrest	Diazepam (10 mg) midazolam (5 mg) adrenalin atropine intubation, ventilation, defibrillation, fatal case	The patient died <4 h after taking the substance.
(31)	BB-22 AM2233 PB-22 5F-PB-22 JWH-122	Male	23	Seizure with urinary incontinence, nausea, dry mouth	Saline (1,500 ml intravenously) Diazepam (orally)	The seizures stopped. The patient was discharged from the hospital.
(22)	MDPV	Male	21	Insomnia, increased physical strength, no pain, delusions, aggression, hallucinations	Midazolam (10 mg intramuscularly) saline hydration	Blood pressure returned to normal after 12 h. Renal function and blood parameters stabilised after treatment.
(38)	MT-45 Methiopropamine PCP 3-MeO-PCP	Male	26	Loss of consciousness, apnea, bruising, dilated pupils, hearing impairment	Naloxone 0.4 mg fatal case	The patient died.
(38)	MT-45 Benzofurans Flubromazepam Pirazolam a-PVP	Male	32	Decreased consciousness, low saturation, sight impairment	Naloxone 0.1 mg fatal case	The patient died.
(38)	MT-45 3-MMC Pyrazolam	Male	24	Decreased consciousness, low saturation, sight impairment	Naloxone 3 × 0.4 mg (total 1.2 mg) fatal case	The patient died.
(32)	K2	Male	41	Acute hypoxia, hypercapnia, respiratory failure resulting from acute congestive heart failure, ST-segment elevation myocardial infarction	Propofol, fentanyl and midazolam to achieve adequate sedation and synchronisation of ventilation, antimicrobial therapy consisting of piperacillin and tazobactam for aspirative pneumonia	The patient was successfully extubated on the 11th day after admission to the intensive care unit (ICU).
(43)	DOC	Male	18	Seizures, left eye deflection, dilated pupils and abnormal movement of the limbs, tonic turning of the head and eyesight	Midazolam 2.5 mg intranasally to stop the attack temporarily, lorazepam 2 mg intravenously to improve tonic head movement, propofol for sedation, starting from 20 μg/min and increasing to 100 μg/min in the next hour additionally: lorazepam 9 mg, phosphenytoin 20 mg/kg intravenously and midazolam at a rate of 7 mg/h for drip	The patient was successfully extubated on the second day in hospital, had amnesia, neurological tests were normal; his memory improved on the third day, but he still had a slower response time.

(Continued)

TABLE 1 | Continued

References	New psychoactive substance	Sex	Age	The effect associated with the intake of NPS	Treatment method	The effect of pharmacotherapy
(35)	Synthetic cannabinoid ("Bonzai")	Male	19	Sinus bradycardia	Bolus 1.5 ml/kg, 20% of lipid, then infusion of 0.25 ml/kg/minute for 60 min	After the infusion, bradycardia resolved completely. The patient was discharged in good health after 24 h of follow-up without complications.
(35)	Synthetic cannabinoid ("Bonzai")	Male	17	Accelerated junctional rhythm	Bolus 1.5 ml/kg, 20% of lipid, then infusion of 0.25 ml/kg/minute for 60 min	At the fifth minute of infusion, the rate of ventricular extrasystole (VES) decreased. At the end of the infusion, at the sixteenth minute, the heart rate was 74/minute without VES. The patient was discharged in good health after 24 h of follow-up without complications.
(35)	Synthetic marijuana	Male	27	Hallucinations, severe psychosis, nausea, vomiting	10 mg of olanzapine orally to manage acute psychosis; prometazine to reduce nausea and vomiting	The patient was discharged after the symptoms of psychosis subsided.
(78)	25B-NBOe	Male	30	Aggression	Midazolam 15 mg lorazepam 2 mg	Three hours after administration, the patient was cooperative and oriented. He was later released from the emergency department in the presence of a family member.
(78)	25B-NBOe	Male	42	Aggression, diaphoresis, dilated pupils, muscle spasms, tremor, hyperflexia	Midazolam 12 mg	The patient was released 13 h after arriving at the emergency department.
(78)	25B-NBOMe	Male	23	Confusion, aggression, dilated pupils	Midazolam 35 mg ketamine 75 mg	Seven hours after drug administration, the patient was oriented and willing to cooperate. He did not remember using drugs.
(78)	25B-NBOMe	Male	26	Diaphoresis, salivation, high blood pressure	Midazolam 10 mg + 6 mg – the second dose within 90 min	After 90 min, the patient was calm and cooperative. Five hours after his arrival, his vital signs returned to normal.
(78)	25B-NBOMe	Male	22	Hyperthermia, increased pressure, dilated pupils	Midazolam 55 mg lorazepam orally 4 mg	The patient was willing enough to cooperate that the symptoms subsided 3 h after arriving at the emergency department.
(78)	25B-NBOMe	Male	21	Dry hot skin, dilated pupils	35 mg of midazolam within 60 min	His airway was maintained, manageable behaviour.
(78)	25B-NBOMe	Male	24	Agitation, aggression, hallucinations, irrational behaviour, self-mutilation, hyperthermia, hyperhidrosis, hypertension, nystagmus, dilated pupils	7.5 mg of intramuscular midazolam twice, 5 mg of haloperidol and midazolam in a total dose of 23.5 mg within 60 min and a combination of propofol (for 9 h), fentanyl and suxamethonium chloride	After 9 h in the ICU, propofol was discontinued. The patient was calm and willing to cooperate, so he was extubated. He did not remember the events of the previous evening. He remained under observation.
(44)	Ethylophenidate+ benzocaine ("el blanco")	Male	>30	Accelerated relapses of schizophrenia	0.5 mg of clonazepam four times a day with haloperidol and lorazepam to control acute behavioural disorders and agitation. 10 mg of olanzapine twice daily as antipsychotic was changed to 50 mg of pipothiazine palmitate every 4 weeks	After reaching therapeutic levels of clozapine, the patient stabilised enough to engage in discussion and education about the use of NPS. He was released from the hospital 6 months after admission.
(65)	U-47700	Male	26	Cyanosis, respiratory collapse, tachycardia	As needed: oxygen therapy, ketamine, lorazepam, rocuronium bromide; chronic treatment: pulmonary ventilation, propofol	The patient was discharged after 3 days of hospitalisation after stabilisation and obtaining normal test results.
(65)	U-47700	Female	24	Drowsiness, anxiety, nausea, stomach ache	Supportive care	After 24 h of observation, the patient was discharged from the hospital.

(Continued)

TABLE 1 | Continued

References	New psychoactive substance	Sex	Age	The effect associated with the intake of NPS	Treatment method	The effect of pharmacotherapy
(75)	Flubromazolam	Male	24	Loss of consciousness, fever, changes in the white matter of the brain, hypoxia brain damage, changes in EEG, permanent dilated pupils, death (due to overdose)	Intubation and oxygen therapy, from the sixth day of hospitalisation with meropenem and fluconazole (no improvement), from the 15th day with levitracetam and scopolamine with albuterol/ipratropium bromide, from the 20th day with flumazenil (no improvement)	After 19 days of hospitalisation, the patient was unresponsive and suffered from pain stimuli. On the 21st day, he was transported to the hospice where he died on the 30th day. The cause of death was complications due to overdose of psychoactive substances.
(79)	U-47700	Male	22	Loss of consciousness, apnea, gasping, cyanosis, hypoxia, difficulty thinking	Oxygen therapy, 2 mg of naloxone	No information.
(50)	MDMB-CHMICA Synthetic cannabinoid ''Sweat leaf"	Male	33	Epilepsy, paranoia, aggression, acidosis	10 mg of diazepam, intravenous electrolytes	The patient was discharged from the hospital after 51/52 hours at his own request.
(50)	MDMB-CHMICA Synthetic cannabinoid 'pandora reborn'	Male	23	Hallucinations, aggression, hyperhidrosis, insomnia, self-harm, hyperactivity, tachycardia, fever, acidosis, dilated pupils	3 mg of lorazepam, intubation and ventilation, phenylephrine and noradrenaline, benzodiazepines and haloperidol	The patient remained aggressive and agitated for several consecutive days of hospitalisation as a result of which he was given high doses of benzodiazepines and haloperidol. He was discharged after 9 days without complications.
(71)	3-MeO-PCP	Male	37	Hypertension, tachycardia, psychosis, increased muscle tone with spastic leg posture	Oxygen therapy, gastric lavage with the application of activated carbon, macrogol, metoclopramide, synostigmine	The first vital signs returned 10 min after naloxone administration, itching and anxiety subsided, the patient was sleepy for 2 h, but she was able to wake up and talk coherently; she was discharged 4 h after arrival.
(53)	U-47700 Fentanyl Acetaminophen	Female	41	Reduced level of consciousness, anxiety, itching	0.4 mg of naloxone intravenously, 1 mg of lorazepam, 50 mg of diphenhydramine	The first vital signs returned 10 min after naloxone administration; itching and anxiety subsided; the patient was sleepy for 2 h, but was able to wake up and talk coherently; she was discharged 4 h after arrival.
(51)	JWH-122	Male	18	Hallucinations, blurred vision, tachycardia	6 mg of clonazepam (daily)	Visual hallucinations and visual disturbances persisted for 4 years.
(56)	Black Mamba	Female	25	Agitation, aggression	2 mg of lorazepam, 5 mg of haloperidol, 50 mg of diphenhydramine	The patient was discharged after 10 h of observation in the emergency department.
(56)	Black Mamba	Female	23	Chest pain, ECG T wave inversion, diarrhea, nausea	15 mg of ketorolac, 4 mg of ondansetron, 1 g of acetaminophen	The patient was discharged after 9 h of observation in the emergency department.
(56)	Black Mamba Marijuana	Male	27	Palpitations, bilateral numbness of the hands, nausea, vomiting	1 mg × 2 of lorazepam, isotonic NaCl 1 l solution	The patient was discharged after 3 h.

(Continued)

TABLE 1 | Continued

References	New psychoactive substance	Sex	Age	The effect associated with the intake of NPS	Treatment method	The effect of pharmacotherapy
(69)	25I-NBOMe	Male	27	Agitation, aggression, blood pressure: 139/90 mm Hg, tachycardia, heart rate: 146 beats per minute (bpm), respiratory rate: 28 breaths/min *Re-hospitalisation after 3 weeks:* II. Temperature: 36.80 C, heart rate: 120 bpm, blood pressure: 153/119 mm Hg and respiratory rate: 22 breaths/min, 4 mm pupils, agitation, aggression, hallucinations	2 mg of lorazepam, 5 mg of haloperidol lactate, 2 l of 0.9% saline lorazepam at the doses of: 4 mg, 2 mg, 8 mg and 16 mg (given within 4.5 h)	I. The patient escaped from the hospital. II. The patient calmed down, vital signs improved, the patient did not require airway support, the symptoms of poisoning disappeared. On the second day of admission, the patient was already vigilant and could be assessed psychiatrically. It was recommended to move the patient to an addiction centre. However, the patient discharged himself after 48 h.
(58)	King Kong	Male	47	Fever, heart rate: 104 beats per minute, respiratory rate: 20 breaths per minute, blood pressure: 153/103 mm Hg, psychosis, delusions, agitation, hallucinations	10 mg of olanzapine, then 10 mg of haloperidol in combination with 2 mg of lorazepam and 50 mg of diphenhydramine	The administration of olanzepine did not cause sedation, the patient was still stimulated and, therefore, the other drugs were administered intramuscularly. The patient stayed in isolation overnight to reduce stimuli. The next day the patient was calm and stable.
(80)	3-MeO-PCP	Male	19	Tachypnea, tachycardia, hypertension, catatonia and mydriasis, fever, lactic acidosis, hallucinations, agitation	Diazepam, haloperidol, propofol	The patient calmed down, but saturation decreased and so he was given propofol, intubated and transferred to the ICU, where he had a high fever. After 22 h of intensive therapy, the patient completely recovered and was transferred to a psychiatric ward.
(81)	3-FPM Etizolam	Male	33	Fever: 38.9°C, coma, sinus heart rhythm, respiratory acidosis, dilated pupils, unresponsive, incorrect four limb movements	2 mg of naloxone intravenously, ketamine and succinylcholine for intubation, infusion of propofol, lorazepam, vancomycin and metronidazole	After 5 days, the patient developed new extensive T-wave inversions. After 7 days, the patient was asymptomatic.
(25)	a-PVP	Male	28	Psychosis	Risperidone (4 mg/day), venlafaxine (75 mg/day), biperiden (4 mg/day), delorazepam (2 mg/day) bupropion (150 mg/day)	Hospitalisation lasted 40 days. In addition to drug treatment, it included psychotherapy and rehabilitation. The patient's health condition improved.
(54)	Synthetic cannabinoid	Male	28	Auditory hallucinations, persecution delusions, disorganisation of thoughts, psychosis, PANSS score 109/210	37.5 mg of risperidal every 2 weeks, olanzapine 10/20 mg/day, pregabalin 100 mg/day clonazepam 8 mg/day	Positive response to the pharmacological treatment used. Symptoms decreased after 24 h, and after 7 days the PANSS score was reduced to 74/210.
(54)	Poly-substance misuse (mainly crack cocaine and heroin) Synthetic cannabinoid	Female	32	Delusions, increased aggression, excessive excitability	Aripiprazole 30 mg/day Lithium carbonate 800 mg/night haloperidol 10 mg/day clonazepam 8 mg/day	The patient's condition improved after the use of pharmacotherapy and the introduction of stricter rules of searching patients for drugs
(54)	Poly-substance misuse (benzodiazepines, synthetic cannabinoides)	Male	20	Excessive sexual arousal, aggression, thinking disorder, PANSS score 116/210	Haloperidol decanoate 50 mg/monthly Haloperidol 10 mg/night Apiprazole 9.75 mg/three times a day Clonazepam 6 mg/day	Clinical improvement after 72 h and reduction of PANSS score to 98/210.

(Continued)

TABLE 1 | Continued

References	New psychoactive substance	Sex	Age	The effect associated with the intake of NPS	Treatment method	The effect of pharmacotherapy
(54)	Poly-substance misuse (benzodiazepines, synthetic cannabinoids, THC)	Male	39	Stimulation, aggression, manic episodes, hyperactivity, PANSS score: 108,123/210	Aripiprazole 400 mg/monthly (intramuscularly) Zuklupentixol 300 mg/week + Sodium valproate 1,200 mg	Positive symptoms decreased and the PANSS score dropped to 66/210. Signs of aggression and delusions disappeared. Satisfactory reaction to zuklupentixol.
(72)	3-HO-PCP N- Ethylhexedrone "heksen/NEH"	Male	56	Drowsiness, diaphoresis, high blood pressure, hallucinations, hyperthermia, tachycardia	4.3 l of electrolytes, 7.5 mg of diazepam	On the second day of hospitalisation, the patient regained partial consciousness, came to full health during 9 days of hospitalisation and was discharged.
(63)	Cyclopropylfentanyl	Male	25	Coma, respiratory failure, myosis, hypothermia, repeated apnea, desaturation and sedation	s needed, administration of two doses of 0.4 mg of naloxone and oxygen therapy. Oxygen therapy and naloxone supply for another 12 h of hospitalisation.	After administration of naloxone, breathing stabilised; the patient also showed reduced oxygen saturation for the following 12 h. After 1 day of observation, he was discharged.
(70)	3-MeO-PC	Male	17	Impaired consciousness, hyperactivity, tremor, nystagmus, dysarthria, respiratory acidosis	1 mg of midazolam, 1,500 ml + 3,000 ml of NaCl solution, cyamemazine and loxapine	In <24 h, neurological disorders decreased and blood pressure and heart rate stabilised. The patient maintained moderate sedation the next day. He was transported to a psychiatric hospital, from which he was discharged after a few days.

showing that in the general population, men, and young people use various types of NPS much more often. For example, according to the 2019 EMCDDA report, the presence of synthetic cannabinoids was found in 60% of all drug-related deaths reported in Turkey, and the majority concerned young men aged 20 to 30 (82).

The main NPS described in the case reports under analysis include synthetic cathinones and cannabinoids. Synthetic cathinones are the most important group of substances structurally related to amphetamine, methamphetamine, and MDMA. The obtained results indicate a greater influence of synthetic cathinone intake on the occurrence of aggression in comparison to cannabinoids. The presence of a pyrrolidine ring and a quaternary amine moiety increases the lipophilicity and potency of these compounds (83). An example of this is MDPV, the consumption of which has been reported to cause fatalities as well as extremely aggressive behavior (84). Stimulation of the central nervous system by synthetic cathinones may cause nervousness, hyperactivity, irritability, anxiety, and tremors, which affects the masticatory muscles. Taking cathinones may also induce symptoms of serotonin syndrome with disorders of the central nervous system, autonomic nervous system instability and neuromuscular hyperactivity. This risk increases with the use of additional psychoactive substances, such as cocaine and amphetamine (85–87). The article has been published recently in which the authors maintain that Serotonin Syndrome (SS) may be related to over-activation of the serotoninergic system produced by several mechanisms resulting in a classic triad of altered mental status, neuromuscular effects, and autonomic hyperactivity. These substances may include: psychedelic phenethylamines and synthetic cathinones (88).

It should be remembered that patients may be aggressive toward the people around them, as well as posing a threat to themselves. The conducted analysis also shows that synthetic cathinones, unlike cannabinoids, have a statistically significant influence on the occurrence of confusion. According to the literature, cathinones contribute to the occurrence of cognitive disorders, such as confusion and long-term impairment of mental performance, as well as mental disorders such as panic attacks, aggression, often accompanied by violence, depression, and suicidal thoughts and acts (89).

The case reports regarding the intake of ever newer psychoactive substances relate to the last few years. Among other things, new synthetic opioids with a different chemical structure to opioid medications used for therapeutic purposes have appeared on the market. They pose a very serious threat to public health (36, 90). In the United States, for example, there have been a particularly high number of deaths due to opioid overdoses in recent years (91). These substances cause a euphoric effect as they bind to the presynaptic μ-opioid receptors (83). One of the main symptoms in the case reports studied was impaired thinking and a decreased level of consciousness. For example, reports on poisoning with U-47700 describe symptoms similar to those in poisoning with traditional opioids (92). Three patients taking MT-45 died as reported in the last part of the discussion. As for the remaining single published case reports, these relate to

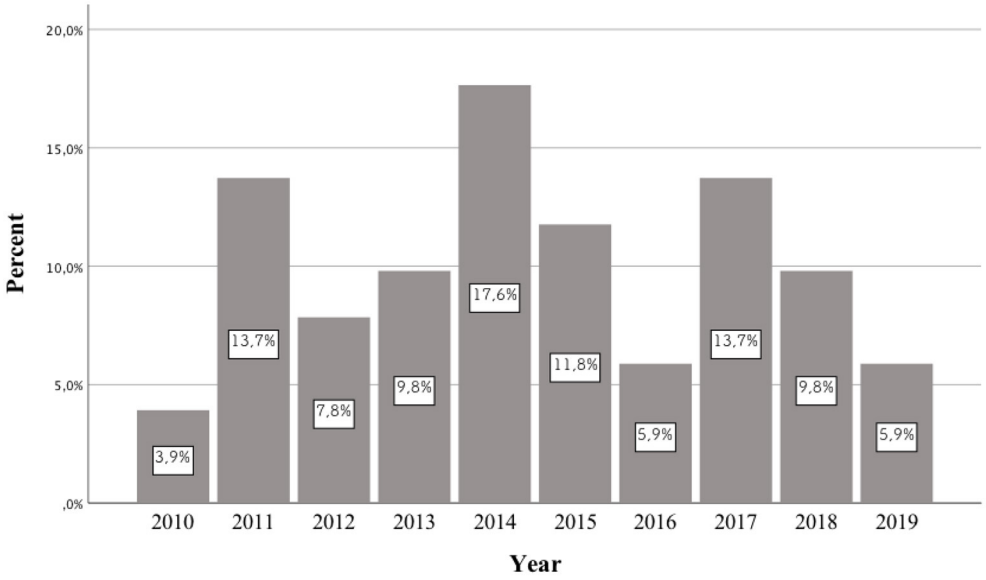


FIGURE 1 | Percentage of case reports concerning patients taking NPS written between 2010 and 2019.

phencyclidine derivatives, amphetamine-derived stimulants and synthetic benzodiazepines. In addition to psychomotor agitation, patients taking phencyclidine derivatives had dilated pupils and nystagmus. Hallucinogenic sleep symptoms, the so-called closed-eye hallucinations are recognized as a characteristic symptom after taking methoxetamine (93). However, more research is needed to investigate the effects of these substances on the human body, their toxicokinetics and toxicity.

Pharmacotherapy of Patients Taking NPS

The major part of pharmacotherapy used in the 51 patients taking various types of NPS consisted of benzodiazepines, and aggression was the most common symptom. The greatest number of authors described patients administered benzodiazepines alone, without any other medications. These mainly include diazepam, lorazepam, and midazolam. In the remaining patients, benzodiazepines were combined primarily with neuroleptics and muscle relaxants. Haloperidol is of the most common neuroleptics, while ocuronium and vecuronium are the most prevalent muscle relaxants.

The reduction of agitation is an essential element, *inter alia*, in the treatment of hyperthermia and high blood pressure in people poisoned with NPS. The results obtained are confirmed in the literature, indicating that benzodiazepines are the medications of choice used to control agitation and aggression. It is recommended using this group of medications in increasingly higher doses. This is related to the patient's safety, interactions between the pharmaceuticals used and the psychoactive substances taken, and the possibility of a quick reversal of the medications' effects (9). However, it should be remembered that the administration of higher doses of benzodiazepines may worsen the symptoms of already existing respiratory failure. It is important to be prepared for mechanical ventilation and endotracheal intubation while sedating (94, 95). In addition to the fact that benzodiazepines have sedative, anxiolytic and hypnotic effects, they also act as anticonvulsants (96). This is important as seizures are a common symptom in patients taking NPS.

The analysis also shows that the total number of medications prescribed to patients taking NPS increases over time. This is confirmed by the latest literature reports. The research carried out in 2020 shows that with the increase in the number of medications administered in those patients taking mephedrone (for a minimum of 2 days), the frequency of hospitalization also grows. The number of additional substances taken with NPS does not correlate with the frequency of hospitalization (3). The increase in the number of simultaneously prescribed medications may also be related to the emergence of newer, unexplored NPS, which, when taken along with other psychoactive substances, intensify the resulting clinical symptoms. The number of hospitalizations of patients who chronically take various types of newer psychoactive substances, which grows from year to year, and the related need to treat these patients with many medications at the same time, increases the risk of pharmacological interactions not only between administered medications, but also between uncontrolled addictive substances. This often makes it difficult to achieve a therapeutic effect, is one of the factors that increases the risk of re-hospitalization, and also increases the costs of treatment. One of the recommendations that may reduce the risk of re-hospitalization is to supplement patients with liver regenerating preparations. This is because both psychotropic substances taken and a series of various medications may intensify the hepatotoxic effects, and thus make it difficult to achieve a therapeutic effect (97, 98).

TABLE 2 | Age, gender, clinical symptoms and treatment of patients taking various types of NPS in reports written between 2010 and 2019; *chi-square.

Variable		*n*	%	Statistical test result*
Age (years)	<20	10	21.7	$\chi^2(3) = 19.74$; $p < 0.001$
	21–30	24	52.2	
	31–40	8	17.4	
	>40	4	8.7	
Gender	Male	43	15.7	$\chi^2(1) = 24.02$; $p < 0.001$
	Female	8	84.3	
New psychoactive substances	Synthetic cathinone	16	31.4	$\chi^2(5) = 40.18$; $p < 0.001$
	Synthetic cannabinoid	21	41.2	
	Synthetic opioid	8	15.7	
	Phencyclidine derivatives	3	5.9	
	Amphetamine-derived stimulants	2	3.9	
	Designer benzodiazepines	1	2	
Clinical symptoms	Tachycardia	17	33.3	$\chi^2(1) = 5.67$; $p = 0.02$
	Nervousness	22	43.1	$\chi^2(1) = 0.96$; $p = 0.33$
	Hallucinations	15	29.4	$\chi^2(1) = 8.64$; $p = 0.003$
	Seizures	11	21.6	$\chi^2(1) = 16.49$; $p < 0.001$
	Hyperthermia	9	17.6	$\chi^2(1) = 21.35$; $p < 0.001$
	Insomnia	4	7.8	$\chi^2(1) = 36.26$; $p < 0.001$
	Disorientation	21	41.2	$\chi^2(1) = 1.59$; $p = 0.21$
Treatment	Benzodiazepines	13	25.5	$\chi^2(12) = 35.92$; $p < 0.001$
	Neuroleptics	3	5.9	
	Benzodiazepines+neuroleptics	8	15.7	
	Opioid drugs	5	9.8	
	Benzodiazepines + muscle relaxants	6	11.8	
	Antipsychotics	3	5.9	
	Benzodiazepines + antipsychotics	3	5.9	
	Neurolepics + antipsychotics	3	5.9	
	Barbiturates	1	2.0	
	Opioid drugs + benzodiazepines	2	3.9	
	ILE bolus	2	3.9	
	Pain medications	1	2.0	
	Antidepressants	1	2.0	

TABLE 3 | Clinical symptoms of synthetic cathinone and cannabinoid intake.

Clinical symptoms	Odds ratio; 95% CI	
	Syntethic cathinones	Syntethic cannabinoids
Tachycardia	0.8; 0.18–3.46 ($p = 0.77$)	0.41; 0.1–1.79 ($p = 0.24$)
Nervousness	**7.71; 1.28–46.36 ($p = 0.03$)**	**6.6; 1.18–37.03 ($p = 0.03$)**
Hallucinations	2.5; 0.55–−11.41 ($p = 0.23$)	0.42; 0.08–2.25 ($p = 0.31$)
Seizures	0.86; 0.1–7.04 ($p = 0.89$)	3; 0.52–17.27 ($p = 0.22$)
Hyperthermia	0.83; 0.16–4.21 ($p = 0.83$)	0.13; 0.01–1.27 ($p = 0.08$)
Disorientation	**10; 1.64–60.92 ($p = 0.01$)**	4.5; 0.8–25.34 ($p = 0.09$)

Bold values, Statistically significant results ($p < 0.05$).

NPS-Related Fatalities

Of the cases of deaths from NPS reported in the literature, three relate specifically to the synthetic opioid MT-45. The Council Implementing Decision (European Union – EU) of 2015 stated that one member state recorded a total of 28 deaths as a result of taking MT-45 between November 2013 and July 2014. The country also recorded about 18 cases of serious poisoning, the clinical features of which were similar to those of opiate intoxication. Single animal studies show that the acute toxicity of MT-45 is several times higher than that of morphine (19). Based on the information currently available, MT-45 is not widely used. The substance appears to be mainly used at home by users who want to try any new substance or are addicted to opioids and have no access to heroin or other opioids. Users combine MT-45 with other psychoactive substances (38, 99). The case reports confirm this fact. Three men combined MT-45 with other psychoactive substances. Probably for this reason, they died despite treatment with naloxone. According to the literature data, combining new synthetic opioids with other substances is considered the main risk factor for death related to their use. Clinical symptoms in patients could result from the action of the nitrogen mustards

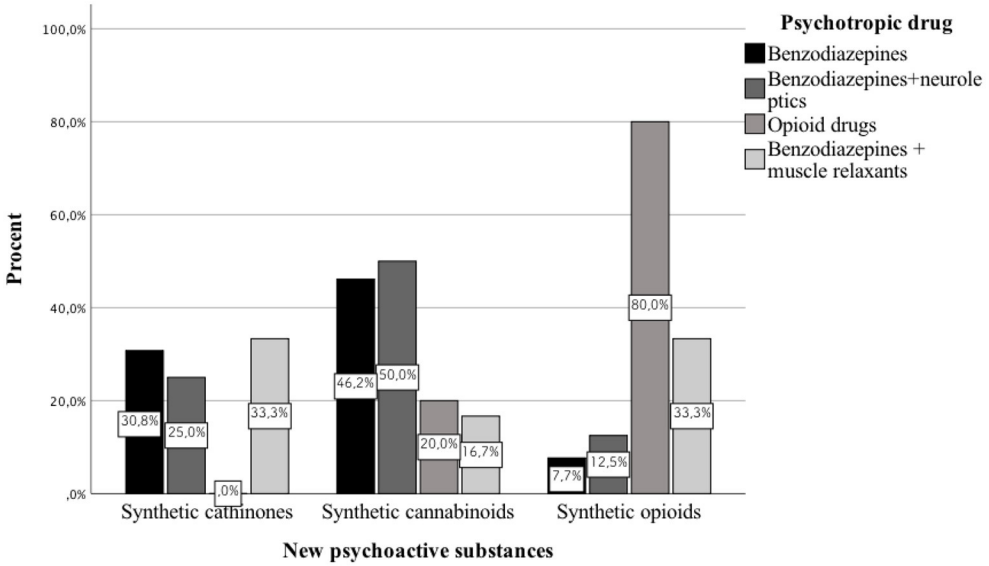


FIGURE 2 | Medications used in patients taking synthetic cathinones, cannabinoids, and opioids.

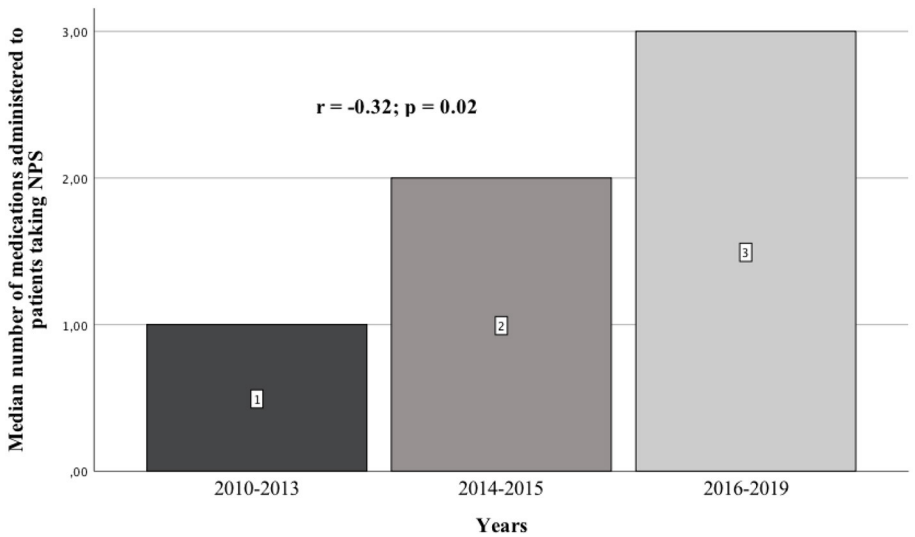


FIGURE 3 | Median number of medications administered to patients taking NPS.

used in MT-45 synthesis, as well as the stimulation of the κ and δ-opioid receptors. The available scientific data on MT-45 are limited and it has been indicated that there is a need for further research to determine the health and social risks of this substance. In the case of many different synthetic opioids, the difference between the euphoric dose and the dose that induces central nervous system depression is very small, as a result of which tolerance develops more rapidly and can cause death (90, 100).

Another reported death case concerns a patient who overdosed on flubromazolam, a new psychoactive substance from the designer benzodiazepines group. The 2017 report of the European Monitoring Center for Drugs and Drug Addiction indicates an increasing number of poisonings with new benzodiazepines (101). This type of NPS group has an inhibitory effect on the activity of the central nervous system, resulting in hypnotic, anxiolytic and amnestic effects. This is due to the antagonistic effect on the $GABA_A$ receptor. According to the literature data, clinical symptoms caused by taking designer benzodiazepines appear very quickly and are much more intense compared to classic medications. Despite the use of flumazenil with other medications, the resulting brain damage due to hypoxia contributed to the patient's death (73, 102, 103).

Another death concerned a patient taking 3-MMC with 5-APB and ethanol. Benzofurans of the 5-APB and 6-APB

TABLE 4 | Number of medications administered to patients taking various types of NPS; Me - median; *chi-square.

New psychoactive substances	Number of medications administered to patients taking NPS	Statistical test result*
	Me	
Synthetic cathinones	1	$\chi^2(30) = 72.03$; $p < 0.001$
Synthetic cannabinoids	2	
Synthetic opioids	2	
Phencyclidine derivatives	3	
Amphetamine-derived stimulants	5	
Designer benzodiazepines	7	

types cause MDMA-like effects, such as euphoria, stimulation and a sense of being at one with the world. However, these symptoms last for up to three times longer (104). These types of NPS are potent inhibitors of norepinephrine, dopamine and serotonin reuptake. Animal studies have shown that 5-APB and 6-APB are potent agonists of 5-HT2B receptors (105, 106). However, the frequency of use of this NPS group is very low. Despite benzodiazepine treatment, a patient's death could occur as a result of more severe symptoms of 5-APB poisoning when combined with 3-MMC and ethanol. In a study carried out in a group of 57 patients reporting the consumption of benzofurans alone, the following symptoms were more frequent: tachycardia, hypertension, pupil dilation, palpitations, fever, increased sweating, tremors, as well as mental health disorders (107). Due to the serotonin agonism of benzofuran, the chronic use of this compound may also be associated with heart valve disease (104).

Limitations

In published articles it lacks of the quantitative determination of new psychoactive substances and the relationship of their concentration with the clinical condition of patients. The reason for this is that quantitative methods for the determination of new psychoactive substances have only been developed in recent years, and the problem of hospitalization of patients who abuse such substances began much earlier. Secondly, another limitation of these analyses is the fact, that they are based on the different case reports and not controlled studies. This is preliminary research referring to a number of the analyzed parameters such as: clinical symptoms, type of NPS taken and applied treatment. There is need for further research on a bigger group of people taking different NPS.

CONCLUSION

Year on year, there are more and more case reports of patients taking ever newer psychoactive substances. Controlling agitation is the first step in treating this patient group. One should strive to reduce the number of medications simultaneously prescribed to patients taking NPS, as this may make it difficult to achieve a therapeutic effect.

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/s.

AUTHOR CONTRIBUTIONS

MO: idea, writing, statistical analysis, and approval the final version of manuscript. AZ, MB, MT, KW, AK, NG, MaZ, MiZ, and EM: writing the manuscript and approval the final version of manuscript. TN: clinical aspect of psychopharmacology and approval the final version of manuscript. MB-Z: approval the final version of manuscript. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

I would like to thank the research team which consists of the co-authors of this article.

REFERENCES

1. Peacock A, Bruno R, Gisev N, Degenhardt L, Hall W, Sedefov A, et al. New psychoactive substances: challenges for drug surveillance, control, and public health responses. *Lancet*. (2019) 394:1668–84. doi: 10.1016/S0140-6736(19)32231-7
2. Schifano F, Napoletano F, Chiappini S, Guirguis A, Corkery JM, Bonaccorso S, et al. New/emerging psychoactive substances and associated psychopathological consequences. *Psychol Med*. (2021) 51:30–42. doi: 10.1017/S0033291719001727
3. Ordak M, Nasierowski T, Muszynska M. The problem of polypharmacotherapy in patients on a mephedrone binge. *Pharmacol Res*. (2019) 143:204. doi: 10.1016/j.phrs.2019.04.003
4. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). New Psychoactive Substances in Europe. *An Update from the EU Early Warning System*. (2015). Available online at: https://www.emcdda.europa.eu/attachements.cfm/att_235958_EN_TD0415135ENN.pdf
5. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). *Health Responses to New Psychoactive Substances*. (2016). Available online at: https://www.emcdda.europa.eu/system/files/publications/2812/TD0216555ENN.pdf
6. Antonowicz JL, Metzger AK, Ramanujam SL. Paranoid psychosis induced by consumption of methylenedioxypyrovalerone: two cases. *Gen Hosp Psychiatry*. (2011) 33:640–5. doi: 10.1016/j.genhosppsych.2011.04.010
7. Rosenbaum, CD, Carreiro, SP, Babu, KM. Here today, gone tomorrow… and back again? A review of herbal marijuana alternatives (K2, Spice), synthetic cathinones (bath salts), kratom, Salvia divinorum, methoxetamine, and piperazines. *J Med Toxicol*. (2012) 8:15–32. doi: 10.1007/s13181-011-0202-2

8. Penders TM, Gestring R. Hallucinatory delirium following use of MDPV: bath salts. *Gen Hosp Psychiatry*. (2011) 33:525–6. doi: 10.1016/j.genhosppsych.2011.05.014
9. Mangewala, V, Sarwar SR, Shah K, Singh T. Bath salts-induced psychosis: a case report. *Innov Clin Neurosci*. (2013) 10:10–1.
10. Lenz J, Brown J, Flagg S, Oh R, Batts K, Ditzler T, et al. Cristalius: a case in designer drugs. *Mi Med*. (2013) 178: e893–5. doi: 10.7205/MILMED-D-12-00393
11. Nakagawa T, Suzuki Y, Nagayasu K, Kitaichi M, Shirakawa H, Kaneko S. Repeated exposure to methamphetamine, cocaine or morphine induces augmentation of dopamine release in rat mesocorticolimbic slice co-cultures. *PLoS ONE*. (2011) 6:e24865. doi: 10.1371/journal.pone.0024865
12. Penders TM, Lang MC, Pagano JJ, Gooding ZS. Electroconvulsive therapy improves persistent psychosis after repeated use of methylenedioxypyrovalerone ("bath salts"). *J ECT*. (2013) 29:e59–60. doi: 10.1097/YCT.0b013e3182887bc2
13. Lev-Ran S. A case of treating cathinone dependence and comorbid depression using bupropion. *J Psychoactive Drugs*. (2012) 44:434–6. doi: 10.1080/02791072.2012.736851
14. Garrett G, Sweeney M. The serotonin syndrome as a result of mephedrone toxicity. *Case Rep*. (2010) 2010:bcr0420102925. doi: 10.1136/bcr.04.2010.2925
15. Kasick DP, McKnight,CA, Klisovic E. "Bath salt" ingestion leading to severe intoxication delirium: two cases and a brief review of the emergence of mephedrone use. *Am J Drug Alcohol Abuse*. (2012) 38:176–80. doi: 10.3109/00952990.2011.643999
16. Benzer TI, Nejad SH, Flood JG. Case 40-2013: a 36-year-old man with agitation and paranoia. *NEJM*. (2013) 369:2536–45. doi: 10.1056/NEJMcpc1304051
17. Simmons J, Cookman L, Kang C, Skinner C. Three cases of "spice" exposure. *Clin Toxicol*. (2011) 49:431–3. doi: 10.3109/15563650.2011.584316
18. Havenon AD, Chin B, Thomas KC, Afra P. The secret "spice": an undetectable toxic cause of seizure. *Neurohospitalist*. (2011) 1:182–6. doi: 10.1177/1941874411417977
19. Castaneto MS, Gorelick DA, Desrosiers NA, Hartman RL, Pirard S, Huestis MA. Synthetic cannabinoids: epidemiology, pharmacodynamics, and clinical implications. *Drug Alcohol Depend*. (2014) 144:12–41. doi: 10.1016/j.drugalcdep.2014.08.005
20. Hopkins CY, Gilchrist BL. A case of cannabinoid hyperemesis syndrome caused by synthetic cannabinoids. *J Emerg Med*. (2013) 45:544–6. doi: 10.1016/j.jemermed.2012.11.034
21. Adamowicz P, Zuba D, Byrska B. Fatal intoxication with 3-methyl-N-methylcathinone (3-MMC) and 5-(2-aminopropyl) benzofuran (5-APB). *Forensic Sci Int*. (2014) 245:126–32. doi: 10.1016/j.forsciint.2014.10.016
22. Hall C, Heyd C, Butler C, Yarema M. "Bath salts" intoxication: a new recreational drug that presents with a familiar toxidrome. *CJEM*. (2014) 16:171–6. doi: 10.2310/8000.2013.131042
23. Murphy CM, Dulaney AR, Beuhler MC, Kacinko S. "Bath salts" and "plant food" products: the experience of one regional US poison center. *J Med Toxicol*. (2013) 9:42–8. doi: 10.1007/s13181-012-0243-1
24. Pichini S, Rotolo MC, García J, Girona N, Leal L, García-Algar O, et al. Neonatal withdrawal syndrome after chronic maternal consumption of 4-methylethcathinone. *Forensic Sci Int*. (2014) 245:e33–5. doi: 10.1016/j.forsciint.2014.10.027
25. Pierluigi S, Laura B, Attilio N, Gurjeet K B, Gloria P, Davide M, et al. "Marvin, the Paranoid Android": the Case of an Alpha-PVP User in the Expanding Galaxy of NPS. *J Psychoactive Drugs*. (2018) 50:306–13. doi: 10.1080/02791072.2018.1447172
26. O'Byrne PM, Williams R, Walsh JJ, Gilmer JF. Synthesis, screening and pharmacokinetic evaluation of potential prodrugs of bupropion. Part one: *in vitro* development. *Pharmaceuticals*. (2014) 7:595–620. doi: 10.3390/ph7050595
27. Oppek K, Koller G, Zwergal A, Pogarell O. Intravenous administration and abuse of bupropion: a case report and a review of the literature. *J Addict Med*. (2014) 8:290–3. doi: 10.1097/ADM.0000000000000044
28. Smith CD, Robert S. 'Designer drugs': update on the management of novel psychoactive substance misuse in the acute care setting. *Clin Med*. (2014) 14:409. doi: 10.7861/clinmedicine.14-4-409
29. Bilici R. Synthetic cannabinoids. *North Clin Istanb*. (2014) 1:121. doi: 10.14744/nci.2014.44153
30. Musselman ME, Hampton JP. "Not for human consumption": a review of emerging designer drugs. *Pharmacotherapy*. (2014) 34:745–57. doi: 10.1002/phar.1424
31. Schep LJ, Slaughter RJ, Hudson S, Place R, Watts M. Delayed seizure-like activity following analytically confirmed use of previously unreported synthetic cannabinoid analogues. *Hum Exp Toxicol*. (2015) 34:557–60. doi: 10.1177/0960327114550886
32. Orsini J, Blaak C, Tam E, Rajayer S, Morante J, Yeh A, et al. The wide and unpredictable scope of synthetic cannabinoids toxicity. *Case Rep Crit Care*. (2015) 2015:542490. doi: 10.1155/2015/542490
33. Sikk K, Taba P. Methcathinone "kitchen chemistry" and permanent neurological damage. *Int Rev of Neurobiol*. (2015) 120:257–71. doi: 10.1016/bs.irn.2015.02.002
34. Greene W, Kinzie E. Mojo rising-evaluation and treatment for synthetic marijuana intoxication. *J La State Med Soc*. (2015) 167:17–8.
35. Aksel G, Güneysel, Ö Taşyürek T, Kozan E, Cevik SE. Intravenous lipid emulsion therapy for acute synthetic cannabinoid intoxication: clinical experience in four cases. *Case Rep Emerg Med*. (2015) 2015:180921. doi: 10.1155/2015/180921
36. Lovrecic B, Lovrecic M, Gabrovec B, Carli M, Pacini M, Maremmani AG, et al. Non-medical use of novel synthetic opioids: a new challenge to public health. *Int J Environ Res Public Health*. (2019) 16:177. doi: 10.3390/ijerph16020177
37. Dennis BB, Naji L, Bawor M, Bonner A, Varenbut M, Daiter J, et al. The effectiveness of opioid substitution treatments for patients with opioid dependence: a systematic review and multiple treatment comparison protocol. *Syst Rev*. (2014) 3:1–11. doi: 10.1186/2046-4053-3-105
38. Helander A, Bäckberg M, Beck O. MT-45, a new psychoactive substance associated with hearing loss and unconsciousness. *Clin Toxicol*. (2014) 52:901–4. doi: 10.3109/15563650.2014.943908
39. Rech MA, Donahey E, Cappiello Dziedzic JM, Oh L, Greenhalgh E. New drugs of abuse. *Pharmacotherapy*. (2015) 35:189–97. doi: 10.1002/phar.1522
40. Rodgman CJ, Verrico CD, Worthy RB, Lewis EE. Inpatient detoxification from a synthetic cannabinoid and control of postdetoxification cravings with naltrexone. *Prim Care Companion CNS Disord*. (2014) 16:10.4088/PCC.13l01594. doi: 10.4088/PCC.13l01594
41. Tang MHY, Ching CK, Tsui MSH, Chu FKC, Mak TWL. Two cases of severe intoxication associated with analytically confirmed use of the novel psychoactive substances 25B-NBOMe and 25C-NBOMe. *Clin Toxicol*. (2014) 52:561–5. doi: 10.3109/15563650.2014.909932
42. Abdulrahim D, Bowden-Jones O. *Harms of synthetic cannabinoid receptor agonists (SCRAs) and their management. The Health Foundation Inspiring Improvement*. London: NEPTUNE (Novel Psychoactive Treatment UK Network) (2016).
43. Burish MJ, Thoren KL, Madou M, Toossi S, Shah M. Hallucinogens causing seizures? A case report of the synthetic amphetamine 2, 5-dimethoxy-4-chloroamphetamine. *Neurohospitalist*. (2015) 5:32–4. doi: 10.1177/1941874414528939
44. Anderson C, Morrell C, Marchevsky D. A novel psychoactive substance poses a new challenge in the management of paranoid schizophrenia. *Case Rep*. (2015) 2015:bcr2015209573. doi: 10.1136/bcr-2015-209573
45. Kinsey B. Vaccines against drugs of abuse: where are we now? *Ther Adv Vaccines*. (2014) 2:106–17. doi: 10.1177/2051013614537818
46. Ellefsen KN, Concheiro M, Huestis MA. Synthetic cathinone pharmacokinetics, analytical methods, and toxicological findings from human performance and postmortem cases. *Drug Metab Rev*. (2016) 48:237–65. doi: 10.1080/03602532.2016.1188937
47. Graddy R, Buresh ME, Rastegar DA. New and emerging illicit psychoactive substances. *Med Clin North Am*. (2018) 102:697–714. doi: 10.1016/j.mcna.2018.02.010
48. Schifano, F, Napoletano, F, Arillotta, D, Zangani C, Gilgar L, Guirguis A, et al. The clinical challenges of synthetic cathinones. *Br J Clin Pharmacol*. (2020) 86:410–9. doi: 10.1111/bcp.14132
49. Corazza O, Roman-Urrestarazu A. editors. *Handbook of Novel Psychoactive Substances: What Clinicians Should Know About NPS*. New York, NY: Routledge. (2018). p. 162–3. doi: 10.4324/9781315158082

50. Hill SL, Najafi J, Dunn M, Acheampong P, Kamour A, Grundlingh J, et al. Clinical toxicity following analytically confirmed use of the synthetic cannabinoid receptor agonist MDMB-CHMICA. A report from the Identification Of Novel psychoActive substances (IONA) study. *Clin Toxicol.* (2016) 54:638–43. doi: 10.1080/15563650.2016.1190980
51. Coppola M, Mondola R. JWH-122 consumption adverse effects: a case of hallucinogen persisting perception disorder five-year follow-up. *J Psychoactive Drugs.* (2017) 49:262–5. doi: 10.1080/02791072.2017.1316431
52. Armenian P, Darracq M, Gevorkyan J, Clark S, Kaye B, Brandenhoff NP. Intoxication from the novel synthetic cannabinoids AB-PINACA and ADB-PINACA: a case series and review of the literature. *Neuropharmacology.* (2018) 134:82–91. doi: 10.1016/j.neuropharm.2017.10.017
53. Armenian P, Vo KT, Barr-Walker J, Lynch KL. Fentanyl, fentanyl analogs and novel synthetic opioids: a comprehensive review. *Neuropharmacology.* (2018) 134:121–32. doi: 10.1016/j.neuropharm.2017.10.016
54. Bonaccorso S, Metastasio A, Ricciardi A, Stewart N, Jamal L, Rujully NUD, et al. Synthetic cannabinoid use in a case series of patients with psychosis presenting to acute psychiatric settings: clinical presentation and management issues. *Brain Sci.* (2018) 8:133. doi: 10.3390/brainsci8070133
55. Tait RJ, Caldicott D, Mountain D, Hill SL, Lenton S. A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. *Clin Toxicol.* (2016) 54:1–13. doi: 10.3109/15563650.2015.1110590
56. Brandehoff N, Adams A, McDaniel K, Banister SD, Gerona R, Monthe AA. Synthetic cannabinoid "Black Mamba" infidelity in patients presenting for emergency stabilization in Colorado: a P SCAN Cohort. *Clin Toxicol.* (2018) 56:193–8. doi: 10.1080/15563650.2017.1357826
57. Klega AE, Keehbauch JT. Stimulant and designer drug use: primary care management. *Am Fam Phys.* (2018) 98:85–92.
58. Sweet G, Kim S, Martin S, Washington NB, Brahm N. Psychiatric symptoms and synthetic cannabinoid use: information for clinicians. *Ment Health Clin.* (2017) 7:156–9. doi: 10.9740/mhc.2017.07.156
59. Pourmand A, Mazer-Amirshahi M, Chistov S, Li A, Park M. Designer drugs: Review and implications for emergency management. *Hum Exp Toxicol.* (2018) 37:94–101. doi: 10.1177/0960327117698542
60. Mehta JJ, Mahendran AK, Bajaj RK, Doshi AR. Myocardial ischemia with cannabinoid use in an adolescent. *Cureus.* (2017) 9:e1899. doi: 10.7759/cureus.1899
61. Monte AA, Calello DP, Gerona RR, Hamad E, Campleman SL, Brent J, et al. Characteristics and treatment of patients with clinical illness due to synthetic cannabinoid inhalation reported by medical toxicologists: a ToxIC database study. *J Med Toxicol.* (2017) 13:146–52. doi: 10.1007/s13181-017-0605-9
62. Warrick BJ, Tataru AP, Gerona R. New psychoactive substances in pediatric patients. *Pediatr Clin North Am.* (2017) 64:1223–41. doi: 10.1016/j.pcl.2017.08.003
63. Wilde M, Sommer MJ, Auwärter V, Hermanns-Clausen M. Acute severe intoxication with cyclopropylfentanyl, a novel synthetic opioid. *Toxicol Lett.* (2020) 320:109–12. doi: 10.1016/j.toxlet.2019.11.025
64. Karila L, Marillier M, Chaumette B, Billieux J, Franchitto N, Benyamina A. New synthetic opioids: part of a new addiction landscape. *Neurosci Biobehav Rev.* (2019) 106:133–40. doi: 10.1016/j.neubiorev.2018.06.010
65. Domanski K, Kleinschmidt KC, Schulte JM, Fleming S, Frazee C, Menendez A, et al. Two cases of intoxication with new synthetic opioid, U-47700. *Clin Toxicol.* (2017) 55:46–50. doi: 10.1080/15563650.2016.1209763
66. Gerace E, Salomone A, Luciano C, Di Corcia D, Vincenti M. First Case in Italy of fatal intoxication involving the new opioid U-47700. *Front Pharmacol.* (2018) 9:747. doi: 10.3389/fphar.2018.00747
67. Rambaran KA, Amin ZM, Fleming SW, Chacko L, Alzghari SK. AH-7921: a review of previously published reports. *Proc Bayl Univ Med Cent.* (2018) 31:303–6. doi: 10.1080/08998280.2018.1465320
68. Zawilska, JB, Kacela, M, Adamowicz, P. NBOMes–highly potent and toxic alternatives of LSD. *Front Neurosci.* (2020) 14:78. doi: 10.3389/fnins.2020.00078
69. Zygowiec J, Solomon S, Jaworski A, Bloome M, Gotlib A. 25C-NBOMe ingestion. *Clin Pract Cases Emerg Med.* (2017) 1:295–7. doi: 10.5811/cpcem.2017.5.33994
70. Berar A, Allain JS, Allard S, Lefevre C, Baert A, Morel I, et al. Intoxication with 3-MeO-PCP alone: a case report and literature review. *Med Baltimore.* (2019) 98:E18295. doi: 10.1097/MD.0000000000018295
71. Zidkova, M, Hlozek, T, Balik, M, Kopecky O, Tesinsky P, Svanda J, et al. Two cases of non-fatal intoxication with a novel street hallucinogen: 3-methoxyphencyclidine. *J Anal Toxicol.* (2017) 41:350–4. doi: 10.1093/jat/bkx009
72. Dunlop LC, Wood D, Archer J, Hudson S, Dargan P. Severe toxicity to the new psychoactive substances 3-hydroxyphencyclidine and N-ethylhexedrone: an analytically confirmed case report. *J Med Toxicol.* (2020) 16:67–70. doi: 10.1007/s13181-019-00734-x
73. Carpenter JE, Murray BP, Dunkley C, Kazzi ZN, Gittinger MH. Designer benzodiazepines: a report of exposures recorded in the National Poison Data System, 2014-2017. *Clin Toxicol.* (2019) 57:282–6. doi: 10.1080/15563650.2018.1510502
74. Penninga EI, Graudal N, Ladekarl MB, Jurgens G. Adverse events associated with flumazenil treatment for the management of suspected benzodiazepine intoxication–a systematic review with meta-analyses of randomised trials. *Basic Clin Pharmacol Toxicol.* (2016) 118:37–44. doi: 10.1111/bcpt.12434
75. Gummin DD, Mowry JB, Spyker DA, Brooks DE, Fraser MO, Banner W. 2016 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 34th Annual Report. *Clin Toxicol.* (2017) 55:1072–252. doi: 10.1080/15563650.2017.1388087
76. Papanti D, Schifano F, Botteon G, Bertossi F, Mannix J, Vidoni D, et al. "Spiceophrenia": a systematic overview of "Spice"-related psychopathological issues and a case report. *Hum Psychopharmacol.* (2013) 28:379–89. doi: 10.1002/hup.2312
77. Schneir AB, Cullen J, Ly BT. "Spice" Girls: synthetic cannabinoid intoxication. *J Emerg Med.* (2011) 40:296–9. doi: 10.1016/j.jemermed.2010.10.014
78. Gee P, Schep LJ, Jensen BP, Moore G, Barrington S. Case series: toxicity from 25B-NBOMe–a cluster of N-bomb cases. *Clin Toxicol.* (2016) 54:141–6. doi: 10.3109/15563650.2015.1115056
79. Schneir A, Metushi IG, Sloane C, Benaron DJ, Fitzgerald RL. Near death from a novel synthetic opioid labeled U-47700: emergence of a new opioid class. *Clin Toxicol.* (2017) 55:51–4. doi: 10.1080/15563650.2016.1209764
80. Johansson A, Lindstedt D, Roman M, Thelander G, Nielsen EI, Lennborn U, et al. A non-fatal intoxication and seven deaths involving the dissociative drug 3-MeO-PCP. *Forensic Sci Int.* (2017) 275:76–82. doi: 10.1016/j.forsciint.2017.02.034
81. Benesch MGK, Iqbal SJ. Novel psychoactive substances: overdose of 3-fluorophenmetrazine (3-FPM) and Etizolam in a 33-year-old man. *BMJ Case Rep.* (2018) 8:bcr2018224995. doi: 10.1136/bcr-2018-224995
82. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). *European Drug Report. Trends Developments.* EMCDDA (2019). Available online at: https://www.emcdda.europa.eu/system/files/publications/11364/20191724_TDAT19001ENN_PDF.pdf
83. Wojcieszak J, Andrzejczak D, Wojtas A, Golembiowska K, Zawilska JB. Comparative neuropharmacological studies on three pyrrolidine-containing synthetic cathinones. *Forensic Toxicol.* (2020) 38:378–93. doi: 10.1007/s11419-020-00523-0
84. Baumann MH, Bukhari MO, Lehner KR, Anizan S, Rice KC, Concheiro M, et al. Neuropharmacology of 3,4-Methylenedioxypyrovalerone (MDPV), its metabolites, and related analogs. *Curr Top Behav Neurosci.* (2017) 32:93–117. doi: 10.1007/7854_2016_53
85. Prosser, JM, Nelson, LS. The toxicology of bath salts: a review of synthetic cathinones. *J Med Toxicol.* (2012) 8:33–42. doi: 10.1007/s13181-011-0193-z
86. Valente MJ, Guedes de Pinho P, de Lourdes Bastos M, Carvalho F, Carvalho M. Khat and synthetic cathinones: a review. *Arch Toxicol.* (2014) 88:15–45. doi: 10.1007/s00204-013-1163-9
87. Gonçalves JL, Alves VL, Aguiar J, Teixeira HM, Câmara JS. Synthetic cathinones: an evolving class of new psychoactive substances. *Crit Rev Toxicol.* (2019) 49:549–66. doi: 10.1080/10408444.2019.1679087
88. Schifano F, Chiappini S, Miuli A, Corkery JM, Scherbaum N, Napoleano F, et al. New psychoactive substances (NPS) and serotonin syndrome onset: a systematic review. *Exp Neurol.* (2021) 339:113638. doi: 10.1016/j.expneurol.2021.113638
89. Leyrer-Jackson JM, Nagy EK, Olive MF. Cognitive deficits and neurotoxicity induced by synthetic cathinones: is there a role for neuroinflammation?

Psychopharmacology. (2019) 236:1079–95. doi: 10.1007/s00213-018-5067-5
90. Wallach JV, Morris H, Brandt SD. Is nitrogen mustard contamination responsible for the reported MT-45 toxicity? *Br J Dermatol*. (2017) 177:594–5. doi: 10.1111/bjd.15507
91. Stoicea N, Costa A, Periel L, et al. Current perspectives on the opioid crisis in the US healthcare system: a comprehensive literature review. *Medicine*. (2019) 98:e15425. doi: 10.1097/MD.0000000000015425
92. Alzghari SK, Fleming SW, Rambaran KA, Long JE, Burkhart S, An J, et al. U-47700: an emerging threat. *Cureus*. (2017) 9:e1791. doi: 10.7759/cureus.1791
93. Kjellgren A, Jonsson K. Methoxetamine (MXE)–a phenomenological study of experiences induced by a "legal high" from the internet. *J Psychoactive Drugs*. (2013) 45:276–86. doi: 10.1080/02791072.2013.803647
94. Schmitz A. Benzodiazepine use, misuse, and abuse: a review. *Ment Health Clin*. (2016) 6:120–6. doi: 10.9740/mhc.2016.05.120
95. Wang SH, Chen WS, Tang SE, Lin HC, Peng CK, Chu HT, et al. Benzodiazepines associated with acute respiratory failure in patients with obstructive sleep apnea. *Front Pharmacol*. (2019) 9:1513. doi: 10.3389/fphar.2018.01513
96. Ochoa JG, Kilgo WA. The Role of benzodiazepines in the treatment of epilepsy. *Curr Treat Options Neurol*. (2016) 18:18. doi: 10.1007/s11940-016-0401-x
97. Luethi D, Liechti ME, Krähenbühl S. Mechanisms of hepatocellular toxicity associated with new psychoactive synthetic cathinones. *Toxicology*. (2017) 387:57–66. doi: 10.1016/j.tox.2017.06.004
98. Ordak M, Nasierowski T. The pharmacological basis of drug interactions: an aspect overlooked in psychiatry. *Lancet Psychiatry*. (2020) 6:984. doi: 10.1016/S2215-0366(19)30432-8
99. Bilel S, Azevedo NJ, Arfè R, Tirri M, Gregori A, Serpelloni G, et al. *In vitro* and *in vivo* pharmacological characterization of the synthetic opioid MT-45. *Neuropharmacology*. (2020) 171:108110. doi: 10.1016/j.neuropharm.2020.108110
100. Zawilska JB. An expanding world of novel psychoactive substances: opioids. *Front Psychiatry*. (2017) 8:110. doi: 10.3389/fpsyt.2017.00110
101. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). *Perspectives on Drugs. The Misuse of Benzodiazepines Among High-Risk Opioid Users in Europe*. (2017). Available online at: https://www.emcdda.europa.eu/system/files/publications/2733/Misuse%20of%20benzos_POD2015.pdf
102. Bohnenberger K, Liu MT. Flubromazolam overdose: a review of a new designer benzodiazepine and the role of flumazenil. *Ment Health Clin*. (2019) 9:133–7. doi: 10.9740/mhc.2019.05.133
103. Greenblatt HK, Greenblatt DJ. Designer benzodiazepines: a review of published data and public health significance. *Clin Pharmacol Drug Dev*. (2019) 8:266–9. doi: 10.1002/cpdd.667
104. Rickli A, Kopf S, Hoener MC, Liechti ME. Pharmacological profile of novel psychoactive benzofurans. *Br J Pharmacol*. (2015) 172:3412–25. doi: 10.1111/bph.13128
105. Dawson P, Opacka-Juffry J, Moffatt JD, Daniju Y, Dutta N, Ramsey J. The effects of benzofury (5-APB) on the dopamine transporter and 5-HT2-dependent vasoconstriction in the rat. *Prog Neuropsychopharmacol Biol Psychiatry*. (2014) 48:57–63. doi: 10.1016/j.pnpbp.2013.08.013
106. Brandt SD, Walters HM, Partilla JS, Blough BE, Kavanagh PV, Baumann MH. The psychoactive aminoalkylbenzofuran derivatives, 5-APB and 6-APB, mimic the effects of 3,4-methylenedioxyamphetamine (MDA) on monoamine transmission in male rats. *Psychopharmacology*. (2020) 237:3703–14 doi: 10.1007/s00213-020-05648-z
107. Kamour A, James D, Lupton DJ, Cooper G, Eddleston M, Vale A, et al. Patterns of presentation and clinical features of toxicity after reported use of ([2-aminopropyl]-2,3-dihydrobenzofurans), the 'benzofuran' compounds. A report from the United Kingdom National Poisons Information Service. *Clin Toxicol*. (2014) 52:1025–31. doi: 10.3109/15563650.2014.973115

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.

frontiers in Psychiatry

SYSTEMATIC REVIEW
published: 29 April 2021
doi: 10.3389/fpsyt.2021.610171

Efficacy and Safety of Traditional Chinese Herbal Medicine for Antipsychotic-Related Constipation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Wen-Wang Rao[1,2,3†], Juan-Juan Yang[4,5†], Han Qi[6†], Sha Sha[6†], Wei Zheng[7], Ling Zhang[8], Gabor S. Ungvari[9,10], Chee H. Ng[11] and Yu-Tao Xiang[2,3*]*

[1] Institute of Mental Health, Hebei Mental Health Centre, Baoding, China, [2] Unit of Psychiatry, Department of Public Health and Medicinal Administration, Faculty of Health Sciences and Institute of Translational Medicine, University of Macau, Macao, China, [3] Centre for Cognitive and Brain Science, University of Macau, Macao, China, [4] Department of Psychiatry, Chaohu Hospital of Anhui Medical University, Hefei, China, [5] Anhui Psychiatric Center of Anhui Medical University, Hefei, China, [6] The National Clinical Research Center for Mental Disorders and Beijing Key Laboratory of Mental Disorders, Beijing Anding Hospital and the Advanced Innovation Center for Human Brain Protection, Capital Medical University, Beijing, China, [7] The Affiliated Brain Hospital of Guangzhou Medical University (Guangzhou Huiai Hospital), Guangzhou, China, [8] Beijing Municipal Key Laboratory of Clinical Epidemiology, Department of Epidemiology and Health Statistics, School of Public Health, Capital Medical University, Beijing, China, [9] The University of Notre Dame Australia, Fremantle, WA, Australia, [10] Division of Psychiatry, School of Medicine, University of Western Australia, Perth, WA, Australia, [11] Department of Psychiatry, The Melbourne Clinic and St. Vincent's Hospital, University of Melbourne, Richmond, VIC, Australia

Background: Constipation is a common but often ignored side effect of antipsychotic treatment, although it is associated with adverse outcomes. The results of the efficacy and safety of traditional Chinese herbal medicine (TCM) in treating constipation are mixed across studies. This is a systematic review and meta-analysis of randomized controlled trials (RCTs) of the efficacy and safety of TCM compared to Western medicine (WM) in treating antipsychotic-related constipation.

Methods: Major international electronic (PubMed, EMBASE, Cochrane Library, and Web of Science) and Chinese (Wanfang, WeiPu VIP, SinoMed, and CNKI) databases were searched from their inception to November 29, 2020. Meta-analysis was performed using the random-effects model.

Results: Thirty RCTs with 52 arms covering 2,570 patients in the TCM group and 2,511 patients in the WM group were included. Compared with WM, TCM alone was superior regarding the moderate response rate [risk ratio (RR) = 1.165; 95% confidence interval (CI): 1.096–1.238; $P < 0.001$], marked response rate (RR = 1.437; 95% CI: 1.267–1.692; $P < 0.001$), and remission rate (RR = 1.376; 95% CI: 1.180–1.606; $P < 0.001$) for constipation, while it was significantly associated with lower risk of rash (RR = 0.081; 95% CI: 0.019–0.342; $P = 0.001$). For the moderate response rate, meta-regression analyses revealed that publication year ($\beta = -0.007$, $P = 0.0007$) and Jadad score ($\beta = 0.067$, $P < 0.001$) significantly moderated the results. For the remission rate, subgroup and meta-regression analyses revealed that the geographical region

OPEN ACCESS

Edited by:
Mirko Manchia,
University of Cagliari, Italy

Reviewed by:
Xin Li,
Shanghai University of Traditional Chinese Medicine, China
Xiao Ma,
Chengdu University of Traditional Chinese Medicine, China
Xiaomin Wang,
Capital Medical University, China
Qingquan Liu,
Capital Medical University, China

***Correspondence:**
Chee H. Ng
cng@unimelb.edu.au
Yu-Tao Xiang
xyutly@gmail.com

† These authors have contributed equally to this work

Specialty section:
This article was submitted to Psychopharmacology, a section of the journal Frontiers in Psychiatry

Received: 28 September 2020
Accepted: 09 March 2021
Published: 29 April 2021

Citation:
Rao W-W, Yang J-J, Qi H, Sha S, Zheng W, Zhang L, Ungvari GS, Ng CH and Xiang Y-T (2021) Efficacy and Safety of Traditional Chinese Herbal Medicine for Antipsychotic-Related Constipation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Front. Psychiatry 12:610171. doi: 10.3389/fpsyt.2021.610171

($P = 0.003$), inpatient status ($P = 0.035$), and trial duration ($\beta = 0.009$, $P = 0.013$) significantly moderated the results.

Conclusions: The efficacy of TCM for antipsychotic-related constipation appeared to be greater compared to WM, while certain side effects of TCM, such as rash, were less frequent.

Keywords: meta-analysis, randomized controlled study, constipation, traditional Chinese medicine, antipsychotic

INTRODUCTION

Constipation is a common side effect of antipsychotics with a prevalence rate between 28.1 and 36.3% (1–3) and is associated with a range of severe consequences, such as paralytic ileus, bowel ischemia, sepsis, intestinal perforation, and even pre-mature mortality (4, 5). The occurrence of constipation in psychiatric patients may be associated with a decrease in gastrointestinal hypomotility due to peripheral muscarinic anticholinergic activity (6, 7). For instance, certain antipsychotics, such as clozapine, quetiapine, and olanzapine (8), have strong affinity to muscarinic cholinergic receptors, which could increase peripheral muscarinic anticholinergic activity (9, 10) and may result in constipation.

Commonly used Western medicine (WM) for constipation, including fiber supplements and laxatives, could cause side effects including nausea, vomiting, diarrhea, and even severe adverse events in certain special populations such as those with renal insufficiency (11, 12). Traditional Chinese herbal medicine (TCM) is commonly prescribed in treating and preventing constipation in clinical practice, particularly in Asian countries such as China (13–15), with good evidence found in some high-quality studies (16–20).

To date, findings on the efficacy and safety of TCM for antipsychotic-related constipation compared with WM have been inconsistent. Recent reviews (21, 22) summarized the efficacy of TCM for antipsychotic-related constipation but only included publications in English databases, even though most relevant studies were only published in Chinese language journals. Consequently, only two studies conducted in China were included; one study (23) focused on physical therapy of traditional Chinese Medicine (e.g., acupuncture and Tuina) and the other focused on the use of 250 ml of 10% mannitol with 2 g of Rhubarb-soda plus 0.8 g of Phenolphthalein Tablets (24). This gave us the impetus to conduct this systematic review and meta-analysis of randomized controlled trials (RCTs) of the efficacy and safety TCM and WM in treating antipsychotic-related constipation.

MATERIALS AND METHODS

This meta-analysis was registered in PROSPERO (CRD42020168832) and was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Eligibility Criteria and Outcome Measures

According to the PICOS acronym (25), the inclusion criteria were as follows: Participants (P): patients with constipation caused by antipsychotic medications. Intervention (I): TCM alone. Comparison (C): WM alone or concurrent use of two or more WMs. Outcomes (O): efficacy and safety of TCM. Study design (S): RCTs. Exclusion criteria included (a) severe physical comorbidities and (b) receiving physiotherapy alone or a combination of physiotherapy plus TCM for constipation. Primary outcome included three efficacy measures: moderate response rate, marked response rate, and remission rate. Secondary outcomes included treatment adherence and adverse drug reactions (ADRs), such as nausea, vomiting, and rash.

Search Strategy and Study Selection

Literature search in both international (PubMed, EMBASE, Cochrane Library, and Web of Science) and Chinese (Wanfang, WeiPu VIP, SinoMed, and CNKI) databases from inception to October 30, 2019, were independently conducted by two researchers (WWR and JJY), using both subject and free terms of the following search terms: "Constipation [MeSH]," "Medicine, Chinese Traditional [MeSH]," and "Randomized Controlled Trial [MeSH]" (**Supplementary Table 2**). An updated search to November 29, 2020, was also performed.

The same two researchers (WWR and JJY) independently screened titles and abstracts and then read full texts of relevant publications for eligibility. Any discrepancy was discussed with a third researcher (ZW). In addition, the reference lists of relevant reviews and previous meta-analysis (21, 22) were searched manually for additional studies.

Data Extraction

A pre-designed Excel data collection sheet was used to independently extract relevant data by two researchers (WWR and JJY). The following study and participant characteristics were extracted: the first author, year of publication and survey, sample size, type of medications, mean age of participants, proportion of males, and diagnostic criteria of psychiatric disorders and constipation. Any disagreement was resolved by consensus.

Quality Assessment and Evidence Level

The two researchers (WWR and JJY) independently assessed study quality using both the Jadad scale (0–5 points) (26) and Cochrane risk of bias tool (27). Studies with a Jadad total score of 3 or higher were considered as "high quality;" otherwise, they were considered as "low quality." The Grading of Recommendations Assessment, Development, and Evaluation

(GRADE) methodology was used to evaluate evidence level of primary and secondary outcomes (i.e., very low, low, moderate, or high) (28).

Statistical Analyses

Due to different sample sizes, types and doses of antipsychotic medications, and demographic characteristics between studies, the random-effects model was used to synthesize outcome data, with risk ratio (RRs) and its 95% confidence intervals (CIs) as the effect size. Heterogeneity was assessed using the Cochran's Q and I^2 statistic. I^2-values of $\geq$50% and P-value of $\leq$0.10 indicated great heterogeneity across studies. Publication bias was tested using forest plots, Egger's regression test, Begg's rank test, and Duval and Tweedie's trim-and-fill analysis. The sources of heterogeneity between studies on primary outcomes (e.g., moderate/marked response and remission rates of constipation) were examined by subgroup analyses for categorical variables [e.g., diagnostic criteria for psychiatry: Chinese Mental Disorder Classification and Diagnosis, Third Edition (CCMD-3) vs. Chinese Mental Disorder Classification and Diagnosis, Second Edition (CCMD-2)/Chinese Mental Disorder Classification and Diagnosis, Second Edition, Revised (CCMD-2-R) vs. International Classification of Diseases, Tenth Edition (ICD-10), geographic region (east vs. middle vs. west), analysis method (intent to treat vs. per-protocol), and inpatient group (Yes vs. Mix)] and meta-regression analyses for continuous variables (e.g., publication year, trial duration, Jadad total score, and overall sample size). Sensitivity analysis was carried out to identify outlying studies. All statistical analyses were performed using Comprehensive Meta Analysis (version 2.0; Biostat), with a significance level of 0.05 (two-sided).

RESULTS

Literature Search and Study Characteristics

A total of 1,725 articles were initially identified. After screening the titles and abstracts, 133 articles were retrieved for full-text review. Finally, 30 studies with 52 arms (2,570 patients in the TCM group and 2,511 patients in the WM group) were included for meta-analyses (**Figure 1**).

Included studies were published from 1993 to 2020. All studies were conducted in China: 19 studies were conducted in the eastern region, 8 in the central region, and 3 in the western region of China. Sixteen studies used the CCMD-3; two used the CCMD-2; one used the CCMD-2-R; one used the ICD-10; and ten studies did not report diagnostic criteria. The sample size ranged from 60 to 328, and mean age ranged between 28.08 and 69.85 years. Study duration ranged from 0.42 to 28 days (**Table 1**).

Assessment Quality and Outcome Evidence

The mean Jadad scores of the 30 studies ranged from 0 to 4 with a median of 1; of them, 3 were considered as "high quality" (**Table 1**). Non-blinded assessment and omission of reported dropout were the major reasons for low quality. For the assessment of Cochrane risk of bias, five RCTs mentioned "randomization" in detail (i.e., low risk), and five RCTs used randomization with incorrect methods (i.e., high risk). In addition, no RCT described allocation concealment; therefore, the biases were unclear. Two RCTs mentioned "blinding" (**Supplementary Figure 1**). The overall quality of the 13 meta-analyzable outcomes was rated as "moderate" (15.4%, 2/13) and "high" (3.03%, 1/13) according to the GRADE approach (**Supplementary Table 1**).

Systematic Review and Meta-Analysis

Response Rate

Traditional Chinese herbal medicine alone had significant advantages in terms of the moderate response rate (RR = 1.165; 95% CI: 1.096–1.238, $P < 0.001$, $I^2 = 77.17\%$, **Table 2**, **Supplementary Figure 2** and **Supplementary Table 3**), marked response rate (RR = 1.437; 95% CI: 1.267–1.692, $P < 0.001$, $I^2 = 81.40\%$, **Table 2**, **Supplementary Figure 3** and **Supplementary Table 3**), and remission rate (RR = 1.376; 95% CI: 1.180–1.606, $P < 0.001$, $I^2 = 78.88$, **Table 2**, **Supplementary Figure 4** and **Supplementary Table 3**) compared to WM. In contrast, no significant difference was found regarding the onset of response after treatment between TCM alone and WM groups (SMD = −0.142; 95% CI: −0.783–0.499; $P = 0.664$; $I^2 = 91.45$, **Table 2**).

Treatment Adherence

No difference was found between TCM alone and WM groups in both overall adherence, full adherence, and partial adherence rates (all P-values > 0.05; **Table 2**).

Adverse Drug Reactions

No group differences were found in most of the ADRs (e.g., diarrhea, nausea and vomiting, bloating/abdominal pain, borborygmus, and loose stools) (all P-values > 0.05; **Table 2**), while rash was less frequent (RR = 0.081, 95% CI: 0.019–0.342; $P = 0.001$; $I^2 = 0.0$) in the TCM alone group compared to the WM group (**Table 2**).

Three RCTs compared relapse or exacerbation rates of constipation after discontinuation and all studies found that those receiving WM has a higher relapse rate than those receiving TCM. Specifically, one RCT found that the TCM group had a significantly lower relapse rate than the WM group at 1, 3, and 6 months after discontinuation (36). Another RCT had a similar finding (TCM: 13.24% vs. WM:36.37%; $X^2 = 8.45$, $P < 0.01$) at 1 month after discontinuation (43). Jiang et al. (45) reported that some participants had relapsed after discontinuation in the WM group, but the result in the TCM group was not reported.

Subgroup and Meta-Regression Analyses

For the moderate response rate, subgroup and meta-regression analyses found that diagnostic criteria of psychiatric disorders (CCMD-2/CCMD-2-R vs. CCMD-3 vs. ICD-10), geographical region (east vs. middle vs. west), analysis method (intent to treat vs. per-protocol), inpatient group (Yes vs. Mix), trial duration ($\beta = -0.002$, $P = 0.128$, $n = 44$ arms), total sample size ($\beta = -0.0002$, $P = 0.473$), and sample size in the TCM group ($\beta = 0.0004$, $P = 0.315$) and WM group ($\beta = 0.0002$, $P = 0.717$) did

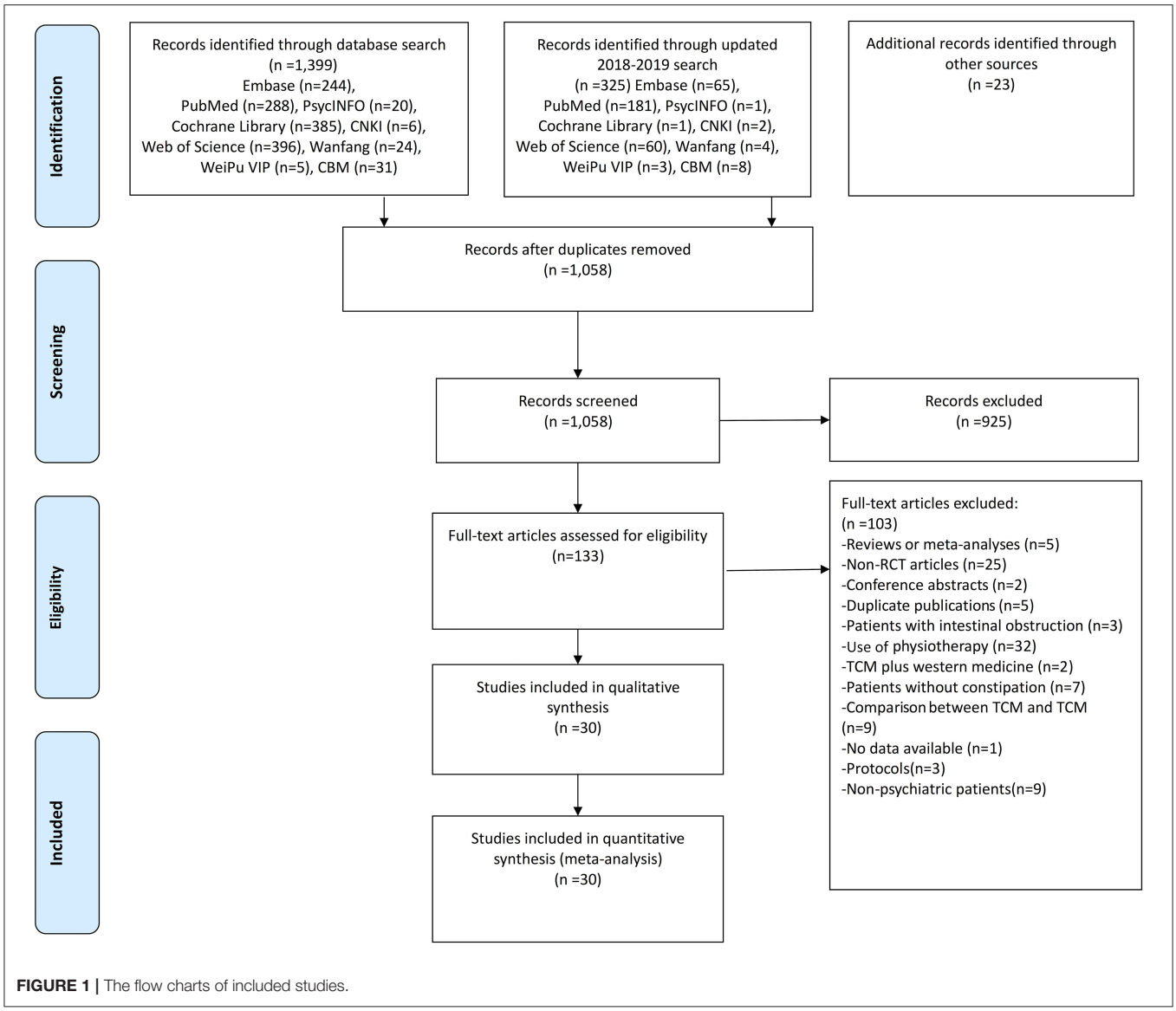


FIGURE 1 | The flow charts of included studies.

not moderate the primary results (all P-values > 0.05, **Table 3**), except for the publication year ($\beta = -0.007$, $P = 0.0007$) and Jadad score ($\beta = 0.067$, $P < 0.001$).

For the remission rate, subgroup analyses revealed that geographical region ($P = 0.003$) and inpatient group ($P = 0.035$) were significantly associated with the results (**Table 3**). Meta-regression analyses did not reveal significant moderating effects of the publication year ($\beta = 0.009$, $P = 0.110$), Jadad score ($\beta = -0.036$, $P = 0.624$), total sample size ($\beta = 0.0007$, $P = 0.337$), and sample size in the TCM ($\beta = 0.001$, $P = 0.469$) and WM groups ($\beta = 0.002$, $P = 0.248$) on the results, except for the trial duration ($\beta = 0.009$, $P = 0.013$, $n = 23$ arms).

Sensitivity Analysis and Publication Bias

After excluding one outlying study (37) with two arms in which two WMs were used, the primary results did not significantly change (moderate response rate: RR = 1.156, 95% CI: 1.087–1.230, $P < 0.001$, $I^2 = 77.47\%$; marked response rate: RR = 1.391, 95% CI: 1.229–1.575, $P < 0.001$, $I^2 = 80.96\%$). In addition, we excluded each study one by one, and no significant changes were found in the moderate response rate, marked response rate, or remission rate (**Supplementary Figures 8–10**).

Both Egger's and Begg's-tests (all P-values > 0.05) and funnel plot did not detect publication bias in most outcomes, but publication bias was found in moderate response rate (Egger's-test: $t = 4.248$, $P < 0.001$; Begg's-test: $Z = 2.793$, $P = 0.005$; **Table 2** and **Supplementary Figure 5**), marked response rate (Begg's-test: $Z = 4.379$, $P < 0.001$; Egger's-test: $t = 5.790$, $P < 0.001$; **Table 2** and **Supplementary Figure 6**), remission rate (Begg's-test: $Z = 3.384$, $P < 0.001$; Egger's-test: $t = 3.855$, $P < 0.001$; **Table 2** and **Supplementary Figure 7**), and rash (Egger's test, $P = 0.017$, **Table 2**). Duval and Tweedie's trim-and-fill analysis did not find any missing study, which indicates that no

TABLE 1 | Characteristics of studies included in this meta-analysis.

No.	First author	Publication year	Survey year	Total sample size	Age (Mean ± SD)	Age range	Male (%)	ACT	Province	Region	Inpatients	Analysis	Diagnostic criteria	Type of disorder	Type of medication	Diagnostic criteria for constipation	Randomization	Blinding	Withdrawal and dropouts	Total score of Jadad	References
1	Zhao et al.	1993	1991–1992	180	38.6 ± 11.64	18–69	144 (80)	(117.3 ± 6.84) h	Shandong	E	Yes	ITT	NR	SCH, AD, ND, and PMD	CL, CH, PE, HA, TF, and others	At least 4 days without stool	2	2	0	4	(29)
2	Ding	1998	1996	174	NR	17–60	144 (82.8)	NR	Jiangsu	E	Yes	ITT	CC-MD-2	SCH, AD, and others	CL and others	72 h without stool	1	0	0	1	(30)
3	Wang et al.	1998	NR	181	36.19 ± 8.80	18–52	117 (64.6)	(4.62 ± 0.60) d	Shanxi	M	Yes	ITT	NR	SCH	CL	Lasting 4 days or more with no stool	1	0	0	1	(31)
4	Liu et al.	2001	NR	60	38.05 ± 7.89	NR	44 (73.33)	NR	Shaanxi	W	Yes	ITT	NR	SCH	PA	Criterion I	1	0	0	1	(32)
5	Hu et al.	2002	2000–2001	90	67.4 ± 12.6	18–87	48 (53.3)	NR	Guangdong	E	Yes	ITT	NR	NR	NR	More than 3 days with no stool	1	0	0	1	(33)
6	Li	2003	2002–2003	261	NR	17–60	216 (82.8)	NR	Beijing	E	Yes	ITT	CC-MD-2	SCH, AD, and others	CL and others	72 h without stool	1	0	0	1	(34)
7	Zhang	2003	2001	60	38.3 ± 11.77	NR	27 (45.0)	(5.39 ± 2.85) d	Henan	M	Yes	ITT	NR	NR	NR	Lasting 3 days with no stool	1	0	0	1	(35)
8	Li et al.	2005	1999–2003	97	28.73 ± NR	17–57	56 (57.7)	NR	Guizhou	W	Mix	ITT	CC-MD-3	SCH, MA, RP, and others	CH	Criterion F	1	0	0	1	(36)
9	Li et al.	2005	2003–2004	90	41.3 ± 17.3	18–72	90 (100)	NR	Shandong	E	Yes	ITT	CC-MD-2-R	NR	NR	Criterion A	1	0	0	1	(37)
10	Sheng et al.	2006	2005–2006	118	32.6 ± 3.2	16–56	72 (61.0)	NR	Anhui	M	Yes	ITT	CC-MD-3	SCH, DP, and others	CL, CH, SU, PE, and others	At least 3 days without stool	0	0	0	0	(38)
11	Meng et al.	2007	2004	328	28.47 ± 10.33	NR	229 (69.8)	NR	Shandong	E	Yes	ITT	NR	NR	NR	Criterion G	1	0	0	1	(39)
12	Wang et al.	2007	2002–2006	120	38.2 ± 15.3	16–64	87 (72.5)	NR	Hebei	E	Yes	ITT	CC-MD-3	SCH, AD, and others	NR	Criterion E	1	0	0	1	(40)
13	Du et al.	2008	2006–2007	115	28.8 ± 13.1	18–65	64 (55.7)	NR	Shanghai	E	Yes	ITT	CC-MD-3	SCH	CL, CH, SU, RI, and others	Criterion B	1	0	0	1	(41)
14	Han et al.	2008	2007–2008	150	39.2 ± 1.66	20–72	126 (84.0)	(115.2 ± 6.34) h	Shandong	E	Yes	ITT	CC-MD-3	SCH, AD, ND, and PMD	CL, CH, PE, HA, SU, RI, and others	More than 4 days with no stool	2	2	0	4	(42)
15	Lin et al.	2008	2007–2008	134	33.83 ± NR	15–58	87 (64.9)	NR	Guangdong	E	Mix	ITT	CC-MD-3	SCH, AD, and others	CH, RI, CL, PE, HA, and others	Criterion H	0	0	0	0	(43)
16	Xie et al.	2008	2007	96	NR	16–59	55 (57.3)	NR	Guangdong	E	Yes	ITT	CC-MD-3	SCH, MD, and SRD	CL, PE, HA, and SU	NR	0	0	0	0	(44)
17	Jiang	2009	2008–2009	87	28.08 ± 12.68	19–52	42 (48.3)	NR	Jiangxi	M	Yes	ITT	CC-MD-3	SCH	CL, CH, OL, and QF	Criterion C	1	0	0	1	(45)
18	Liu et al.	2010	2007	305	31.97 ± 10.29	NR	175 (57.4)	NR	Tianjin	E	Yes	ITT	NR	NR	NR	Criterion G	1	0	0	1	(46)
19	Li	2011	2008–2010	76	39.82 ± 11.00	NR	76 (100.0)	(5.33 ± 1.30) d	Henan	M	Yes	ITT	NR	SCH	CL	Lasting 3 days with no stool	1	0	0	1	(47)
20	Pan et al.	2012	2006–2007	80	33.15 ± 15.38	16–60	39 (48.8)	NR	Henan	M	Yes	ITT	CC-MD-3	SCH, AD, and others	CL, CH, SU, CLO, AM, and others	Lasting 3 days with no stool	1	0	0	1	(48)
21	Wang et al.	2013	NR	87	NR	17–60	NR	NR	Shandong	E	Yes	ITT	CC-MD-3	SCH, AD, and others	CL, RI	72 h without stool	1	0	0	1	(49)
22	Chen et al.	2014	2012–2013	258	48 ± 5	27–65	117 (45.4)	NR	Jiangsu	E	Yes	ITT	CC-MD-3	SCH, AD, and SAP	CL, RI, and others	72 h without self-defecation	1	0	0	1	(50)
23	Tian et al.	2014	2010–2011	119	69.85 ± 9.65	60–80	0 (0.0)	NR	Beijing	E	Yes	ITT	NR	SCH, ALD, VD, and DP	NR	Criterion J	1	0	0	1	(51)
24	Han	2015	2011–2013	100	NR	18–65*	54* (54.0)	NR	Tianjin	E	Yes	PP	CC-MD-3	SCH	NR	Criterion D	2	0	1	3	(52)
25	Ye et al.	2016	2015	192	NR	16–60	110 (57.3)	NR	Zhejiang	E	Yes	ITT	CC-MD-3	SCH and MD	CL, OL, QF, and RI	Criterion E	0	0	0	0	(53)
26	Zhao et al.	2016	2008–2009	120	49 ± NR	17–86	61 (50.8)	NR	Auhui	M	Yes	ITT	NR	NR	NR	More than 3 days with on stool	1	0	0	1	(54)

(Continued)

TABLE 1 | Continued

No.	First author	Publication year	Survey year	Total sample size	Age (Mean ± SD)	Age range	Male (%)	ACT	Province	Region	Inpatients	Analysis	Diagnostic criteria	Type of disorder	Type of medication	Diagnostic criteria for constipation	Randomization	Blinding	Withdrawal and dropouts	Total score of Jadad	References
27	Tang	2018	2015–2017	80	41.61 ± 11.13	20–60	47 (58.8)	(4.36 ± 1.25) d	Hubei	M	NR	ITT	CC-MD-3	NR	CL	Criterion G	0	0	0	0	(55)
28	Wang et al.	2019	2015–2017	100	38.6 ± 3.2	18–60	NR	NR	Guangdong	E	Yes	PP	ICD-10	SCH	NR	Lasting 3 days without stool + Criterion D	1	0	1	2	(56)
29	Zhu	2019	2017–2018	120	48.1 ± 4.87	25–68	76 (63.3)	NR	Zhejiang	E	Yes	ITT	CC-MD-3	SCH, AD	NR	Lasting 3 days without stool	2	0	0	2	(57)
30	Wu et al.	2020	2018–2019	70	38.85 ± 2.15	22–56	41 (58.6)	NR	Shanxi	W	Yes	ITT	CC-MD-3	SCH	NR	NR	2	0	0	2	(58)

Order of arms	*N*	Age (Mean ± SD)	Age range	Male (%)	ACT	Trial duration (days)	TCM						WM					
							N	Age (Mean ± SD)	Age range	Male (%)	ACT	Name	*N*	Age (Mean ± SD)	Age range	Male (%)	ACT	Name
1	120	NR	NR	NR	NR	1	60	NR	NR	NR	NR	Senna	60	NR	NR	NR	NR	Phenolphthalein
2	120	NR	NR	NR	NR	1	60	NR	NR	NR	NR	Rhei Radix Et Rhizoma	60	NR	NR	NR	NR	Phenolphthalein
1	95	NR	NR	NR	NR	23.38 (average)	51	NR	NR	NR	NR	Senna Mixture	44	NR	NR	NR	NR	Vitamin B1
2	84	NR	NR	NR	NR	22.94 (average)	51	NR	NR	NR	NR	Senna mixture	33	NR	NR	NR	NR	1.5% Saline
3	97	NR	NR	NR	NR	23.19 (average)	51	NR	NR	NR	NR	Senna Mixture	46	NR	NR	NR	NR	Glycerine Enema/0.2% Soapsuds Enema
1	181	36.19 ± 8.80	18–52	117 (64.6)	(4.62 + 0.60) d	1	89	35.54 ± 8.63	18-47	56 (62.9)	(4.65 ± 0.66) d	Senna	92	36.82 ± 8.92	20–52	61 (66.3)	(4.59 ± 0.54) d	Phenolphthalein
1	60	38.05 ± 7.89	NR	44 (73.33)	NR	7	30	38.3 ± 8.2	NR	23 (76.7)	NR	Yu Zhu Shu Tong	30	37.8 ± 7.7	NR	21 (70.0)	NR	Phenolphthalein
1	60	NR	NR	NR	NR	1	30	NR	NR	NR	NR	Senna	30	NR	NR	NR	NR	Phenolphthalein and Glycerine Enema
2	60	NR	NR	NR	NR	1	30	NR	NR	NR	NR	Senna	30	NR	NR	NR	NR	Phenolphthalein
1	117	NR	NR	NR	NR	25.14 (average)	66	NR	NR	NR	NR	Apricot seed and Linum formula	51	NR	NR	NR	NR	1.5% Saline
2	134	NR	NR	NR	NR	25.00 (average)	66	NR	NR	NR	NR	Apricot seed and Linum formula	68	NR	NR	NR	NR	Glycerine Enema/0.2% Soapsuds Enema
3	127	NR	NR	NR	NR	25.94 (average)	76	NR	NR	NR	NR	Senna mixture	51	NR	NR	NR	NR	1.5% Saline
4	144	NR	NR	NR	NR	25.72 (average)	76	NR	NR	NR	NR	Senna Mixture	68	NR	NR	NR	NR	Glycerine Enema/0.2% Soapsuds Enema
1	60	38.3 ± 11.77	NR	27 (45.0)	(5.39 ± 2.85) d	28	30	39.8 ± 11.1	NR	14 (46.7)	(5.32 ± 3.12) d	Qi Rong Run Chang oral liquid	30	36.8 ± 12.4	NR	13 (43.3)	(5.46 ± 2.61) d	Phenolphthalein

(Continued)

TABLE 1 | Continued

Order of arms	*N*	Age (Mean ± SD)	Age range	Male (%)	ACT	Trial duration (days)	TCM						WM					
							N	Age (Mean ± SD)	Age range	Male (%)	ACT	Name	*N*	Age (Mean ± SD)	Age range	Male (%)	ACT	Name
1	97	28.73 ± NR	17–57	56 (57.7)	NR	5	52	28.5 ± NR	18–55	29 (55.8)	NR	Peony and Licorice combination	45	29 ± NR	17–57	27 (60.0)	NR	Phenolphthalein
1	60	NR	NR	60 (100)	NR	1	30	NR	NR	NR	NR	Rhubarb and Mirabilite and Magnolia Officinalis Rehd et Wils formula	30	NR	NR	NR	NR	Phenolphthalein and Glycerine Enema
2	60	NR	NR	60 (100)	NR	1	30	NR	NR	NR	NR	Senna	30	NR	NR	NR	NR	Phenolphthalein and Glycerine Enema
1	118	32.6 ± 3.2	16–56	72 (61.0)	NR	0.42	58	NR	NR	NR	NR	Senna	60	NR	NR	NR	NR	10% Mannitol
1	328	28.47 ± 10.33	NR	229 (69.8)	NR	1	165	NR	NR	NR	NR	Senna	163	NR	NR	NR	NR	Phenolphthalein
1	80	NR	NR	NR	NR	3	40	NR	NR	NR	NR	Tongfu Qingyu decoction	40	NR	NR	NR	NR	Phenolphthalein
2	80	NR	NR	NR	NR	3	40	NR	NR	NR	NR	Senna	40	NR	NR	NR	NR	Phenolphthalein
1	87	29.10 ± 13.20	NR	46 (52.9)	NR	28	38	28.87 ± 13.81	NR	22 (57.9)	NR	Constipation-relief Capsule	49	29.27 ± 12.85	NR	24 (49.0)	NR	Phenolphthalein
2	77	28.80 ± 12.77	NR	42 (54.6)	NR	28	28	27.97 ± 12.81	NR	18 (64.3)	NR	Angelica and Rhubarb Combination	49	29.27 ± 12.85	NR	24 (49.0)	NR	Phenolphthalein
1	100	NR	NR	NR	NR	1	50	NR	NR	NR	NR	Senna	50	NR	NR	NR	NR	Phenolphthalein
2	100	NR	NR	NR	NR	1	50	NR	NR	NR	NR	Rhubarb	50	NR	NR	NR	NR	Phenolphthalein
1	134	33.83 ± NR	15–58	87 (64.9)	NR	7	68	34.34 ± NR	15–58	45 (66.2)	NR	Mazi Ren Wan	66	33.42 ± NR	15–56	42 (63.6)	NR	Phenolphthalein
1	64	NR	18–57	37 (57.8)	NR	1	32	NR	18–57	19 (59.4)	NR	Senna	32	NR	16–56	18 (56.3)	NR	20% Mannitol
2	64	NR	18–59	37 (57.8)	NR	1	32	NR	18–57	19 (59.4)	NR	Senna	32	NR	19–59	18 (56.3)	NR	Glycerine Enema
1	87	28.08 ± 12.68	19–52	42 (48.3)	NR	10	41	27.96 ± 12.75	NR	20 (48.8)	NR	Peony and Licorice combination	46	28.19 ± 12.77	NR	22 (47.8)	NR	Phenolphthalein
1	305	31.97 ± 10.29	NR	175 (57.4)	NR	NR	163	31.59 ± 10.12	NR	97 (59.5)	NR	Rheum Glycyrrhiza decoction	142	32.40 ± 10.51	NR	78 (54.9)	NR	Phenolphthalein
1	76	39.82 ± 11.00	NR	76 (100)	(5.33 ± 1.30) d	28	38	41.39 ± 10.47	NR	NR	(5.39 ± 1.22) d	Maren Runchang Wan	38	38.25 ± 11.43	NR	NR	(5.27 ± 1.39) d	Glycerine Enema/0.2% Soapsuds Enema
1	80	33.15 ± 15.38	16-60	39 (48.8)	NR	28	40	32.6 ± 16.2	18–60	18 (45.0)	NR	Tongbianling	40	33.7 ± 14.7	16–59	21 (52.5)	NR	Blank control
1	39	NR	NR	NR	NR	21	22	NR	NR	NR	NR	Ma Ren Wan	17	NR	NR	NR	NR	Saline
2	43	NR	NR	NR	NR	21	26	NR	NR	NR	NR	Senna	17	NR	NR	NR	NR	Saline
3	44	NR	NR	NR	NR	21	22	NR	NR	NR	NR	Ma Ren Wan	22	NR	NR	NR	NR	Glycerine Enema/Soapsuds Enema
4	48	NR	NR	NR	NR	21	26	NR	NR	NR	NR	Senna	22	NR	NR	NR	NR	Glycerine Enema/Soapsuds Enema

(Continued)

TABLE 1 | Continued

Order of arms	*N*	Age (Mean ± SD)	Age range	Male (%)	ACT	Trial duration (days)	TCM						WM					
							N	Age (Mean ± SD)	Age range	Male (%)	ACT	Name	*N*	Age (Mean ± SD)	Age range	Male (%)	ACT	Name
1	123	NR	NR	NR	NR	NR	57	NR	NR	NR	NR	Senna	66	NR	NR	NR	NR	Lactulose
2	128	NR	NR	NR	NR	NR	57	NR	NR	NR	NR	Senna	71	NR	NR	NR	NR	Phenolphthalein
3	121	NR	NR	NR	NR	NR	57	NR	NR	NR	NR	Senna	64	NR	NR	NR	NR	Glycerine Enema/0.2% Soapsuds Enema
1	119	69.85 ± 9.65	60–80	0 (0.0)	NR	28	60	69.3 ± 10.70	60–78	0 (0.0)	NR	Honeyed glycyrrhiza compound decoction	59	70.4 ± 8.5	61–80	0 (0.0)	NR	Glycerine Enema
1	98	NR	18–65*	54* (54.0)	NR	28	49	NR	18–65*	28* (56.0)	NR	Chinese medicine laxative capsule	49	NR	18–61*	26* (52.0)	NR	Phenolphthalein
1	128	NR	16–59	78 (60.9)	NR	3	64	NR	16–57	40 (62.5)	NR	Maren Ruan Capsule	64	NR	19–59	38 (59.4)	NR	Phenolphthalein
2	128	NR	17–59	74 (57.8)	NR	3	64	NR	17–57	36 (56.3)	NR	Senna	64	NR	19–59	38 (59.4)	NR	Phenolphthalein
1	60	NR	NR	NR	NR	0.5	30	NR	NR	NR	NR	Senna	30	NR	NR	NR	NR	Phenolphthalein
2	60	NR	NR	NR	NR	0.5	30	NR	NR	NR	NR	Senna	30	NR	NR	NR	NR	Retention enema with Glycerine Enema
3	60	NR	NR	NR	NR	0.5	30	NR	NR	NR	NR	Senna	30	NR	NR	NR	NR	Glycerine Enema
1	80	41.61 ± 11.13	20–60	47 (58.8)	(4.36 ± 1.25) d	NR	40	41.77 ± 11.34	20–60	32 (80.0)	(4.38 ± 1.25)d	Senna	40	41.45 ± 11.05	21–59	23 (57.5)	(4.33 ± 1.27) d	Phenolphthalein
1	96	38.6 ± 3.2	18–60	NR	NR	28	50	NR	NR	NR	NR	Maren Ruan Capsule	46	NR	NR	NR	NR	Phenolphthalein
1	60	48.15 ± 5.01	25–67	41 (68.3)	NR	NR	30	48.1 ± 5.0	25–67	22 (73.3)	NR	Senna	30	48.2 ± 5.1	26–66	19 (63.3)	NR	Lactulose
2	60	47.95 ± 4.91	25–68	40 (66.7)	NR	NR	30	48.1 ± 5.0	25–67	22 (73.3)	NR	Senna	30	47.8 ± 4.9	26–68	18 (60.0)	NR	Phenolphthalein
3	60	48.2 ± 4.80	25–67	39 (65.0)	NR	NR	30	48.1 ± 5.0	25–67	22 (73.3)	NR	Senna	30	48.3 ± 4.68	25–66	17 (56.7)	NR	Glycerine Enema/0.2% Soapsuds Enema
1	70	38.85 ± 2.15	22–56	41 (58.6)	NR	14	35	38.6 ± 2.2	24–56	21 (60.0)	NR	Peony and Licorice combination	35	39.1 ± 2.1	22–55	20 (57.1)	NR	Phenolphthalein

**Including patients with dropout.*

ACT, Average constipation time; h, Hour; d, Day; TCM, Traditional Chinese medicine; WM, Western medicine; CCMD-2, Chinese Mental Disorder Classification and Diagnosis, Second Edition; CCMD-2-R, Chinese Mental Disorder Classification and Diagnosis, Second Edition, Revised; CCMD-3, Chinese Mental Disorder Classification and Diagnosis, Third Edition; ICD-10, International Classification of diseases, Tenth Edition; Criterion A, Patient with abdominal distension, loss of appetite, difficulty in defecation, and no stool discharge for more than 3 days; Criterion B, One of three symptoms (decreasing times of fecal discharge or dry stool or difficult defecation) and a sign cluster (abdomen fullness and discomfort, palpable cord-like mass, dizziness, headache, short urination, dry mouth, bitter mouth, fatigue, irritability, etc.) due to the accumulation of belly stool (59); Criterion C, Patients with difficult fecal discharge, prolonging defecation time, only defecates once or has a feeling of defecation but cannot defecate in 4–6 days; Criterion D, Rome terion D difficult fe on Functional Constipation; Criterion E, diagnostic criteria from Thompson et al. (60); Criterion F, Diagnostic criteria for constipation with Yin deficiency syndrome (61); Criterion G, Lasting 3 days with no stool; dry stool; laborious defecation; Criterion H, Constipation severity criteria (level 0: without constipation and defecation one time in 1–2 days with soft stool; level 1: defecation one time in 2–3 days after medication and stiff stool into strips with difficulty in defecation; level 2: defecation one time in 3–4 days after medication and stiff stool into granular lumpy with difficulty in defecation; level 3: defecation one time in more than 5 days after medication, and lumpy stool with difficulty in defecation by yourself, even defecation by external forces); Criterion I, difficulty in defecation, no stool discharge for more than 3 days and change of defecation habits; Criterion J, Guideline for the diagnosis and treatment of chronic constipation (62); ITT, Intention to treat analysis; PP, per-protocol analysis; NR, Not Reported; SD, Standard deviation; SCH, Schizophrenia; AD, Affective disorders; DP, Depression; MD, Mood disorders; SRD, Stress-related disorders; ND, Neurotic disorders; PMD, Psychogenic mental disorders, Ma, Mania; RP, Reactive psychosis; SAP, Schizo-affective psychosis; ALD, Alzheimer's disease; VD, Vascular dementia; CL, Clozapine; CH, Chlorpromazine; SU, Sulpiride; PE, Perphenazine; RI, Risperidone; HA, Haloperidol; OL, Olanzapine; QF, Quetiapine fumarate; TF, Trifluoperazine; PA, Phenothiazine antipsychotics; CLO, Clomipramine; AM, Amitriptyline.

TABLE 2 | Primary and secondary outcomes of traditional Chinese medicine for constipation.

Variables	Number of studies	Case (*n*)	Control (*n*)	RRs/SMD (95% CI)	I^2 (%)	Q (*P*)	*P*	Classic fail-safe *N*	Begg (*P*)	Egger (*P*)	Trim and fill (adjusted value, RRs, 95% CI)		
Clinical efficacy:													
Moderate response rate	52	2,570	2,511	1.165 (1.096–1.238)	77.17	210.27 (<0.001)	**<0.001**	933	0.005	<0.001	8	1.100	1.030–1.174
Marked response rate	44	2,167	2,105	1.437 (1.267–1.692)	81.40	231.16 (<0.001)	**<0.001**	1,126	<0.001	<0.001	10	1.219	1.067–1.392
Remission rate	31	1,641	1,581	1.376 (1.180–1.606)	78.88	142.02 (<0.001)	**<0.001**	368	<0.001	<0.001	2	1.440	1.231–1.685
Time of onset	5	276	216	−0.142 (−0.783–0.499)	91.45	46.78 (<0.001)	0.664	0	0.624	0.653	1	−0.028	−0.592–0.536
Treatment adherence:													
Total adherence rate	4	192	192	0.988 (0.785–1.242)	78.18	13.75 (0.003)	0.915	0	0.497	0.872	0	0.988	0.785–1.242
Full adherence rate	4	192	192	0.974 (0.558–1.700)	86.14	21.65 (<0.001)	0.926	0	0.497	0.859	0	0.974	0.558–1.700
Partial adherence rate	4	192	192	1.024 (0.725–1.448)	1.51	3.05 (0.385)	0.891	0	1.000	0.716	0	1.024	0.725–1.448
Adverse drug reactions:													
Diarrhea	18	822	733	1.596 (0.976–2.610)	58.15	40.63 (0.001)	0.063	22	0.880	0.762	0	1.596	0.976–2.610
Nausea and vomiting	8	450	396	2.602. (0.885–7.650)	0.00	3.305 (0.855)	0.082	0	0.711	0.756	3	1.880	0.752–4.702
Bloating/abdominal pain	24	1,274	1,250	1.464 (0.934–2.296)	71.06	79.47 (<0.001)	0.097	29	0.691	0.182	4	1.126	0.708–1.792
Borborygmus	4	418	391	0.964 (0.517–1.798)	55.37	6.72 (0.081)	0.908	0	0.497	0.292	0	0.964	0.517–1.798
Loose stools	4	418	391	0.695 (0.287–1.685)	85.16	20.21 (<0.001)	0.421	0	0.497	0.672	0	0.695	0.287–1.685
Rash	4	418	391	0.081 (0.019–0.342)	0.00	0.17 (0.981)	**0.001**	9	0.174	0.017	0	0.081	0.019–0.342

Bold values: P < 0.05. CI, confidence intervals; RRs, risk ratio; SMD, standard mean differences.

missing effect size qualitatively influence the primary results in all outcomes, except for the moderate response rate (missing studies = 8; new RR = 1.1, 95% CI: 1.030–1.174), marked response rate (missing studies = 10; new RR = 1.219, 95% CI: 1.067–1.392), remission rate (missing studies = 2; new RR = 1.440, 95% CI: 1.231–1.685), time of onset (missing studies = 1; new SMD = −0.028, 95% CI: −0.592–0.536), nausea and vomiting (missing studies = 3; new RR = 1.880, 95% CI: 0.752–4.702), and bloating/abdominal (missing studies = 4; new RR = 1.126, 95% CI: 0.708–1.792).

DISCUSSION

This was the first systematic review and meta-analysis that examined the efficacy and safety of TCM in treating antipsychotic-related constipation. Commonly prescribed TCM included Senna, Apricot Seed and Linum Formula, Ma Ren Wan, etc., while WM included Phenolphthalein, Glycerine Enema, etc. We found that TCM alone was superior to WM in terms of moderate response rate, marked response rate, and remission rate for constipation, while TCM alone was significantly associated with lower risk of rash. Skin rash is a common side effect associated with certain Western drug allergy (63) including antipsychotic drugs (64–66). In this meta-analysis compared to WM, TCM has a lower risk of rash. Traditional Chinese herbal medicine has been widely prescribed in China in treating antipsychotic drug-induced constipation (67), and TCM prescriptions strictly follow relevant treatment guidelines and regulations (68).

Our efficacy findings are similar to the findings of large case–control studies (69). An earlier review found that TCM was more effective than cisapride (RR = 0.24, 95% CI: 0.17–0.34), polyethylene glycol (RR = 0.14, 95% CI: 0.06–0.34), mosapride (RR = 0.33, 95% CI: 0.23–0.46), and phenolphthalein (RR = 0.24, 95% CI: 0.13–0.46) in treating functional constipation (13), which is consistent with the findings of this study and another meta-analysis (70). Traditional Chinese herbal medicine appears more effective for constipation than WM; however, due to the variety of components found across TCM, the mechanisms are still not clear. To date, no basic science research on the efficacy of TCM for constipation have been published.

Subgroup analyses revealed that the remission rate for treating constipation was moderated by geographical regions. When comparing TCM with WM, the RR of TCM vs. WM was 1.219 (95% CI: 1.044–1.423) in the eastern region and 3.713 (95% CI: 1.988–6.902) in the central region, while no difference was found in the western region of China. It should be noted that most studies were conducted in the eastern region, and only two studies with small sample size were conducted in the western region of China; therefore, the results of this subgroup analysis may not be stable. The different dietary habits among populations between regions in China may be partly responsible for the discrepancy. For example, many people in the central region of China (e.g., Hunan, Hubei, and Jianxi provinces) prefer spicy foods, which could increase the risk of constipation (71), while

TABLE 3 | Subgroup analyses of response rate and remission of traditional Chinese medicine compared with Western medicine for constipation.

Subgroups	Categories (number of studies)	Sample size	RRs	95% Confidence interval (%) (lower, upper)	I^2 (%)	*P* within subgroup	*P* across subgroups
Moderate response rate							
Diagnostic criteria	CCMD-2/2-R (9)	918	1.214	(0.978, 1.509)	70.0	0.001	0.470
	CCMD-3 (27)	2,301	1.084	(1.012, 1.162)	75.1	<0.001	
	ICD-10 (1)	96	1.176	(0.989, 1.397)	0.0	1.000	
Analysis	ITT (47)	4,595	1.169	(1.097, 1.246)	78.0	<0.001	0.475
	PP (2)	194	1.112	(0.983, 1.257)	0.0	0.368	
Region	East (38)	3,873	1.136	(1.067, 1.208)	71.9	<0.001	0.118
	Middle (9)	786	1.465	(1.157, 1.856)	89.4	<0.001	
	West (2)	130	1.120	(0.946, 1.326)	12.7	0.284	
Inpatient	Yes (47)	4,575	1.172	(1.097, 1.251)	77.9	<0.001	0.064
	Mix (1)	134	1.066	(0.989, 1.149)	0.0	1.000	
Publication year*	≤2,008 (25)	2,788	1.152	(1.062, 1.251)	78.3	<0.001	0.627
	>2,008 (24)	2,293	1.189	(1.079, 1.310)	76.9	<0.001	
Remission rate							
Diagnostic criteria	CCMD-2 (7)	798	1.168	(0.883, 1.544)	74.2	0.001	0.818
	CCMD-3 (19)	1,536	1.212	(1.039, 1.414)	67.0	<0.001	
Analysis	ITT (30)	3,124	1.386	(1.185, 1.622)	79.6	<0.001	0.487
	PP (1)	98	1.083	(0.550, 2.133)	0.0	1.000	
Region	East (24)	2,672	1.219	(1.044, 1.423)	71.9	<0.001	**0.003**
	Middle (5)	383	3.713	(1.988, 6.902)	68.6	0.013	
	West (2)	167	1.191	(0.803, 1.767)	74.1	0.049	
Inpatient	Yes (28)	2,854	1.425	(1.185, 1.713)	80.2	<0.001	**0.035**
	Mix (2)	231	1.078	(0.898, 1.294)	42.7	0.186	
Publication year*	≤2,011 (16)	2,049	1.310	(1.074, 1.598)	77.7	<0.001	0.478
	>2,011 (15)	1,173	1.475	(1.137, 1.914)	81.0	<0.001	

**Based on the median splitting method.*

Bold values: P < 0.05. CCMD-2, Chinese Mental Disorder Classification and Diagnosis, Second Edition; CCMD-2-R, Chinese Mental Disorder Classification and Diagnosis, Second Edition, Revised; CCMD-3, Chinese Mental Disorder Classification and Diagnosis, Third Edition; ICD-10, International Classification of diseases, Tenth Edition; ITT, Intention to treat analysis; PP, per-protocol analysis.

those in the eastern region prefer bland foods. The advantage of TCM in terms of remission rate was more obvious in the inpatient group compared to the mixed inpatient and outpatient group, which may be related to better treatment adherence among inpatients (72, 73) or due to a small number of studies on mixed patient sample ($n = 2$). As expected, meta-regression analysis found that a longer trial duration ($\beta = 0.009$, $P = 0.013$) was associated with a higher remission rate of constipation, probably because the delivery of TCM is more stable in longer studies. Meta-regression demonstrated that the moderate response rate was negatively related to the publication year ($\beta = -0.007$, $P = 0.0007$). We speculate that first-generation antipsychotics (FGAs) were widely used in the past, which often led to severe constipation (1). In the past decade, however, FGAs have been gradually replaced by second-generation antipsychotics (SGAs). In contrast, SGAs are less likely to cause severe constipation (74, 75). Unexpectedly, compared to those with only mild constipation, patients with severe constipation were often more likely to respond to TCM. We speculate that the doses of TCM and types of constipation may moderate this association although relevant data were insufficient to clarify this finding, which needs to be confirmed in future studies. The association of the higher response rate with higher-quality studies might be due to the fact that response is more likely to be identified in higher-quality studies, e.g., those with well-trained researchers and sensitive assessment tools.

The strengths of this systematic review and meta-analysis included the inclusion of both international and Chinese databases, large number of included studies, large sample size, and use of sophisticated analyses (e.g., subgroup, meta-regression, and sensitivity analyses). Some methodological limitations should be noted. First, all studies were conducted in China, which may limit the generalizability of the findings to other parts of the world. Additionally, the included studies were not large-scale RCTs. Second, the active ingredients of TCM and their optimal doses for constipation were not analyzed due to insufficient data. Unlike WM, due to the varied ingredients in most TCM, no dosages were provided as they were only administered as tablets and/or capsules in clinical practice. Also, due to different components and forms of TCM between

included RCTs, head-to-head comparisons of TCM could not be conducted in this meta-analysis. Third, some factors related to constipation, such as lifestyle, outdoor activities and physical exercise status of participants, types and doses of antipsychotic medications, and major physical conditions, were not reported in most of the included studies. Finally, the efficacy and side effects between different TCMs were not compared due to the small number of studies in each subgroup.

In conclusion, this meta-analysis found that the efficacy of TCM on antipsychotic-related constipation was greater compared to WM, but certain side effects of TCM, such as rash, were less frequent. Hence, TCM appears to be an effective and safe treatment for antipsychotic-related constipation in clinical practice. However, these findings will need to be confirmed in future high-quality studies.

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-WR, Y-TX, and WZ: study design. W-WR, J-JY, HQ, and SS: data collection, analysis, and interpretation. W-WR, HQ, and Y-TX: drafting of the manuscript. LZ, GU, and CN: critical revision of the manuscript. All authors: approval of the final version for publication.

FUNDING

This study was supported by the National Science and Technology Major Project for investigational new drug (2018ZX09201-014), the Beijing Municipal Science and Technology Commission (No. Z181100001518005), and the University of Macau (MYRG2019-00066-FHS).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.610171/full#supplementary-material

REFERENCES

1. De Hert M, Dockx L, Bernagie C, Peuskens B, Sweers K, Leucht S, et al. Prevalence and severity of antipsychotic related constipation in patients with schizophrenia: a retrospective descriptive study. *BMC Gastroenterology.* (2011) 11:17. doi: 10.1186/1471-230X-11-17
2. Lu Y-S, Chen Y-C, Kuo S-H, Tsai C-H. Prevalence of antipsychotic drugs related to constipation in patients with schizophrenia. *Taiwan J Psychiatry.* (2016) 30:294–9.
3. Shirazi A, Stubbs B, Gomez L, Moore S, Gaughran F, Flanagan RJ, et al. Prevalence and predictors of clozapine-associated constipation: a systematic review and meta-analysis. *Int J Mol Sci.* (2016) 17:863. doi: 10.3390/ijms17060863
4. Freudenreich O, Goff DC. Colon perforation and peritonitis associated with clozapine. *J Clin Psychiatry.* (2000) 61:950. doi: 10.4088/JCP.v61n1210e
5. De Hert M, Hudyana H, Dockx L, Bernagie C, Sweers K, Tack J, et al. Second-generation antipsychotics and constipation: a review of the literature. *Eur Psychiatry.* (2011) 26:34–44. doi: 10.1016/j.eurpsy.2010.03.003
6. Talley NJ, Jones M, Nuyts G, Dubois D. Risk factors for chronic constipation based on a general practice sample. *Am J Gastroenterol.* (2003) 98:1107–11. doi: 10.1111/j.1572-0241.2003.07465.x
7. Nielsen J, Meyer JM. Risk factors for ileus in patients with schizophrenia. *Schizophr Bull.* (2012) 38:592–8. doi: 10.1093/schbul/sbq137
8. Stroup TS, Lieberman JA, McEvoy JP, Swartz MS, Davis SM, Rosenheck RA, et al. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *Am J Psychiatry.* (2006) 163:611–22. doi: 10.1176/ajp.2006.163.4.611
9. Every-Palmer S, Nowitz M, Stanley J, Grant E, Huthwaite M, Dunn H, et al. Clozapine-treated patients have marked gastrointestinal hypomotility, the probable basis of life-threatening gastrointestinal complications: a cross sectional study. *EBioMedicine.* (2016) 5:125–34. doi: 10.1016/j.ebiom.2016.02.020
10. West S, Rowbotham D, Xiong G, Kenedi C. Clozapine induced gastrointestinal hypomotility: a potentially life threatening adverse event. *Rev Lit Gen Hosp Psychiatry.* (2017) 46:32–7. doi: 10.1016/j.genhosppsych.2017.02.004
11. Arnaud M. Mild dehydration: a risk factor of constipation? *Eur J Clin Nutr.* (2003) 57:S88–95. doi: 10.1038/sj.ejcn.1601907
12. Gallagher P, O'Mahony D. Constipation in old age. *Best Pract Res Clin Gastroenterol.* (2009) 23:875–87. doi: 10.1016/j.bpg.2009.09.001
13. Cheng CW, Zhao-Xiang B, Tai-Xiang W. Systematic review of Chinese herbal medicine for functional constipation. *World J Gastroenterol.* (2009) 15:4886–95. doi: 10.3748/wjg.15.4886
14. Lin L-W, Fu Y-T, Dunning T, Zhang AL, Ho T-H, Duke M, et al. Efficacy of traditional Chinese medicine for the management of constipation: a systematic review. *J Altern Complement Med.* (2009) 15:1335–46. doi: 10.1089/acm.2008.0373
15. Zhai J, Li Y, Lin J, Dong S, Si J, Zhang J. Chinese herbal medicine for postpartum constipation: a protocol of systematic review and meta-analysis. *BMJ Open.* (2019) 9:e023941. doi: 10.1136/bmjopen-2018-025891
16. Eliasvandi P, Khodaie L, Mohammad Alizadeh Charandabi S, Mirghafourvand M. Effect of an herbal capsule on chronic constipation among menopausal women: a randomized controlled clinical trial. *Avicenna J Phytomed.* (2019) 9:517–29. doi: 10.22038/AJP.2019.13109
17. Zhong LLD, Cheng CW, Kun W, Dai L, Hu DD, Ning ZW, et al. Efficacy of MaZiRenWan, a Chinese herbal medicine, in patients with functional constipation in a randomized controlled trial. *Clin Gastroenterol Hepatol.* (2019) 17:1303–20. doi: 10.1016/j.cgh.2018.04.005
18. Chen P, Jiang L, Geng H, Han X, Wu S, Wang Y, et al. Effectiveness of Xinglouchengqi decoction on constipation in patients with acute ischemic stroke: a randomized controlled trial. *J Tradit Chin Med.* (2020) 40:112–20. doi: 10.19852/j.cnki.jtcm.2020.01.012
19. Huang T, Zhao L, Lin CY, Lu L, Ning ZW, Hu DD, et al. Chinese herbal medicine (MaZiRenWan) improves bowel movement in functional constipation through down-regulating oleamide. *Front Pharmacol.* (2020) 10:1570. doi: 10.3389/fphar.2019.01570
20. Jin ZH, Liu ZT, Kang L, Yang AR, Zhao HB, Yan XY, et al. A randomized double-blind placebo-controlled multicenter trial of Bushen Yisui and Ziyin Jiangzhuo formula for constipation in Parkinson disease. *Medicine.* (2020) 99:e21145. doi: 10.1097/MD.0000000000021145
21. Every-Palmer S, Newton-Howes G, Clarke MJ. Pharmacological treatment for antipsychotic-related constipation. *Schizophr Bull.* (2017) 43:490–2. doi: 10.1093/schbul/sbx011
22. Every-Palmer S, Newton-Howes G, Clarke MJ. Pharmacological treatment for antipsychotic-related constipation. *Cochrane Database Syst Rev.* (2017) 1:CD011128. doi: 10.1002/14651858.CD011128.pub2

23. Fan YW, Luo WL. Clinical study on treatment of constipation caused by antipsychotic drugs with acupuncture and Tuina combined with laxative suppository. *J Acupunct Tuina Sci.* (2004) 2:51–4. doi: 10.1007/BF02845405
24. Wang SM, Wang GZ. Oral administration of 10% mannitol treatment of psychiatric drug-induced constipation (in Chinese). *J Zhangjiakou Med Coll.* (1995) 2:110–1.
25. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med.* (2009) 151:264–9. doi: 10.7326/0003-4819-151-4-200908180-00135
26. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials.* (1996) 17:1–12. doi: 10.1016/0197-2456(95)00134-4
27. Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane Collaboration Version 5.1.0 (2011).
28. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. *BMJ.* (2004) 328:1490. doi: 10.1136/bmj.328.7454.1490
29. Zhao LM, Wang YX, Sun SH, Zou JH. Senna treatment for drug-induced constipation: a double-blind, randomized controlled tria (in Chinese). *Shanghai Arch Psychiatry.* (1993) 5:107–8.
30. Ding ZM. Study on the best therapy for neuroleptic-induced astriction (in Chinese). *J Nurs Sci.* (1998) 13:197–9.
31. Wang LH, Dong GH, Li JK. Clinical observation on senna in the treatment of 89 cases with clozapine-induced constipation (in Chinese). *Shanxi J Tradit Chin Med.* (1998) 14:10–1.
32. Liu ZJ, He L, Yao DG, Zhai HJ. Clinical research of Yu Zhu Shu Tong treatment on antipsychotic-induced constipation (in Chinese). *Med J Chin Civil Admin.* (2001) 13:333. doi: 10.3969/j.issn.1672-0369.2001.06.031
33. Hu CR, Jiang YB, Nie S. Clinical observation on senna in the treatment for constipation in patients with psychiatric disorders (in Chinese). *J Nurs Sci.* (2002) 17:338–9. doi: 10.3969/j.issn.1001-4152.2002.05.007
34. Li CW. Clinical observation on Apricot Seed and Linum Formula in the treatment of 261 cases with antipsychotic-related constipation (in Chinese). *Chin J Geriatr Care.* (2003) 1:33–4. doi: 10.3969/j.issn.1672-4860-B.2003.03.010
35. Zhang ZF. Qi Rong Run Chang oral liquid treatment for antipsychotic-induced constipation: a randomized controlled tria (in Chinese). *Henan J Pract Nerv Dis.* (2003) 6:115. doi: 10.3969/j.issn.1673-5110.2003.06.087
36. Li KQ, Xu Y, Jiang Y. Clinical observation on Peony and Licorice combination in the treatment of 52 cases with chlorpromazine-induced constipation (in Chinese). *Acta Academiae Medicinae Zunyi.* (2005) 28:470–1. doi: 10.3969/j.issn.1000-2715.2005.05.036
37. Li XY, Wang XL. Clinical study on treatment of antipsychotic-related constipation with Rhubarb and Mirabilite and Magnolia Officinalis Rehd et wils formula (in Chinese). *J Nurs Sci.* (2005) 20:43–4. doi: 10.3969/j.issn.1001-4152.2005.13.025
38. Sheng CD, Xie LY. Clinical study on treatment of antipsychotic-related constipation with oral 10 % Mannitol (in Chinese). *Chronic Pathematol J.* (2006) 12X: 45–6.
39. Meng QL, Zhang FY, Ruan JQ, Xu LR. A clinical control study between Senna and phenolphthalein in treatment of the coprostasis about patient with psychosis (in Chinese). *Medicine World.* (2007) 3:51–3.
40. Wang ZF, Sun SG. Clinical research of Tongfu qingyu decoction treatment on antipsychotic-induced constipation (in Chinese). *Chin J Postgrad Med.* (2007) 30:20–1. doi: 10.3760/cma.j.issn.1673-4904.2007.z2.011
41. Du YH, Yi ZH, Deng HY, Long B. Clinical study on treatment of antipsychotic-related constipation with constipation-relief capsule (in Chinese). *J Mod Clin Med.* (2008) 7:43–4.
42. Han YD, Ding LY, Liu GM, Yue DH. Clinical effective analysis of senne and rhubarb and phenolphthalein in the treatment of 150 patients with drug-induced constipation. *Chin J Pract Chin Mod Med.* (2008) 21:1619–20.
43. Lin H, Zhang HY, Xiang XX. Clinical observation on traditional chinese medicine in the treatment of 68 cases with antipsychotic-induced constipation (in Chinese). *Nei Mongol J Tradit Chin Med.* (2008) 7:17–8. doi: 10.3969/j.issn.1006-0979.2008.07.007
44. Xie ZY, Yao XF, Su M, Zhao YH. Clinical study on treatment of antipsychotic-related constipation with three methods of catharsis (in Chinese). *Int Med Health Guid.* (2008) 14:52–5. doi: 10.3760/cma.j.issn.1007-1245.2008.09.021
45. Jiang XJ. Clinical study on treatment of antipsychotic-related constipation with Peony and Licorice combination (in Chinese). *Chin Commun Doctors.* (2009) 19:120. doi: 10.3969/j.issn.1007-614x.2009.19.159
46. Liu BZ, Zhang J. Clinical observation on Rheum Glycyrrhiza decoction in the treatment of 163 pasychatic patients with constipation (in Chinese). *Shandong Med J.* (2010) 50:31. doi: 10.3969/j.issn.1002-266X.2010.52.016
47. Li ZY. Clinical research of Maren Runchang Wan treatment on clozapine-induced constipation: a randomized controlled tria (in Chinese). *China Foreign Med Treat.* (2011) 12:118. doi: 10.3969/j.issn.1674-0742.2011.12.093
48. Pan HP, Wu GX. Comparative observation on laxative drug treatment of constipation (in Chinese). *J Henan Univ Sci Technol (Med Sci).* (2012) 30:131–2. doi: 10.3969/j.issn.1672-688X.2012.02.026
49. Wang ZL, Yu X, Li ZC, Li ZX. Clinical study on treatments of constipation caused by antipsychotic drugs (in Chinese). *J Front Med.* (2013) 19:20. doi: 10.3969/j.issn.2095-1752.2013.19.015
50. Chen X, Yang Q. Clinical research of lactulose treatment on antipsychotic-induced constipation (in Chinese). *Chin J Clin Ration Drug Use.* (2014) 17:72. doi: 10.15887/j.cnki.13-1389/r.2014.17.122
51. Tian JB, Wang BM. Clinical observation on honeyed glycyrrhiza compound decoction in the treatment of 60 patients with drug-induced constipation (in Chinese). *Henan Tradit Chin Med.* (2014) 34:1226–7. doi: 10.16367/j.issn.1003-5028.2014.07.012
52. Han ZM. Clinical observation on Chinese medicine laxative capsule in the treatment of 50 cases with antipsychotic-related constipation (in Chinese). *Nei Mongol J Tradit Chin Med.* (2015) 4:8. doi: 10.3969/j.issn.1006-0979.2015.04.008
53. Ye FZ, Zhang SJ, Chen YL. Clinical study on treatment of antipsychotic-related constipation with Maren Ruan capsule (in Chinese). *Chin Tradit Herbal Drugs.* (2016) 47:2502–5. doi: 10.7501/j.issn.0253-2670.2016.14.019
54. Zhao JT, Tong YR, Yang YH, Huang J, Wang DB, Yang B. 40ml Glycerine with retention enema treatment for psychiatirc patients with constipation (in Chinese). *J Today Health.* (2016) 15:186. doi: 10.3969/j.issn.1671-5160.2016.07.173
55. Tang Y. Clinical efficacy of TCM medicine on constipation from clozapine (in Chinese). *Clin J Chin Med.* (2018) 10:84–5. doi: 10.3969/j.issn.1674-7860.2018.16.038
56. Wang Z, Liao JL, Zhong YH. Analysis on curative effect of Maren soft capsules on inpatients with schizophrenia complicated with constipation (in Chinese). *China Med Pharm.* (2019) 9:194–7. doi: 10.3969/j.issn.2095-0616.2019.01.056
57. Zhu Q. A randomized controlled trial of lactulose for antipsychotic-related constipation (in Chinese). *Home Med.* (2019) 7:127–8.
58. Wu XH, Cao GR. Clinical study on treatment of antipsychotic-related constipation with Peony and Licorice Combination (in Chinese). *Health Everyone.* (2020) 8:96.
59. He JC, Wen R. Diagnosis and treatment of constipation: a perspective of traditional Chinese medicine (in Chinese). *Liaoning J Tradit Chin Med.* (1998) 5:110.
60. Thompson W, Longstreth G, Drossman D, Heaton K, Irvine E, Müller-Lissner S. Functional bowel disorders and functional abdominal pain. *Gut.* (1999) 45(Suppl. 2):II43–7. doi: 10.1136/gut.45.2008.ii43
61. Xu AZ. *Chinese Medicine (in Chinese).* Beijing: People's Health Publishing House (2004).
62. Gastrointestinal Dynamics Group of Chinese Digestive Society. Guideline for the diagnosis and treatment of chronic constipation (in Chinese). *Chin Gen Pract.* (2005) 8:119–21. doi: 10.3969/j.issn.1007-9572.2005.02.016
63. Ardern-Jones MR, Friedmann PS. Skin manifestations of drug allergy. *Br J Clin Pharmacol.* (2011) 71:672–83. doi: 10.1111/j.1365-2125.2010.03703.x
64. Chae B-J, Kang B-J. Rash and desquamation associated with risperidone oral solution. *Prim Care Companion J Clin Psychiatry.* (2008) 10:414. doi: 10.4088/PCC.v10n0511e
65. Nath S, Rehman S, Kalita KN, Baruah A. Aripiprazole-induced skin rash. *Ind Psychiatry J.* (2016) 25:225. doi: 10.4103/0972-6748.207862
66. Shah M, Karia S, Merchant H, Shah N, De Sousa A. Olanzapine-induced skin rash: a case report. *Telangana J Psychiatry.* (2019) 5:70–1. doi: 10.18231/j.tjp.2019.013

67. Wang M, Li MC, Wang JH, Xin X, Ren L. Traditional medicine for antipsychotic drugs induced constipation: a bibliometric analysis of clinical studies. *Adv Integr Med*. (2019) 6:S115. doi: 10.1016/j.aimed.2019.03.333
68. World Traditional Medcine Forum. *Law of the People's Republic of China on Traditional Chinese Medicine*. (2020). Available online at: http://www.worldtmf.org/index/article/view/id/14008.html (accessed January 16, 2021).
69. Pan HP, Duan YS. Observation on 48 cases of drug-induced constipation treated by modified cannabis seed pills (in Chinese). *J Pract Tradit Chin Med*. (2010) 3:150–1. doi: 10.3969/j.issn.1004-2814.2010.03.003
70. Qi H, Liu R, Zheng W, Zhang L, Ungvari GS, Ng CH, et al. Efficacy and safety of traditional Chinese medicine for Tourette's syndrome: a meta-analysis of randomized controlled trials. *Asian J Psychiatry*. (2020) 47:101853. doi: 10.1016/j.ajp.2019.101853
71. Song J, Bai T, Zhang L, Hou XH. Clinical features and treatment options among Chinese adults with self-reported constipation: an internet-based survey. *J Dig Dis*. (2019) 20:409–14. doi: 10.1111/1751-2980.12792
72. Yun LJ. The impact of traditional chinese medicine pharmaceutical care on the medication compliance (in Chinese). *Hosp Dir Forum*. (2014) 4:47–9. doi: 10.3969/j.issn.1673-1700.2014.04.420
73. Dong M, Zeng LN, Zhang Q, Ungvari GS, Ng CH, Chiu HF, et al. Concurrent antipsychotic use in older adults treated with antidepressants in Asia. *Psychogeriatrics*. (2019) 19:333–9. doi: 10.1111/psyg.12416
74. Liu JF, Tong Y, Huang Y, Liu M, Ma J, Song T. Clinical efficacy and adverse effects of first and second generation antipsychotics (in Chinese). *J Clin Psychosom Dis*. (2008) 14:111–4. doi: 10.3969/j.issn.1672-187X.2008.02.006
75. Tang CT, Chua EC, Chew QH, He Y-L, Si T-M, Chiu HF-K, et al. Patterns of long acting injectable antipsychotic use and associated clinical factors in schizophrenia among 15 Asian countries and region. *Asia-Pacific Psychiatry*. (2020) 12:e12393. doi: 10.1111/appy.12393

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

The reviewer XW declared a shared affiliation, though no other collaboration, with several of the authors, HQ, SS, and LZ, to the handling Editor.

The reviewer QL declared a shared affiliation, though no other collaboration, with several of the authors, HQ, SS, and LZ, to the handling Editor.

frontiers in Psychiatry

REVIEW
published: 07 May 2021
doi: 10.3389/fpsyt.2021.658328

Acquired Brain Injury and Interventions in the Offender Population: A Systematic Review

Esther Q. J. de Geus[1], Maarten V. Milders[1], Joan E. van Horn[2], Frank A. Jonker[1,3], Thijs Fassaert[4], Juliette C. Hutten[2], Femke Kuipers[2], Christel Grimbergen[4] and Siri D. S. Noordermeer[1]*

[1] Department of Clinical Neuro- and Development Psychology, Faculty of Behavioral Sciences, Section of Clinical Neuropsychology, Vrije Universiteit Amsterdam, Amsterdam, Netherlands, [2] De Waag, Amsterdam, Netherlands, [3] Altrecht, Vesalius, Amsterdam, Netherlands, [4] Public Health Services, Amsterdam, Netherlands

Background and Aims: The prevalence of acquired brain injury (ABI) in offender populations appears much higher than in the general population, being estimated at 50% compared to 12%, respectively. Taking into account ABI-related cognitive and social impairments or behavioral changes in forensic treatments might be relevant and may improve treatment outcomes. The aim of the current review is to summarize and integrate the literature on psychological interventions or treatments for consequences of ABI in the forensic setting. Reviewing this literature could provide crucial information for improving treatment options for offenders with ABI, which may contribute to reducing recidivism.

Methods: The PubMed/MEDLINE, PsychInfo, CINAHL, COCHRANE, and Web of Science databases were searched for studies in adult offenders with ABI that evaluated the effect of psychological interventions with a focus on ABI-related impairments and recidivism.

Results: This review identified four intervention studies that met the inclusion criteria. These included an adult population (≥18-year-old) in a forensic setting (given the focus of the current review on treatment, defined here as an environment in which offenders are treated while being incarcerated or as outpatients), non-pharmacological treatments and were published in English or Dutch between 2005 and 2020. All studies reported some positive effects of the intervention on interpersonal behavior, cognition and recidivism. The aspects of the interventions that seemed most beneficial included personalized treatment and re-entry plans, support for the individual and their environment and psychoeducation about the effects of ABI.

Discussion: Although positive effects were reported in the studies reviewed, all studies had methodological limitations in terms of sample size, study design and outcome measures which affects the strength of the evidence. This limits strong conclusions and generalizability to the entire offender population.

Conclusion: Despite high prevalence of ABI in offender populations, interventions in forensic settings seldom address the effect of ABI. The few studies that did take ABI

OPEN ACCESS

Edited by:
Peter Andiné, University of Gothenburg, Sweden

Reviewed by:
Kirsten Jordan, University of Göttingen, Germany
Märta Wallinius, Lund University, Sweden

***Correspondence:**
Esther Q. J. de Geus
e.q.j.de.geus@vu.nl

Specialty section:
This article was submitted to Forensic Psychiatry, a section of the journal Frontiers in Psychiatry

Received: *25 January 2021*
Accepted: *08 April 2021*
Published: *07 May 2021*

Citation:
de Geus EQJ, Milders MV, van Horn JE, Jonker FA, Fassaert T, Hutten JC, Kuipers F, Grimbergen C and Noordermeer SDS (2021) Acquired Brain Injury and Interventions in the Offender Population: A Systematic Review. Front. Psychiatry 12:658328. doi: 10.3389/fpsyt.2021.658328

into account reported positive effects, but those results should be interpreted with caution. Future studies are warranted, since this does seem an important venue to improve treatment, which could eventually contribute to reducing recidivism.

Keywords: forensic, prison, intervention, recidivism, acquired brain injured, offenders

INTRODUCTION

Several studies in offender populations, which includes prisoners and in-patients and out-patients in forensic psychiatric settings, have reported considerably high acquired brain injury (ABI) prevalence estimates, with a mean estimated at 50%, ranging from 6% to 100% (1–4). This finding is important, as ABI-related cognitive and social impairments are associated with several deficits, among which are behavioral deficits such as aggression, substance abuse and even criminal behavior (2, 5). Research showed that ABI-related cognitive and social impairments contributed to more (previous) convictions and higher recidivism rates (6, 7). This underlines the importance of ABI awareness in forensic settings (i.e., environments in which offenders are treated while being incarcerated or as outpatients), and offender interventions, to possibly improve treatment options and ultimately reduce recidivism.

ABI is defined as "an injury to the brain that is not congenital, degenerative, hereditary or caused by a birth trauma" (8), and can be the result of both traumatic and non-traumatic causes. Non-traumatic causes include stroke, infection, tumor, or oxygen deficiency, affecting the brain. Traumatic brain injury (TBI) occurs when an external force injures the brain, with or without penetration of the skull, such as with falls, traffic accidents, or violence (9). Negative outcomes are seen in cognitive, emotional, and behavioral domains following all ABI types, but especially following TBI types (10, 11). The neurocognitive and behavioral consequences can be extensive and disabling. There is evidence that cognitive behavioral therapy (CGT), behavioral management techniques and metacognitive strategy training (e.g., self-monitoring, self-regulation and time pressure management) are effective interventions for ABI outcomes, such as aggression, executive dysfunction and social communication problems. For memory impairments it is recommended to use internalized strategies and external memory compensations. For all interventions it is important to promote generalization to daily functioning (12, 13).

Prevalence estimates of ABI in the general adult population vary widely, where prevalence rates between 1 and 35% have been reported (14–18). More specifically, the average prevalence of TBI is estimated at 12% according to a meta-analysis (19), whereas the prevalence of non-traumatic brain injury (stroke) is estimated at 5–10% (20). Variations in reported prevalence rates are largely due to the use of different definitions, assessment methods, and samples included. For instance, high prevalence rate studies included information from all ABI types, regardless of severity, collected through self-report, whereas low prevalence rate studies often only included cases based on objective TBI measurements from hospitalized TBI survivors (17). In comparison with the general population, prevalence of ABI in the offender population is considerably higher (21), and those estimations are likely to be underestimations because research in offender populations typically only focuses on TBI, and information about non-traumatic brain injury is usually not available. With regard to a specific subgroup of the offender population, namely forensic psychiatric patients who undergo treatment, comparable high prevalence rates have been reported (21, 22). The prevalence and extent of brain pathology in institutionalized offenders, compared to non-offenders, was significantly higher with a prevalence of 46% vs. 8% (21).

As in the general population, different definitions, assessment methods, and sample populations contributed to the wide variations in prevalence rates. More specifically, characteristics of the sample population that can contribute to higher TBI prevalence rates include low socioeconomic status and sex, with men being up to twice as likely to suffer a TBI than women (15, 19, 23). Age is also a contributing factor to the prevalence estimates, where men between the age of 18 and 25 are at a relatively high risk of TBI due to risk-taking behaviors, and individuals over 70 are at a higher risk of TBI due to falls (14, 19). Furthermore, different assessment methods of TBI have been used in forensic settings. In-depth interviews conducted by a trained psychological professional resulted in more accurate assessments and higher prevalence rates of TBI than the more frequently used short screening tools (1). Self-report measurements for TBI can be difficult because of memory deficits and lack of comprehension or understanding of the injury. Only a few studies used valid and reliable measurements to assess TBI, but even the use of valid and reliable screening tools does not fully account for the wide range of prevalence rates (3, 4). Lastly, different definitions of TBI are used (1). For example, taking into account the severity of TBI, often measured with the Glasgow Coma Scale (GCS), TBI can be classified as mild, moderate, or severe. Mild TBI corresponds with a high GCS score, while severe TBI corresponds with a low GCS score (24). However, this specific classification, that includes important characteristics using the GCS score, is often only reported for hospitalized TBIs, since it is difficult to obtain retroactively or with self-report (1).

The finding that TBI, as a form of ABI, is clearly more common in the offender than in the general population (25) is important, as TBI is associated with several deficits and negative outcomes. In terms of TBI-related cognitive impairments; executive functioning deficits, memory and attention deficits, and slowed information-processing are frequently reported (26–28). Negative outcomes following TBI are also seen in emotional functioning, including deficits in social communication, social cognition, emotion recognition, empathy, self-regulation or

self-control and self-awareness (26, 29–31). These deficits can be related to failures to understand others, to make appropriate emotional contributions, and problems with controlling one's behavior (32, 33). TBI-related impairments in social and cognitive functions can contribute to a wide range of anti-social behaviors, such as aggression, rule-breaking, and other risk-increasing behaviors such as substance abuse, which makes TBI a risk factor for prosecution and imprisonment (2, 3, 29, 34, 35). Prevalence rates of verbal and physical aggression were reported in the range from 4% up to 88% in TBI survivors and reflected a higher risk of convictions and (re)offending (6, 7, 36, 37). Severity of TBI could further exacerbate these behavioral problems (5, 38). Several longitudinal studies confirmed the positive relationship between severity of TBI and criminal behavior and an elevated risk of developing mental disorders, such as drug and alcohol dependence (5, 39, 40).

In sum, cognitive, emotional, and behavioral changes are common outcomes of ABI. As the prevalence of ABI, which mainly consists of TBI in the offender population, appears to be high, it is likely that the associated impairments are present in a substantial proportion of the offender population. In addition to difficulties in daily life, these impairments can also have a negative impact on treatment outcomes. For example, impaired self-awareness can cause difficulties in understanding the need for treatment and has been linked to poor treatment adherence (41). Furthermore, executive dysfunctions can be misunderstood as deliberate problem behavior, which can contribute to misconduct in prison. A mismatch between treatment and capacities can lead to low treatment adherence or discontinuation of treatment. The relationship between brain injury, recidivism, and prior incarcerations has been confirmed, showing that TBI-related violence and aggression contributed to more (previous) convictions and higher recidivism rates (6, 7, 36).

The primary aim of forensic interventions is to reduce recidivism, and these are often based on the Risk-Needs-Responsivity Model (42). To date, forensic treatment, which is mostly based on cognitive-behavioral techniques, results in modest improvements in terms of recidivism reduction in only 8–30% of those who complete treatment (43–45). However, attrition rates are relatively high, on average 30% (46–48). It is possible that the modest effectiveness of forensic treatment is in part due to ABI-related impairments not sufficiently being taken into account in treatment. Treatment in forensic settings is typically developed for patients with intact cognitive functions. Thus, even though ABI-related cognitive, emotional, and behavioral impairments are presumably common in this population, it is unclear whether forensic treatment takes these impairments into account. Suggestions for improving treatment or rehabilitation programs, by improving executive cognitive functioning have been reported and include individualized assessment of deficits and individualized functional rehabilitation (49). Reducing ABI-related cognitive, emotional, and behavioral impairments could result in better treatment outcomes (both adherence and continuation) and reduced recidivism, and may therefore become important treatment goals. The aim of the current study was to review the literature on interventions and treatment in offender populations suffering from ABI, or the influence of ABI on treatment. In the long run, improved treatment options and treatment outcomes may reduce the ABI-related impairments in offenders and, ultimately reduce recidivism.

METHODS

Search Strategy

A PRISMA systematic literature search was conducted using the following scientific databases: PubMed/MEDLINE, PsychInfo, CINAHL, COCHRANE, and Web of Science. Inclusion criteria were; research in adult populations (≥18-year-old) in a forensic setting (i.e., an environment in which offenders are treated while being incarcerated or as outpatients), non-pharmacological treatments, published in English or Dutch between 2005 and 2020. Key terms were adapted for each database and included variations of "acquired brain injury," "traumatic brain injury," "brain injury" OR "head injury" AND "rehabilitation," "treatment," "intervention," "therapy," "neurorehabilitation," "management" OR "psychotherapy" AND "forensic setting," "forensic population," "incarcerated," "prison" OR "offender population." To ensure that no articles were missed in the original search, the reference list of the articles meeting the inclusion criteria were also scanned.

Study Selection

In total 378 articles were retrieved from the databases and another 15 articles were retrieved from reference lists. After excluding duplicates, 234 articles remained. Two assessors independently conducted all the steps for article inclusion based on the inclusion criteria. Disagreements between the assessors were discussed until agreement was reached. Interrater reliability was excellent with high kappa scores for title inclusion (0.85), abstract inclusion (0.84), and article inclusion (1.00).

After screening of the 234 article titles, 154 articles were excluded based on the title, which indicated non-compliance with the inclusion criteria of this review. The abstracts of the remaining 80 articles were screened. Based on the abstracts, 58 articles were excluded because the article failed to meet the inclusion criteria, mostly because the study population was too young (aged <18), or relevant information about the intervention was missing. The 22 remaining articles were selected and reviewed in their entirety for inclusion. Finally, four articles were identified as meeting the criteria for inclusion in this review, see **Figure 1** for the PRISMA flow chart. Two of the studies were single case experimental design studies (51, 52) and two were single group experimental design studies (53, 54).

RESULTS

The two case studies had a total of 6 participants (all male) (51, 52) and the two group studies had a total of 80 participants (3 female and 77 male) (53, 54). In all studies, participants received a type of psychological intervention or treatment for consequences of ABI in the forensic setting. The characteristics of each study, including age, gender, sample size, intervention,

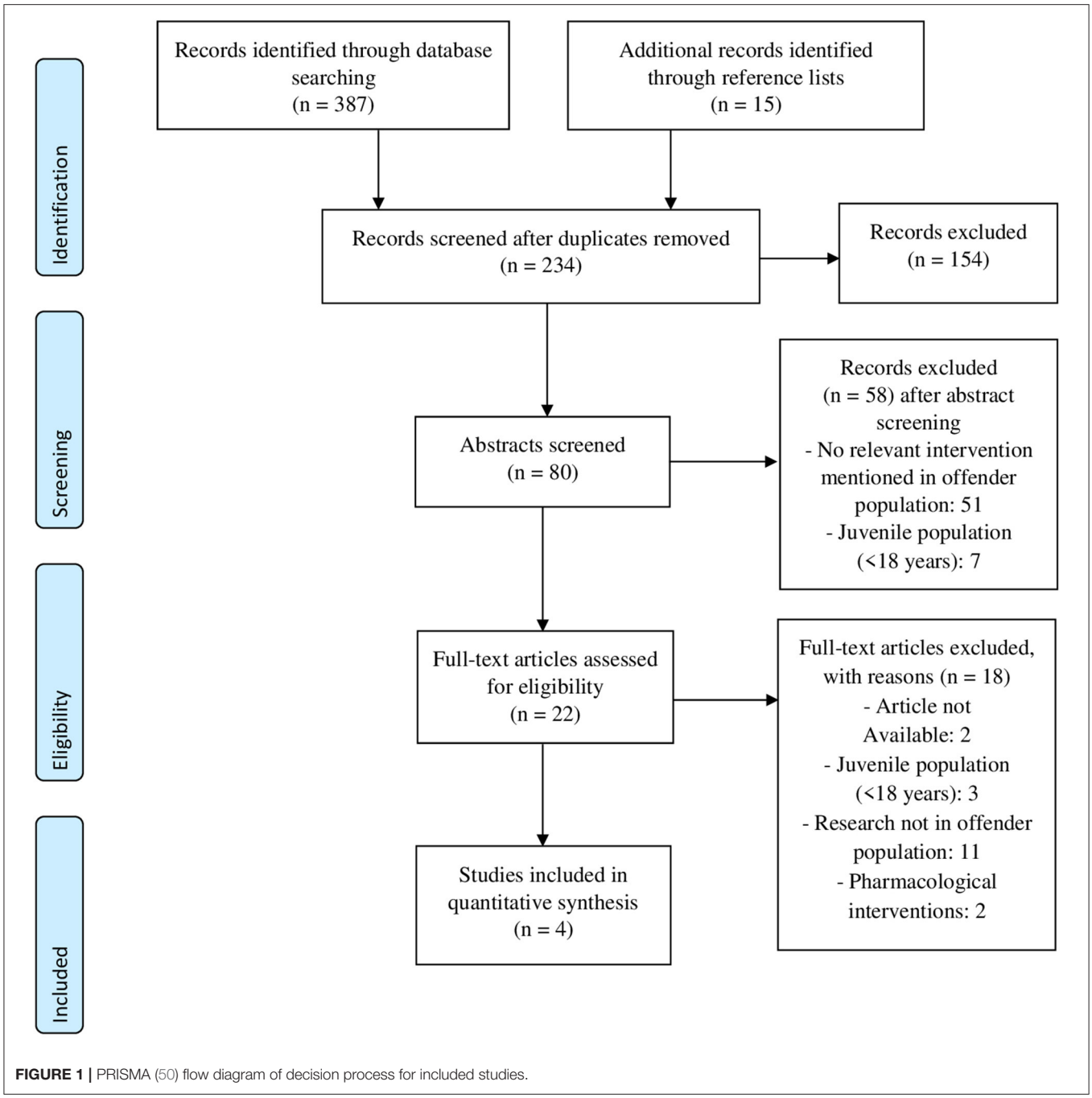


FIGURE 1 | PRISMA (50) flow diagram of decision process for included studies.

outcome measure, setting of the intervention, and country are summarized in **Table 1**.

Equip: A Forensic Peer Group Approach

The multiple case study by Manchester et al. (51) included Equip, a forensic peer group approach for young adults (18–23 years), to study bullying behavior, aggression, and antisocial attitudes after TBI in a rehabilitation facility. All three participants had sustained severe TBI and had a history of criminality. The participants were highly resistant to other forms of treatment, such as neurobehavioral rehabilitation. The Equip intervention program focused on social interaction skills, sociomoral development, and social cognitive distortions, such as moral misjudgments, aggressive and impulsive reactions, and egocentric biases. The program consisted of four 30-min group sessions per week, for 6 weeks. Outcome measures were two self-report questionnaires, the How I Think Questionnaire (HIT), measuring self-serving cognitive distortions with externalizing pathology, and the Coopersmith Self-Esteem Inventory (SEI), measuring evaluative self-attitudes, completed by the participants

before and after the program. Aggressive behaviors were recorded by the staff with the Overt Aggression Scale (OAS), 2 weeks prior to the start of the intervention program, 2 weeks after the end of the program, and 2 weeks after the three-month follow-up. After completing the program, two of the three participants had altered their beliefs regarding antisocial behavior, for example, a reduction in pro-aggressive beliefs was seen. At the three-month follow-up, one participant maintained this progress, while the others returned to baseline. A reduction in verbal aggression was seen in all participants after completing the program. Therefore, the authors suggested that a group approach may help modify underlying antisocial behaviors and attitudes and verbal aggression in patients with severe TBI. However, the causal relationship cannot be determined due to the absence of multiple baseline measurements and of a control group. Furthermore, the very small sample size and the heterogeneity of the sample (all participants had different intervals between brain injury, admission to a rehabilitation facility, and start of the group program) were limitations of this study. Lastly, it was unclear how treatment effects could be maintained once a client had left the structured rehabilitation environment (51).

Cognitive Remediation Therapy (CRT)

The second study, by Marcer et al. (53), found improvements in cognitive functions following cognitive remediation therapy (CRT) in a sample of offenders with complex mental health problems (e.g., personality disorder) in addition to TBI and/or substance abuse. The single group design study consisted of a small sample ($N = 13$) with only two participants suffering from TBI. The remaining 11 participants were diagnosed with substance abuse and personality disorders, without TBI ($N = 6$) or of whom it was unknown whether they had suffered from TBI ($N = 5$). CRT is a cognitive and behavioral manualized intervention that aims to improve cognitive abilities. With drill and practice techniques, strategy implementation, and application of principles of learning such as errorless learning and scaffolding, CRT aims to improve cognitive abilities. The participants started with a 2-weekly half-hour introduction (1-h total), where they increased their understanding of cognitive skills and enhanced their engagement in CRT. After the introduction the participants completed a full battery of cognitive tests, the pre-intervention assessment. In the 14-week full program the participants received five CRT modules which each consisted of 8 sessions (40 total) and completed approximately 15 tasks per module (total of 75 tasks). During those sessions the participants had to think about the most helpful strategy to solve a cognitive task, reflect on strategies, and evaluate the effectiveness of the strategy in improving their performance. Inhibition, rule shifting, planning and problem solving, and attention and working memory were assessed pre- and post-intervention. Participants' performance in terms of inhibition, rule shifting, attention, and working memory, including performance of participants with TBI, had improved post-intervention. In addition, the authors performed a sensitivity analyses comparing the patients with TBI ($N = 2$) and those without TBI ($N = 6$), showing equal gains from the CRT. Therefore, the authors concluded that CRT improved cognitive functioning in all patients, including those with TBI. However, there were several limitations to this study. First, the sample was small, especially the TBI group, and no control group was included. Second, because the same tasks were used at pre- and post-intervention, rather than parallel versions of the tasks, it is possible that improvements were produced by practice effects. Finally, long-term effects of the CRT intervention were not considered.

Link Worker or Facilitator Intervention

Ramos et al. reported a link worker intervention offered to three prison inmates who reported severe TBI or multiple mild TBIs (52). Link workers were usually psychology graduates who received a training about TBI, including psychoeducation on the causes and consequences of TBI, coping with the impact of TBI, and how to address problems. This service approach was designed to identify and support inmates with TBI. The link worker could respond to specific needs and their role compromised support, guidance, and providing psychoeducation to both staff and inmate about TBI. In addition, link workers tried to set up a support system for after the inmate's release. The link worker helped to make a support plan, formulate goals, and identify steps required to meet those goals. The intervention consisted of a 30–60 min session, 1–3 times a week, for ∼8–12 weeks. One of the three participants was released during the intervention. He did not recidivate during the follow-up period of 3 years and was able to live independently with only little support. The other two participants were still in prison by the end of the study, but they showed no violations of prison rules since the intervention. One had successfully learned to apply support plans with basic guidelines to organize himself, his life and to successfully undertake the tasks he needed to do. Thereby he replaced his challenging behavior with constructive behavior. The third participant had no further infractions since the intervention. Before, he had memory difficulties and during the intervention, he learned to ask for information in small chunks so that he could understand and remember information better. Furthermore, he gained the "advisor role" qualification with charity work in prison after the intervention and his role was advising inmates close to release. These three case studies suggest that a link worker can lead to positive outcomes and that helping inmates in identifying and intervening with problems may be feasible. Limitations of the study were the small sample, the absence of a control group, and no multiple long-term follow-ups. Furthermore, no standardized treatment protocols or guidelines where used, which makes it difficult to repeat this intervention. It remains unclear whether the positive outcomes could be fully attributed to the intervention and whether these effects persisted over time.

Nagele et al. employed a model of TBI screening for men in a maximum secured prison (54). Of the 158 inmates screened in a semi-structured interview conducted by a staff member, 75% had a history of TBI. Additionally, 74% had neurocognitive impairments based on results of a neurocognitive test battery, testing executive function and memory abilities/capacities. The researchers included 67 participants with neurocognitive impairments likely to interfere with successful re-entry into the

TABLE 1 | Characteristics of studies included within the current review.

Autor/Year	Design	N (pre)	N (post)	Follow-up	Age (years)	Gender	Time of first TBI	TBI assessment	Measured outcomes	Summary intervention	Findings	Setting (country)
Manchester, Wall, Dawson & Jackson (2007)	Single case design	3	2	3 months	19 19 21	3 M	12 years 17 years 19 years	Medical records (CGS and PTA).	"How I Think Questionnaire" (HIT), Coopersmith Self-Esteem Inventory (SEI), Overt Aggression Scale (OAS).	Equip intervention program for improving social interaction skills, sociomoral development and social cognitive distortions.	Moderate effects were found for HIT outcomes, pro-aggressive attitudes and beliefs were modified in two patients, all participants showed reductions of aggression (OAS), and little effect on self-esteem was found (SEI).	Rehabilitation facility (United Kingdom; U.K.).
Ramos, Oddy, Liddement & Fortescue (2018)	Single case design	3	3	N/A	22 47 40	3 M	2 years 25 years 10 years	Brain Injury Screening Index (BISI) and medical records.	Independence, Constructive activity, reoffending/prison infractions, use of cognitive strategies.	Link worker intervention.	Link worker intervention can lead to positive outcomes and that help with identifying and intervening problems seems to be feasible.	Prison (U.K.).
Marcer, Mills & Clarke (2016)	Single group design	13	13	N/A	Mean 33.9	10 M 3 F	N/A	Demo-graphic and clinical information.	Different executive functions with repeated measures design.	Cognitive remediation therapy (CRT).	CRT demonstrates improvement in cognitive functioning.	Low secured prison, mental health department (U.K.).
Nagele, Vaccaro, Schmidt & Keating (2018)	Single group design	67	44	2 years	N/A	67 M	75% occurred in child-hood (< 21 years)	Traumatic Brain Injury Question-naire (TBIQ).	Employment, re-incarceration, violation of parole.	Intervention program named NeuroResource Facilitation (NRF) with goal to reduce recidivism and improve productivity.	The intervention program showed a reduction in recidivism and an increase in productivity.	Maximum secured prison (United States of America; U.S.A.).

community once released, in a 2-year intervention program, named NeuroResource Facilitation (NRF). Neurocognitive impairments investigated were (working) memory, attention, initiation, organization, problem-solving, inhibition of behavior, self-monitoring, planning/anticipation, and mental flexibility. NRF was a service designed to identify needs, resources and provide support to individuals with TBI and their families. The goal of the intervention was to reduce recidivism and improve productivity (work, volunteering or training) of the incarcerated participants. The participants received person-specific psychoeducation and help regarding identifying goals and needs, re-entry planning and resource application from a facilitator, comparable to a link worker. For example, a personalized treatment plan to prepare the individual for return to society was formulated. There was also the possibility to join an eight-week support group, that provided the possibility to talk about all sorts of TBI related problems with fellow sufferers and professionals. After release from prison (44 participants) the facilitator and the participant met approximately twice a month for 1 year to implement the personalized re-entry plan. Those meetings focused on supportive counseling, crisis management, and learning and applying strategies. Outcome measurement at 2 years after release showed that 65% of those released were engaged in some kind of productive activity and 50% had a full- or part-time job. Only 17% were re-incarcerated within 2 years due to new convictions or violation of parole, which contrasts with typical re-incarceration rates after 2 years of ∼50% in the USA (55, 56). Although the findings were promising, the study also had limitations, of which the primary limitation was the use of self-report to screen for TBI and the absence of a control group. Thus, it remains unclear whether the effects can be attributed to the intervention.

DISCUSSION

Previous literature showed that prevalence rates of ABI in offender populations are high. The aim of this review was to provide an overview of the literature on interventions in adult offender populations with ABI. Given the relatively high prevalence rates of ABI in offender populations, interventions aimed at ABI-related impairments could have added value in reducing recidivism rates, by improving treatment outcomes. With only four studies identified, the literature search revealed a paucity of studies reporting such interventions. In addition, the reported evidence for the effectiveness of the interventions was weak, mainly due to methodological shortcomings of the studies, in particular lack of control conditions, small sample sizes and no long-term outcomes.

All four included studies reported some improvements, albeit in different outcome domains. Manchester et al. (51) focused on aggression and antisocial behavior Marcer et al. (53), on cognitive functions and Ramos et a The link workers in Ramos et al. (52) and Nagele et al. (54) on recidivism, i.e., chance of re-offending. The reported studies also differed in how presence of ABI was assessed, their approach, and focus. Therefore, providing an integral and overall conclusion is difficult, but the positive outcomes are encouraging and warrant further investigation.

The focus of the interventions ranged from strategy learning and training cognitive functions [CRT intervention; (47)], looking into improvement of antisocial attitudes and behavior by focusing on social interaction skills, sociomoral development and social cognitive distortions [the Equip program; (45)], using a facilitator or a link worker, to provide psychoeducation, guidance, help the individual to identify goals and needs and provide support with re-entry into the community [NRF; (54)– link worker; (46)]. The NRF and link worker programs intended to reduce recidivism and problem behavior and improve productivity (52, 54). Although there was a difference in strategy and focus, the focus on psychoeducation about ABI, identification of weaknesses and strengths, providing learning strategies and giving support was shared between the programs and together these comprise the clinical implications. Psychoeducation was not only given to the incarcerated individual, but also to prison staff and family members. With identification of weaknesses and strengths it was possible to formulate a personal (re-entry) plan with corresponding goals.

The primary aim of treatments in offender populations is to reduce recidivism. Two of the included studies assessed recidivism in participants (52, 54) and both reported promising results. Both studies involved link worker interventions, where personalized treatment and re-entry plans, providing support and psychoeducation about TBI contributed to reducing recidivism. These interventions strategies are in line with the Risk-Need-Responsivity model for offender rehabilitation (42). This rehabilitation model relies on three basic principles stating that forensic treatment is most effective when (1) treatment dosage is tuned to an offender's risk level (high risk offenders are to receive more intensive treatment (risk principle); (2) treatment is targeted at the offender's dynamic (i.e., changeable through intervention) risk factors most strongly associated with criminal behavior (need principle); and (3) treatment approach is tailored to individual characteristics, such as motivation and intellectual functioning (responsivity principle). Not considering possible TBI-related cognitive and social impairments could be problematic for the responsivity principle.

Following the WHO guidelines (57), mental healthcare in forensic settings should include screening for mental disorders, addressing views and needs (of different groups), provide awareness training or psychoeducation to staff members and continued care (58). Support during the months immediately following release from prison, may be helpful for all former inmates, regardless of whether they have sustained ABI. Psychological treatment in prison and forensic outpatient facilities is often based on cognitive-behavioral techniques and has moderately positive outcomes (45). The emphasis is on specialized individual treatment, provided by a qualified (neuro-) psychologists (59). However, not all forensic settings employ qualified psychologists educated in offering specialized individual treatment focused on ABI. What the studies reviewed here suggest is that interventions can be presented by staff who are not fully qualified clinicians as well. The link workers in (52) had a psychology degree, but no further professional training

and used manual-based interventions, such as EQUIP. This suggests the possibility of involving a broader range of staff in presenting the interventions, as long as they are familiarized with the intervention.

At the moment, standard treatment in forensic settings does not take the presence and consequences of ABI into account. More awareness of the risk and the consequences of ABI in forensic settings and of ABI among the psychologists and other staff will hopefully result in (developing) more suitable treatments and psychoeducation on the consequences of brain injury, with a focus on impairments in cognition and social cognition.

The studies reviewed show some positive outcomes and clinical implications, however, they have methodological weaknesses and other limitations. The absence of control conditions and a matched control group prevents strong conclusions regarding the effectiveness of the interventions. Therefore, it is recommended that future studies include these control conditions, to demonstrate that the effects are due to the specific interventions. A limitation of this review is that the study samples reviewed were largely based on prison populations, while many offenders are treated and seen in outpatient care facilities or under probation supervision. It may be possible that prison populations have worse ABI-related impairments in comparison to forensic outpatients care populations, although this needs further investigation given the possible influence of other psychiatric disorders in the prison population. A second limitation is that the studies reviewed used different ABI assessment methods, namely self-report measurements, semi-structured interviews and information from medical records, with and without considering ABI severity. Other recommendations for future research could be to use a standardized ABI assessment instrument, such as a structured interview to asses both (a history of) ABI and current cognitive deficits. In clinical practices there are several instruments available that may be used in the forensic setting as well. For example, the Ohio State University (OSU) Traumatic Brain Injury (TBI) Identification Method (OSU TBI-ID) is a standardized procedure to elicit a person's lifetime history of TBI during a 3–5 min structured interview (60). Similar instruments, where necessary complemented with neuropsychological tests, would be a valuable addition to current practices in forensic settings. Longer follow-up periods, to study the long-term outcomes of the intervention, are also warranted. Ideally a follow-up of 2 year after release is incorporated, since most recidivism occurs within that period (61). Finally, larger sample sizes and including recidivism as an outcome measure are important suggestions for improving future research. Almost all research on ABI in the offender population focused on TBI and virtually none on non-traumatic brain injury. This might be because TBI is more common in offender populations than non-traumatic brain injury, because of a lack of focus in assessment non-traumatic brain injury, or because of limited knowledge of non-traumatic brain injury in forensic settings. Further suggestions for interventions to address ABI related impairments and behavioral changes in offender populations can be derived from literature on neuropsychological rehabilitation and treatment after ABI in the general, i.e., non-offender, populations. However, one difficulty when comparing ABI-related interventions from the general population with ABI interventions for forensic settings, is that the former does not focus on reducing recidivism, which is an important outcome measurement in the latter.

CONCLUSIONS

The aim of the current study was to review the literature on interventions and treatment in offender populations suffering from ABI, or the influence of ABI on treatment. In the long run, improved treatment options and treatment outcomes may reduce the ABI-related impairments in offenders and, ultimately reduce recidivism. A systematic literature search identified a limited number of intervention studies in the offender population ($N = 4$) that reported some positive effects on interpersonal behavior, cognition and recidivism. However, due to methodological limitations the findings may not be generalizable to other samples and interpretations of intervention effectiveness should be considered with caution. Future studies are warranted, since this does seem as an important venue. Suggestions for future studies include standardized assessment of ABI, longer follow-up periods and inclusion of recidivism as outcome measure.

AUTHOR CONTRIBUTIONS

EdG, SN, MM, and FJ developed the research question. EdG carried out the database search. JH replicated the database search. EdG, MM, and SN drafted the manuscript. Earlier versions of the manuscript were revised by MM, SN, and JvH, more finalized versions were revised by MM, SN, JvH, FJ, JH, CG, TF, and FK. Preparation of the final manuscript in line with journal guidelines and submission were done by EdG, MM, and SN. All authors contributed to the article and approved the submitted version.

FUNDING

Supported by Program Quality Forensic Care (Programma Kwaliteit Forensische Zorg), grant 2019-102.

REFERENCES

1. Durand E, Chevignard M, Ruet A, Dereix A, Jourdan C, Pradat-Diehl P. History of traumatic brain injury in prison populations: a systematic review. *Ann Phys Rehabil Med.* (2017) 60:95–101. doi: 10.1016/j.rehab.2017.02.003
2. Kuin NC, Scherder EJ, Gijsbers H, Masthoff EDM. Traumatic brain injury in prisoners: relation to risky decision-making, aggression and criminal behavior. *J Behav Brain Sci.* (2019) 9:289–99. doi: 10.4236/jbbs.2019.97021
3. O'Rourke C, Linden MA, Lohan M, Bates-Gaston J. Traumatic brain injury and co-occurring problems in prison populations: A systematic review. *Brain Inj.* (2016) 30:839–54. doi: 10.3109/02699052.2016.1146967

4. Shiroma EJ, Ferguson PL, Pickelsimer EE. Prevalence of traumatic brain injury in an offender population: a meta-analysis. *J Correct Health Care.* (2010) 16:147–59. doi: 10.1177/1078345809356538
5. McKinlay A, Corrigan J, Horwood LJ, Fergusson DM. Substance abuse and criminal activities following traumatic brain injury in childhood, adolescence, and early adulthood. *J Head Trauma Rehabil.* (2014) 29:498–506. doi: 10.1097/HTR.0000000000000001
6. Ray B, Richardson NJ. Traumatic brain injury and recidivism among returning inmates. *Crim Just Behav.* (2017) 44:472–86. doi: 10.1177/0093854816686631
7. Williams WH, Mewse AJ, Tonks J, Mills S, Burgess CN, Cordan G. Traumatic brain injury in a prison population: prevalence and risk for re-offending. *Brain Inj.* (2010) 24:1184–8. doi: 10.3109/02699052.2010.495697
8. Brain Injury Association of America. *About Brain Injury Biausa.Org.* (2019). Available online at: https://www.biausa.org/brain-injury/about-brain-injury/basics/overview (accessed February 5, 2020).
9. Lezak MD, Howieson DB, Bigler ED, Tranel. *Neuropsychological Assessment*. 5th ed. St. New York, NY: Oxford University Press (2012).
10. Menon DK, Schwab K, Wright DW, Maas AI. Position statement: definition of traumatic brain injury. *Arch Phys Med Rehabil.* (2010) 91:1637–40. doi: 10.1016/j.apmr.2010.05.017
11. Colantonio A, Stamenova V, Abramowitz C, Clarke D, Christensen B. Brain injury in a forensic psychiatry population. *Brain Injury.* (2009) 21:1353–60. doi: 10.1080/02699050701785054
12. Verberne DPJ, Spauwen PJJ, Van Heugten CM. Psychological interventions for treating neuropsychiatric consequences of acquired brain injury: a systematic review. *Neuropsychol Rehabil.* (2019) 29:1509–42. doi: 10.1080/09602011.2018.1433049
13. Cicerone KD, Goldin Y, Ganci K, Rosenbaum A, Wethe JV, Langenbahn DM, et al. Evidence-based cognitive rehabilitation: systematic review of the literature from 2009 through 2014. *Arch Physical Med Rehabil.* (2019) 100:1515–33. doi: 10.1016/j.apmr.2019.02.011
14. Global Burden of Disease. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* (2019) 18:56–87. doi: 10.1016/S1474-4422(18)30415-0
15. Peeters W, van den Brande R, Polinder S, Brazinova A, Steyerberg EW, Lingsma HF, et al. Epidemiology of traumatic brain injury in Europe. *Acta Neurochir.* (2015) 157:1683–96. doi: 10.1007/s00701-015-2512-7
16. Silver JM, Kramer R, Greenwald S, Weissman M. The association between head injuries and psychiatric disorders: findings from the new haven NIMH epidemiologic catchment area study. *Brain Inj.* (2001) 15:935–45. doi: 10.1080/02699050110065295
17. Whiteneck GG, Cuthbert JP, Corrigan JD, Bogner JA. Prevalence of self-reported lifetime history of traumatic brain injury and associated disability: a statewide population-based survey. *J Head Trauma Rehabil.* (2016) 31:E55–62. doi: 10.1097/HTR.0000000000000140
18. Feigin VL, Abajobir AA, Abate KH, Abd-Allah F, Abdulle AM, Abera SF, et al. Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the global burden of disease study 2015. *Lancet Neurol.* (2017) 16:877–97. doi: 10.1016/S1474-4422(17)30299-5
19. Frost RB, Farrer TJ, Primosch M, Hedges DW. Prevalence of traumatic brain injury in the general adult population: a meta-analysis. *Neuroepidemiology.* (2013) 40:154–9. doi: 10.1159/000343275
20. Truelsen T, Piechowski-Jozwiak B, Bonita R, Mathers C, Bogousslavsky J, Boysen G. Stroke incidence and prevalence in Europe: a review of available data. *Eur J Neurol.* (2006) 13:581–98. doi: 10.1111/j.1468-1331.2006.01138.x
21. Witzel JG, Bogerts B, Schiltz K. Increased frequency of brain pathology in inmates of a high-security forensic institution: a qualitative CT and MRI scan study. *Eur Arch Psychiatry Clin Neurosci.* (2016) 266:533–41. doi: 10.1007/s00406-015-0620-2
22. Crespo de Souza CA. Frequency of brain injury in a forensic psychiatric population. *Braz J Psychiatry.* (2003) 25:206–11. doi: 10.1590/S1516-44462003000400005
23. Corrigan JD, Selassie AW, Orman JA. the epidemiologiy of traumatic brain injury. *J Head Trauma Rehabil.* (2010) 27:95–101. doi: 10.1097/HTR.0b013e3181ccc8b4
24. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet.* (1974) 2:81–4. doi: 10.1016/S0140-6736(74)91639-0
25. Farrer TJ, Hedges DW. Prevalence of traumatic brain injury in incarcerated groups compared to the general population: a meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry.* (2011) 35:390–4. doi: 10.1016/j.pnpbp.2011.01.007
26. Azouvi P, Arnould A, Dromer E, Vallat-Azouvi C. Neuropsychology of traumatic brain injury: an expert overview. *Rev Neurol.* (2017) 173:461–72. doi: 10.1016/j.neurol.2017.07.006
27. Pitman I, Haddlesey C, Ramos SD, Oddy M, Fortescue D. The association between neuropsychological performance and self-reported traumatic brain injury in a sample of adult male prisoners in the UK. *Neuropsychol Rehabil.* (2015) 25:763–79. doi: 10.1080/09602011.2014.973887
28. Rabinowitz AR, Levin HS. Cognitive sequelae of traumatic brain injury. *Psychiatr Clin North Am.* (2014) 37:1–11. doi: 10.1016/j.psc.2013.11.004
29. Ryan NP, Anderson V, Godfrey C, Eren S, Rosema S, Taylor K, et al. Social communication mediates the relationship between emotion perception and externalizing behaviors in young adult survivors of pediatric traumatic brain injury (TBI). *Int J Dev Neurosci.* (2013) 31:811–9. doi: 10.1016/j.ijdevneu.2013.10.002
30. Osborne-Crowley K, McDonald S. A review of social disinhibition after traumatic brain injury. *J Neuropsychol.* (2018) 12:176–99. doi: 10.1111/jnp.12113
31. Robertson K, Schmitter-Edgecombe M. Self-awareness and traumatic brain injury outcome. *Brain Inj.* (2015) 29:848–58. doi: 10.3109/02699052.2015.1005135
32. Arciniegas DB, Wortzel HS. Emotional and behavioral dyscontrol after traumatic brain injury. *Psychiatr Clin North Am.* (2014) 37:31–53. doi: 10.1016/j.psc.2013.12.001
33. Schwartz JA, Connolly EJ, Brauer JR. Head injuries and changes in delinquency from adolescence to emerging adulthood. *J Res Crime Delin.* (2017) 54:869–901. doi: 10.1177/0022427817710287
34. Bellesi G, Barker ED, Brown L, Valmaggia L. Pediatric traumatic brain injury and antisocial behavior: are they linked? A systematic review. *Brain Inj.* (2019) 33:1272–92. doi: 10.1080/02699052.2019.1641621
35. Roberts S, Henry JD, Molenberghs P. Immoral behaviour following brain damage: a review. *J Neuropsychol.* (2019) 13:564–88. doi: 10.1111/jnp.12155
36. Ray B, Sapp D, Kincaid A. Traumatic brain injury among indiana state prisoners. *J Forensic Sci.* (2014) 59:1248–53. doi: 10.1111/1556-4029.12466
37. Williams WH, Chitsabesan P, Fazel S, McMillan T, Hughes N, Parsonage M, et al. Traumatic brain injury: a potential cause of violent crime? *Lancet Psychiatry.* (2018) 5:836–44. doi: 10.1016/S2215-0366(18)30062-2
38. Pouwels C, Wolters Gregorio G, Spauwen PJJ, Bus BAA, Winkens I, Ponds R. Prevalence and manifestations of aggression in adult patients with acquired brain injury: a review. *Tijdschr Psychiatr.* (2019) 61:862–78.
39. Elbogen EB, Wolfe JR, Cueva M, Sullivan C, Johnson J. Longitudinal predictors of criminal arrest after traumatic brain injury: results from the traumatic brain injury model system national database. *J Head Trauma Rehabil.* (2015) 30:E3–13. doi: 10.1097/HTR.0000000000000083
40. Timonen M, Miettunen J, Hakko H, Zitting P, Veijola J, von Wendt L, et al. The association of preceding traumatic brain injury with mental disorders, alcoholism and criminality: the northern finland 1966 birth cohort study. *Psychiatry Res.* (2002) 113:217–26. doi: 10.1016/S0165-1781(02)00269-X
41. Trahan E, Pepin M, Hopps S. Impaired awareness of deficits and treatment adherence among people with traumatic brain injury or spinal cord injury. *J Head Trauma Rehabil.* (2006) 21:226–35. doi: 10.1097/00001199-200605000-00003
42. Bonta J, Andrews DA. The psychology of criminal conduct routledge, taylor & francis group (2017) 2:45–65. doi: 10.4324/9781315677187
43. Hofmann SG, Asnaani A, Vonk IJ, Sawyer AT, Fang A. The efficacy of cognitive behavioral therapy: a review of meta-analyses. *Cognit Ther Res.* (2012) 36:427–40. doi: 10.1007/s10608-012-9476-1
44. Lipsey MW, Cullen FT. The effectiveness of correctional rehabilitation: a review of systematic reviews. *Ann Rev Law Soc Sci.* (2007) 3:297–320. doi: 10.1146/annurev.lawsocsci.3.081806.112833
45. Yoon IA, Slade K, Fazel S. Outcomes of psychological therapies for prisoners with mental health problems: a systematic review and meta-analysis. *J Consult Clin Psychol.* (2017) 85:783–802. doi: 10.1037/ccp0000214

46. Cornet LJM, van der Laan PH, Nijman HLI, Tollenaar N, de Kogel CH. Neurobiological factors as predictors of prisoners' response to a cognitive skills training. *J Crim Justice.* (2015) 43:122–32. doi: 10.1016/j.jcrimjus.2015.02.003
47. Fishbein D, Sheppard M, Hyde C, Hubal R, Newlin D, Serin R, et al. Deficits in behavioral inhibition predict treatment engagement in prison inmates. *Law Hum Behav.* (2009) 33:419–35. doi: 10.1007/s10979-008-9163-7
48. Olver ME, Stockdale KC, Wormith JS. A meta-analysis of predictors of offender treatment attrition and its relationship to recidivism. *J Consult Clin Psychol.* (2011) 79:6–21. doi: 10.1037/a0022200
49. Ross EH, Hoaken PNS. Correctional remediation meets neuropsychological rehabilitation. *Crim Just Behav.* (2010) 37:656–77. doi: 10.1177/0093854810363104
50. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred reporting items for systematic reviews and meta analyses: the PRISMA statement. *PLoS Med.* 6:e1000097. doi: 10.1371/journal.pmed1000097
51. Manchester D, Wall G, Dawson P, Jackson H. A forensic peer group approach to bullying after traumatic brain injury. *Neuropsychol Rehabil.* (2007) 17:206–29. doi: 10.1080/09602010600696472
52. Ramos SDS, Oddy M, Liddement J, Fortescue D. Brain injury and offending: the development and field testing of a linkworker intervention. *Int J Offender Ther Comp Criminol.* (2018) 62:1854–68. doi: 10.1177/0306624X17708351
53. Marcer K, Mills L, Clarke C. Cognitive remediation therapy for forensic inpatients: a preliminary evaluation. *J Psychiatr Int Care.* (2016) 12:27–36. doi: 10.20299/jpi.2016.010
54. Nagele D, Vaccaro M, Schmidt MJ, Keating D. Brain injury in an offender population: implications for reentry and community transition. *J Offen Rehabil.* (2019) 57:562–85. doi: 10.1080/10509674.2018.1549178
55. Baillargeon J, Binswanger IA, Penn JV, Williams BA, Murray OJ. Psychiatric disorders and repeat incarcerations: the revolving prison door. *Am J Psychiatry.* (2009) 166:103–9. doi: 10.1176/appi.ajp.2008.08030416
56. Wilson AB, Draine J, Hadley T, Metraux S, Evans A. Examining the impact of mental illness and substance use on recidivism in a county jail. *Int J Law Psychiatry.* (2011) 34:264–8. doi: 10.1016/j.ijlp.2011.07.004
57. World Health Organization. *Mental health and prisons (Information Sheet).* Geneva:World Health Organization (2005).
58. Enggist S, Møller L, Galea G, Udesen C. *Prisons and health: World Health Organization Regional Office for Europe.* (2014). Available online at: http://www.who.int/iris/handle/10665/128603 (accessed October 14, 2020).
59. Gannon TA, Olver ME, Mallion JS, James M. Does specialized psychological treatment for offending reduce recidivism? A meta-analysis examining staff and program variables as predictors of treatment effectiveness. *Clin Psychol Rev.* (2019) 73:1–18. doi: 10.1016/j.cpr.2019.101752
60. Corrigan JD, Bogner J. Ohio State University traumatic brain injury identification method. *Encyclo Clin Neuropsychol.* (2018) 2502–4. doi: 10.1007/978-3-319-57111-9_9053
61. Yukhnenko D, Sridhar S, Fazel S. A systematic review of criminal recidivism rates worldwide: 3-year update [version 3; peer review: 3 approved]. *Wellcome Open Res.* (2020) 4:28. doi: 10.12688/wellcomeopenres.14970.3

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.

frontiers in Psychiatry

SYSTEMATIC REVIEW
published: 10 May 2021
doi: 10.3389/fpsyt.2021.618860

A Systematic Review of Non-pharmacological Strategies to Reduce the Risk of Violence in Patients With Schizophrenia Spectrum Disorders in Forensic Settings

Rudolf Slamanig[1†], Andreas Reisegger[1†], Hildegard Winkler[1], Giovanni de Girolamo[2], Giuseppe Carrà[3], Cristina Crocamo[3], Heiner Fangerau[4], Inga Markiewicz[5], Janusz Heitzman[5], Hans Joachim Salize[6], Marco Picchioni[7,8] and Johannes Wancata[1]*

[1] Clinical Division of Social Psychiatry, Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria, [2] Unit of Epidemiological and Evaluation Psychiatry, IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli, Brescia, Italy, [3] Department of Medicine and Surgery, University of Milano Bicocca, Milan, Italy, [4] Department of the History, Philosophy and Ethics of Medicine, Medical Faculty, Heinrich-Heine-University Duesseldorf, Duesseldorf, Germany, [5] Department of Forensic Psychiatry, Institute of Psychiatry and Neurology, Warsaw, Poland, [6] Medical Faculty Mannheim, Central Institute of Mental Health, Heidelberg University, Mannheim, Germany, [7] St Magnus Hospital, Surrey, United Kingdom, [8] Department of Forensic and Neurodevelopmental Science, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom

OPEN ACCESS

Edited by:
Thomas Nilsson,
University of Gothenburg, Sweden

Reviewed by:
Peter Andiné,
University of Gothenburg, Sweden
Märta Wallinius,
Lund University, Sweden

***Correspondence:**
Johannes Wancata
johannes.wancata@meduniwien.ac.at

[†]These authors have contributed equally to this work

Specialty section:
This article was submitted to Forensic Psychiatry, a section of the journal Frontiers in Psychiatry

Received: 21 October 2020
Accepted: 06 April 2021
Published: 10 May 2021

Citation:
Slamanig R, Reisegger A, Winkler H, de Girolamo G, Carrà G, Crocamo C, Fangerau H, Markiewicz I, Heitzman J, Salize HJ, Picchioni M and Wancata J (2021) A Systematic Review of Non-pharmacological Strategies to Reduce the Risk of Violence in Patients With Schizophrenia Spectrum Disorders in Forensic Settings. Front. Psychiatry 12:618860. doi: 10.3389/fpsyt.2021.618860

Background: The purpose of this systematic review is to systematically investigate which non-pharmacological interventions are effective in reducing violence risk among patients with schizophrenia spectrum disorders (SSD) in forensic settings.

Methods: Six electronic data bases were searched. Two researchers independently screened 6,003 abstracts resulting in 143 potential papers. These were analyzed in detail by two independent researchers yielding 10 articles that could be used.

Results: Of the 10 articles, four were non-randomized controlled trials, three were pre-post studies without controls, and one was observational. Only two studies applied a randomized controlled trial design. Cognitive behavioral treatment programs were investigated in three studies. A broad range of other interventions were studied. Often outcome measures were specific to each study and sample sizes were small. Frequently, important methodological information was missing from the papers. It was not possible to carry out a meta-analysis due to the heterogeneity of the study designs and outcome measures.

Conclusion: Because of methodological limitations it is difficult to draw firm conclusions about the effectiveness of non-pharmacological interventions to reduce the risk of violence in patents with SSD in forensic psychiatry settings. Studies applying better methods in terms of study design, sample sizes and outcome measures are urgently needed.

Keywords: schizophrenia, forensic psychiatry, non-pharmacological interventions, psychological interventions in forensic settings, violence, systematic review

INTRODUCTION

One in 100 of the population will develop a schizophrenia spectrum disorder (SSD) during their lifetime. Schizophrenia is a disease with hallucinations, delusions and thought disorders (i.e., positive symptoms). A marked proportion also develops negative symptoms, such as reduced drive or affective blunting (1). While some schizophrenia sufferers recover after some episodes, others have numerous relapses or develop a chronic course. Among those with a chronic course frequently impairments of the cognitive and social skills can be observed. This can lead to the inability of independent housing or to difficulties in working (2, 3).

In addition, several studies reported an increased risk of committing violent crimes among patients with SSD as compared to persons without this disorder. A systematic review (4) demonstrated a clear association between schizophrenia, substance use disorders and violence. They reported an OR of 2.1 for those with schizophrenia only as compared to the general population, with that risk rising when comorbid substance use was also present (OR 8.9). As in non-psychiatric offenders, criminal offenses in patients with SSD are linked profoundly to situational factors. Victims and perpetrators often know each other (5). Even before they develop schizophrenia, a subgroup of patients experienced conduct problems, environmental difficulties and trauma in their childhood (6).

Persons with SSD who had committed violent crimes are usually treated in forensic psychiatric services. Such services usually consist of special high security units providing psychiatric treatment and long-term care in order to limit further harm to the patient as well as the general public. The organization of such forensic services differ largely between countries, e.g., some are stand-alone psychiatric hospitals, while others are part of regular psychiatric inpatient services or are part of prisons (7). As a result, the prevalence and incidence of those treated in these services differ largely between countries (8).

Antipsychotic drugs are effective in improving positive and negative symptoms as well as preventing relapses as had been shown in numerous randomized controlled trials (RCTs) (9, 10). Using national register data Fazel et al. (11) reported that antipsychotics reduce the risk for violent crime among SSD patients, but their data did not give information about patients of forensic settings.

Meta-analyses reported that cognitive-behavioral therapy (CBT) significantly reduces psychotic symptoms in schizophrenia (12). However, a smaller number of studies investigated the effects of CBT or other psychosocial interventions on SSD patients who were aggressive or violent (13). Nevertheless, Haddock et al. (14) reported from a RCT that CBT was effective in violence reduction among SSD patients in general psychiatric services. Some studies investigated the effectiveness of non-pharmacological interventions on violence reduction in other settings such as prisons, but among people without psychiatric diagnoses and reported that cognitive interventions were effective in reducing violence [e.g., (15, 16)]. Other studies among persons with personality disorders found that CBT (17) and Schema therapy (18) were effective in reducing physical aggression or violent attacks.

Rampling et al. (19) performed a systematic review of 23 studies investigating non-pharmacological interventions among severely mentally ill (i.e., with SSD or affective disorders) and reported an improvement in physical aggression after cognitive behavioral interventions for psychoses in general psychiatric settings. A recently published umbrella review of non-pharmacological violence reduction strategies across psychiatric settings identified five reviews, but none in forensic psychiatric services (20).

All these findings indicate that studies of non-pharmacological interventions for violence prevention are scarce for SSD patients in forensic settings. As a result forensic psychiatrists frequently must rely on studies conducted in general psychiatry settings. However, there are differences between patients with SSD in general psychiatric and forensic settings. Forensic patients tend to have a more difficult chronic illness course, higher numbers of short-term admissions before their index violence, higher rates of comorbid substance use disorders, lower treatment compliance and lower levels of insight into both their mental disorder and the risk of violence (21, 22). Forensic patients also have more persistent positive psychotic symptoms and higher levels of cognitive impairment (23). Thus, it remains unclear if the non-pharmacological interventions developed and evaluated in general psychiatry are effective in forensic psychiatry, too.

Aims

To date there has been no systematic reviews of non-pharmacological interventions for reducing the risk for violence in people with SSD within forensic settings (24). Considering that a lot of financial and clinical resources are used for these services it seems to be an urgent necessity to provide such a systematic review of available research. Thus, we decided to conduct a systematic review of studies among forensic patients with SSD, having evaluated non pharmacological interventions without any limitations in order to prevent the risk of violence. Since we expected a rather small number of studies in this area we did not limit our search regarding study designs or comparison groups.

METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines [PRISMA; (25)]. The protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration number CRD42019146381).

We conducted a systematic literature search of Medline, PsycINFO, and Psyndex Lit & AV via Ovid search engine, CINAHL via EBSCOhost, Scopus, Web of Science (Core Collection) and EMBASE. The search strategy is listed in the **Supplementary Material Table S1**. We decided to adopt an explicitly broad search query in order to include the widest variety of possible interventions. Since the demarcation between violence and aggression is not always consistent, we included both terms into our search pattern. Some authors would put the

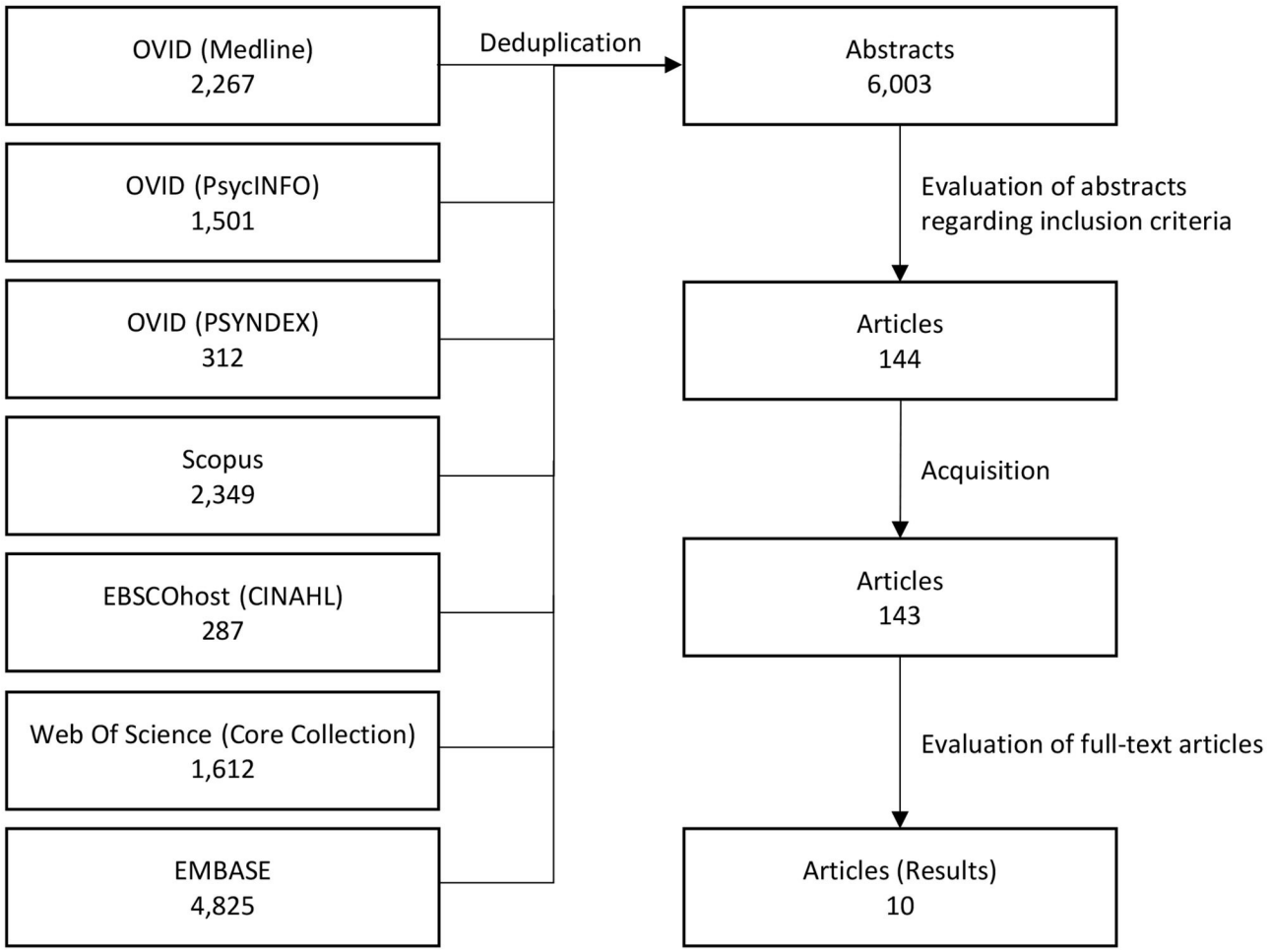


FIGURE 1 | Flow diagram.

term "violence" on the far end of the spectrum of aggressive behavior: i.e., representing actions with the purpose to inflict severe physical harm, as injury or death, on another person (26).

The EMBASE search was performed on November 15th, 2019. All other searches were performed on November 12th, 2019. After duplicates were removed using search engine tools and the EndNote deduplication function, 6,003 articles remained (**Figure 1**). Two out of three researchers (RS, AR, HW) then independently screened the abstracts according to our inclusion criteria:

- participants aged 18 years or older;
- participants suffering from SSD;
- non-pharmacological interventions;
- randomized and non-randomized controlled trials as well as observational studies performed in forensic psychiatric in- or outpatient settings;
- outcome measure: violent or aggressive behavior;
- published in peer reviewed journal;
- published in 1990 or later;
- Published in English.

Of the remaining 144 papers, one paper could not be sourced in either electronic or paper version. The 143 available texts underwent an in-depth analysis by two researchers (RS, AR) against the inclusion criteria and extracted suitable outcomes from relevant papers. Publications were excluded because:

- 2 texts were duplicates.
- 11 texts covered other topics (e.g., genetic risk factors for violence).
- 32 texts were not original research papers, for example reviews, meta-analyses, or abstracts.
- 27 articles either did not investigate non-pharmacological interventions or did not measure the effect of the intervention.
- 14 articles contained exclusively qualitative measures,
- 12 articles reported the findings of studies exclusively outside forensic settings.
- 21 articles had insufficient data on violence outcomes

- 12 articles covered either other diagnoses, excluded SSDs or did not discriminate across diagnostic groups at all
- 2 articles failed to meet the age criterion.

The raters agreed perfectly on the exclusions [Cohen's kappa = 1 (27)]. This left only 10 articles that qualified for the systematic evaluation. For each eligible article and intervention, the most direct violence measures were extracted and evaluated. A structured sheet was used for data extraction from each study (i.e., year of publication; country; inclusion criteria; setting; sample size; tested non-pharmacological treatments; study duration; main findings). Two researchers independently extracted the data, and any differences were resolved by consensus with other co-authors.

Quality of Evidence

The quality of evidence was assessed using the GRADE method (28). Outcomes were rated individually by two researchers and disagreements settled by consensus. The final rating included estimates of the

- risk of bias
- inconsistency
- indirectness
- imprecision
- and publication bias.

The overall quality of evidence for an outcome can be rated between very low and high, starting at high for RCTs and low for observational studies.

Due to heterogeneity in both outcome measures and design it was impossible to compare the results of the included studies from a statistical point of view. Where appropriate, standardized effect sizes (Cohen's d) were estimated.

RESULTS

The final analysis yielded 10 studies that included a total of 1,551 subjects, of whom <1% were female. Five studies were performed in the United Kingdom, two in the USA, and one each in Germany, New Zealand and in the Netherlands (**Table 1**).

The evaluated interventions broadly speaking broke down into neurocognitive training (one study), cognitive-behavioral therapy (three studies), and other non-pharmacological interventions (six studies). Five studies investigated the effects of group interventions, two of individual interventions and another two combinations of group and individual interventions. One study analyzed the influence of staff-patient-ratio. In line with the vast differences in these treatment approaches, there was also an enormous variation in both the duration of the intervention programs (between 5 days and 12 months) and the follow up observation periods (up to 56 months). Three were non-randomized controlled trials, three were pre-post studies without controls, and one was merely observational. Only two studies applied a RCT design. Seven studies used scales or questionnaires to assess violence or aggression, and three studies counted incidents of violence or of seclusions.

Neurocognitive Training

Ahmed et al. (29) performed an unblinded RCT to examine the effects of a cognitive remediation program over 20 weeks. Eligible patients who had been violent were randomized to either the intervention or an active control group (**Table 2**). A sample of 42 patients (4 female) with a diagnosis of schizophrenia ($N = 27$) or schizoaffective disorder ($N = 15$) from both forensic and general adult settings received 50 h of computer-based cognitive remediation therapy. Results were compared with a control group, who followed a comparable program of 3 weekly computer game sessions. In the combined general psychiatric and forensic sample patients in the intervention group were less violent at follow up as measured by the Overt Aggression Scale [OAS (40)] over the 20 week follow up period. Due to a small sample size, without a power analysis, the quality of evidence was considered moderate.

Cognitive-Behavioral Treatment Programs

Cullen et al. (31) performed an RCT to examine the impact of a Reasoning and Rehabilitation (R&R) program on the reduction of violence and antisocial behavior in a forensic psychiatric population. R&R is a highly structured manualized cognitive-behavioral intervention (41). All participants who attended at least 30 sessions were included in this study. The sample included patients with schizophrenia, schizoaffective disorder, bipolar disorder or any other psychotic disorder. Participants were randomized to the intervention or a passive control group. The effectiveness of the intervention was measured by the number of violent or antisocial incidents during treatment and at 12 months. Of the 44 initial participants, more than half failed to complete 30-sessions (52.3%). There were no significant differences in violence incident rates between the two groups either at the end of the intervention (Incidence Rate Ratio = IRR: 0.52 [0.23–1.15]; $p = 0.11$), or at the 12-month follow-up (IRR: 0.86 [0.44–1.66]; $p = 0.65$). The authors conducted a power analysis for estimating the necessary sample size. We considered this a high quality study.

Yip et al. (39) enrolled 30 adult male inpatients in a high-secure hospital in a Reasoning and Rehabilitation program adapted for offenders with severe mental illness (R&R2 MHP). Around 80% of the participants completed the program. Allocation to the intervention group was determined by order of referral, and the sample was compared to a control group of 29 forensic male inpatients placed on a waiting list, undergoing treatment as usual. For the purpose of this review, violence outcome data were extracted from subscales of the Maudsley Violence Questionnaire [MVQ; (42)], and the Novaco Anger Scale—Provocation Inventory: Reaction to Provocation/Personal Affect Questionnaire [NAS-PI (43)]. While the NAS-PI showed no statistically significant differences, the "acceptance of violence" subscale from the MVQ produced a significant moderate reduction in violence (Cohen's d = 0.53; $p < 0.01$). The study included an unspecified number of patients with a primary diagnosis of an affective disorder. The lack of randomization and blinding lead us to consider the study as having a very low quality.

TABLE 1 | Description of the papers included.

References	Lang.	Country	Setting	Intervention	Measure	Design
Ahmed et al. (29)	EN	USA	Hospital with forensic and mental health units	Cognitive remediation group (+ med. Treatment); three 60-min sessions (50 min computerized cognitive activities + 10 min bridging group discussion) per week	OAS: physical aggression	RCT
Carmel et al. (30)	EN	USA	Maximum security forensic hospital	Patients per physician/psychiatrist	Number of incidents of patient aggression (Atascadero Monthly Massed Special Incident Data Base)	Observational study
Cullen et al. (31)	EN	UK	Six medium secure forensic hospitals in the United Kingdom	Reasoning and Rehabilitation (RandR) vs. TAU; 36 sessions á 2 h, 2–3/week (completion at 30 sessions)	Violent incidents as any physically violent behavior (Mac Arthur Community Violence Instrument)	RCT
Daffern et al. (32)	EN	UK	Detained patients under UK Mental Health Act	Life Minus Violence-Enhanced (LMV-E); > 125 treatment sessions, total ∼300 h; group and individual setting	HCR-20; no. of acts of aggression (verbal, physical aggression, deliberate property damage)	Non-randomized controlled trial
Davies et al. (33)	EN	UK	Medium secure mental health forensic service	Positive Behavioral Support (PBS); comprehensive plan for support of individual needs and interests	Checklist of Challenging Behavior (CBC)—aggression frequency and aggression severity subscales	Non-randomized controlled trial
Fluttert et al. (34)	EN	Belgium, Nether-lands, Norway	16 wards of a maximum security forensic hospital	Early Recognition Method (ERM); weekly assessment	Number of seclusions, severity of inpatient incidents	Pre-post study, no controls
Lohner et al. (35)	DE	Germany	Adult patients within the penal system with acute need of psychiatric treatment	Integrated medical, psychotherapeutical, sociotherapeutical treatment program; daily group therapy	Estimated risk of harm to others (by treating psychiatrist)	Non-randomized controlled trial
Reiss et al. (36)	EN	UK	High security ('special') hospital.	Theater project (drama therapy + CBT concepts); 5 days: 2 plays, series of workshops, final "challenge."	Custom 25-items, 5-point Likert-scale; State-Trait Anger Expression Inventory (STAXI AX/out dimension)	Pre-post study, no controls
Sistig et al. (37)	EN	New Zealand	Forensic inpatient service	Mindful yoga; 8 weekly 60 min classes, 30 min guided homework, 2-page A4 poster	CORE-OM subscale "risk to self and others."	Pre-post study, no controls
Yip et al. (39)	EN	UK	Detainment under the U.K. Mental Health Act	Reasoning and Rehabilitation Mental Health Programme (R&R2MHP) vs. TAU; 16 session, 1/week, 90 min; "completion": 80% attendance	Maudsley Violence Questionnaire (MVQ)/acceptance-of-violence subscale, Novaco Anger Scale—Provocation Inventory (NAS-PI)	Non-randomized controlled trial

TABLE 2 | Effects of non-pharmacological trials (Treatment as usual = TAU).

References	Intervention	Outcome	Control condition (TAU)	Intervention condition	Absolute effect	Relative effect	Effect size (Cohen's d)	Persons in control group (studies)	Persons in intervention group (studies)	Quality of the evidence (GRADE)
Ahmed et al. (29)	Cognitive Remediation Group (+ TAU) vs. TAU	OAS: physical aggression score	Mean = 0.61; SD = 1.08	Mean = 0.17; SD = 0.49	MD = 0.440; SE = 0.185		0.54	36 (1 study)	42 (1 study)	⊕⊕⊕◯ Moderate[a,b,c]
Carmel et al. (30)	Number of present physicians	Number of incidents of patient aggression				r = 0.38 (p/phys)	0.82		973 (1 study)	⊕◯◯◯ Very Low[g]
	Number of present psychiatrists	Number of incidents of patient aggression				r = 0.35 (p/psy)	0.74		973 (1 study)	⊕◯◯◯ Very Low[g]
Cullen et al. (31)	Reasoning and Rehabilitation (R&R) vs. TAU	Violent incidents as any physically violent behavior (Mac Arthur Community Violence Instrument)				IRR: 0.52 [0.23, 1.15] (end of treatment); 0.86 [0.44, 1.66] (12 mo follow-up)		40 (1 study)	44 (1 study)	⊕⊕⊕⊕ High[b,h]
Daffern et al. (32)	Effect of Life Minus Violence-Enhanced (LMV-E) program on estimated risk for violence	HCR-20	Mean = 17.5; SD = 3.86	Mean = 25.28; SD = 5.8	MD = −8.13; SE = 1.463		−1.575	42 (1 study)	33 (1 study)	⊕◯◯◯ Very Low[a,d,e,i]
Davies et al. (33)	Positive Behavioral Support (PBS)	"Aggression frequency" CBC (adapted) subscale	Mean = 7.94 (range 0–40)	Mean = 2.35 (range 0–9)	MD = 5.2; SE = n/a			17 (1 study)	17 (1 study)	⊕◯◯◯ Very Low[a,d,e,g]
	Positive Behavioral Support (PBS)	"Aggression severity" CBC (adapted) subscale	Mean = 3.24 (range 0–17)	Mean = 0.88 (range 0–5)	MD = 2.36; SE = n/a			17 (1 study)	17 (1 study)	⊕◯◯◯ Very Low[a,d,e,g]
Fluttert et al. (34)	Early Recognition Method for psychosis	Number of seclusions/ patient/month	Mean = 0.09; SD = n/a	Mean = 0.04; SD = n/a	MD = 0.05 (frequency); SE = n/a		0.43		86 (1 study)	⊕◯◯◯ Very Low[a,e]
	Early Recognition Method for psychosis	Severity of incidents. SOAS-R × seclusions/patient/month	Mean = 0.8; SD = n/a	Mean = 0.41; SD = n/a	MD = 0.35 (severity); SE = n/a		0.39		86 (1 study)	⊕◯◯◯ Very Low[a,e]
Lohner et al. (35)	Integrated medical, psychotherapeutic, sociotherapeutic treatment program	Estimated risk of harm to others (by treating psychiatrist)				RR = 1.13		n/a	124 (1 study)	⊕◯◯◯ Very Low[a,b,i]
Reiss et al. (36)	Therapeutic theater project	Customized questionnaire, scale "how angry"	Mean = 35.2; SD = 14.3	Mean = 22; SD = 12.2	MD = 13.2; SE = 5.426		0.99		12 (1 study)	⊕◯◯◯ Very Low[a,d,e,j]

(Continued)

TABLE 2 | Continued

References	Intervention	Outcome	Control condition (TAU)	Intervention condition	Absolute effect	Relative effect	Effect size (Cohen's d)	Persons in control group (studies)	Persons in intervention group (studies)	Quality of the evidence (GRADE)
	Therapeutic theater project	Customized questionnaire, scale "how react"	Mean = 16.3; SD = 12.4	Mean = 5.2; SD = 6.2	MD = 11.1; SE = 4.002		1.132		12 (1 study)	⊕◯◯◯ Very Low[a,d,e,j]
	Therapeutic theater project	STAXI, AX/out	Mean = 16.; SD = 2.1	mean = 14; SD = 3.6	MD = 2; SE = 1.203		0.679		12 (1 study)	⊕◯◯◯ Very Low[a,d,e,j]
Sistig et al. (37)	Mindful Yoga	"Risk to self and others" CORE-OM subscale	Mean = 1.85; SD = 3.65	Mean = 13.5; SD = 2.64	MD = 0.5; SE = 0.852		0.163		26 (1 study)	⊕◯◯◯ Very Low [a,d,e,k]
Yip et al. (39)	Reasoning and Rehabilitation Mental Health Programme (R&R2MHP) vs. TAU	Maudsley Violence Questionnaire (MVQ)/acceptance of violence	Mean = 8.48; SD = 3.97	Mean = 6.60; SD = 3.12	MVQ/acceptance: MD = 2.450; SE = 0.965		0.53	29 (1 study)	30 (1 study)	⊕◯◯◯ Very Low[a,d,e,f]
	Reasoning and Rehabilitation Mental Health Programme (R&R2MHP) vs. TAU	Novaco Anger Scale—Provocation Inventory (NAS-PI)/Behavior domain	Mean = 26.14; SD = 7.30	Mean = 25.20; SD = 5.91	NAS-PI: MD = 0.130; SE = 5.109		0.14	29 (1 study)	30 (1 study)	⊕◯◯◯ Very Low[a,d,e,f]

[a] *Small sample size.*
[b] *Limited allocation concealment and blinding, probably no limitation to validity.*
[c] *Mixed general and forensic sample, but statistically checked for comparability.*
[d] *No or insufficient allocation concealment.*
[e] *No or insufficient blinding.*
[f] *Unknown number of participants with inadequate diagnosis.*
[g] *No exact information about patient diagnoses (but "majority schizophrenia").*
[h] *Single study, small sample size, but power analysis.*
[i] *Outcome data incomplete.*
[j] *Majority with inadequate diagnosis.*
[k] *Around 25% with inadequate diagnosis.*

A recent study involving a sample of forensic patients with a history of violence and diagnoses of paranoid schizophrenia ($n = 19$) and paranoid schizophrenia as well as antisocial personality disorder ($n = 14$), tested the effect of the Life Minus Violence-Enhanced (LMV-E) program on violence and aggressive behavior (32). The study was conducted in a high security mental health hospital in the UK. A control group of potentially eligible candidates who did not participate in the program was included. The violence outcome was the HCR-20 total score at the end of the intervention. Although violence risk reduced in both groups, surprisingly the control group showed a significantly greater reduction in violence risk ($p < 0.001$). Due to the lack of randomization and blinding, as well as a small sample size, we rated this as a study of very low quality.

Other Interventions

Lohner et al. (35) analyzed the impact of an integrated treatment program in a forensic hospital in Germany, which consisted of pharmacological treatment with behavioral and educational elements. Structured educational groups focused on coping strategies and cooperation. Other elements involved occupational therapy, art therapy, sports therapy, cognitive training, and psychodynamic therapy. One hundred and twenty four male inpatients in one of the treatment program wards were compared to patients in other forensic psychiatric wards at the same hospital. Patients ward allocation was determined by bed availability. All patients had a primary ICD-10 F2 diagnosis. There was no significant difference for the staff estimated risk of causing harm to others at hospital discharge ($p > 0.05$). This paper provided no information on the method of staff risk assessment. Together with the limits concerning randomization (allocation to each ward potentially influenced by medical indication and individual capacity), the quality of evidence has to be considered very low.

Using a pre-post-design Fluttert et al. (34) evaluated the effect of an Early Recognition Method (ERM) in 16 wards of a maximum security forensic hospital in the Netherlands. ERM aims to improve patients ability to perceive and communicate the need for preventive actions. ERM was integrated into pre-existing scheduled interactions between patients and staff, and required ∼30 min per week. One hundred and sixty eight male patients of whom 90 had a schizophrenia diagnosis were included. The number of incidents before and after treatment was compared. The number of seclusions and the severity of violent incidents significantly decreased ($p < 0.05$) after the implementation of the ERM, in both the wider sample and the schizophrenia subsample. Due to the lack of a control group, lack of randomization and blinding, this study is considered to have a very low quality.

Davies et al. (33) investigated the impact of Positive Behavioral Support (PBS) plans in UK medium secure forensic hospitals. After a functional assessment of each participant's violent behavior, measures were planned cooperatively between patients and ward staff to address violence triggering or supporting factors. Twenty two patients with a PBS-plan (18% female, 59% with a SSD diagnosis) were compared to 17 patients on a waiting list for the same treatment. Group allocation was clinical decision. Violence outcome was assessed using the Checklist of Challenging Behavior [CBC (44)]. Compared to the control group, the frequency of violence and the management difficulty at 12 months-follow up was significantly ($p < 0.05$) lower in the PBS group. Methodological limitations such as the lack of randomization and rater blinding indicated that the quality of evidence was very low.

Carmel et al. (30) looked at the relationship between the number of medical staff and violent incidents in a maximum-security forensic hospital in California, USA. In that 973-bed institution, over a 56-month period, all 13,209 special incident reports including 7,389 incidents of patient aggression/violence were identified, as was the number of medical staff present at the hopital at the time for these incidents. The number of incidents with physical aggression was negatively correlated with both the number of patients per general physician ($r = 0.38$; $p < 0.005$) and the number of patients per psychiatrist ($r = 0.35$; $p < 0.01$). Non-violent episodes of dangerous behavior were also related to the number of patients per psychiatrist. This observational study offered no information about the diagnoses in the sample other than that the "majority" had SSD. On that basis we assessed the study as having a very low quality.

Reiss et al. (36) evaluated the effects of a therapeutic theater project on anger in forensic psychiatric patients. This study was included because anger strongly predicts an aggressive predisposition (45). A total of 12 male patients (5 with a SSD) at the young persons' unit (age 18–30 years) at a high security hospital in the United Kingdom, took part in a 5-day theater project, following drama therapy and CBT principles. Two plays were staged after a series of workshops. Self-report of aggressiveness was assessed at baseline, after the 5-day project, and at 3 months follow-up, using a custom 25-item anger inventory, and the State-Trait Anger Expression Inventory [STAXI (46)]. The subscales "how angry" (affective response) and "how react" (behavioral response), and the "anger-out" (anger expressed toward other people) subscale of the 25-item anger inventory showed significant improvements both after the intervention and at later follow-up, while the STAXI showed no statistically significant differences at either time point. Due to the lack of blinding and randomization and the small sample size, the quality of evidence was rated as very low.

Sistig et al. (37) evaluated the impact of a specially adapted yoga program on stress and anxiety in patients in a forensic psychiatric institution in New Zealand. The "mindful yoga" program consisted of 8 weekly classes of 60 min, 30 min of guided homework, and a 2-page A4 poster. Of the 32 initial participants, 7 of whom were female and 77% had a diagnosis of SSD, 26 completed the program. The sub-score "risk to self and others" of the Clinical Outcomes in Routine Evaluation—Outcome Measure (CORE-OM) indicating the staff perception of the patients' risk of violent behavior showed no statistically significant effect. The study had no control group, was unblinded and gave no information about the allocation procedure so the quality of evidence is very low.

DISCUSSION

This is the first systematic review reporting the effects of non-pharmacological interventions on the risk of violent behavior among SSD patients in forensic psychiatry. Overall, despite a very comprehensive search strategy we found only 10 studies on this topic. This matches with the recently published paper by Howner et al. (38) who reported that they independent of type of mental diagnosis treated in forensic psychiatry found no systematic review with a low risk of bias, and only four systematic reviews having a moderate risk of bias. Most of the original studies included into these four systematic reviews had a high risk of bias prohibiting quantitative meta-analyses. None of these systematic reviews had a focus on SSD. This indicates a huge lack of research in this area.

Study Design and Analyses

The studies used a wide range of research designs from RCTs, non-randomized controlled trials, pre-post comparisons without controls and observational studies. Studies without controls can definitely not be used to establish whether the interventions yielded any beneficial effects. Even studies using a control group can be biased, if the control group differs in key characteristics from the intervention group. For example, Daffern et al. (32) reported better results in the control group than the intervention group without establishing if there were any differences between the two groups. That raises the possibility that confounding variables might explain the results. Of course, the results could be influenced by other interventions such as psychotropic treatment, staff-patient ratio, severity of psychiatric symptoms or illness history. Psychotropic medicines remain the key intervention in the treatment of most patients with SSDs, pharmacological regimes will often differ between clinical teams, wards and institutions. RCTs provide the best approach to minimize the problem of confounding. However, in real life it is often impossible to use RCTs in forensic clinical settings due to various practical reasons. If randomization is not feasible, researchers should at least report relevant baseline data from study groups, which might influence the effect of treatment and attempt to match groups as closely as possible on such factors (47). We note that for very novel and innovative interventions small scale studies may yield important information of a therapeutic effect, that will then help to justify plans for more sophisticated and costly studies (48).

Both studies that applied an RCT design (29, 31) used an intention-to-treat approach for their analyses. This approach takes into account all subjects included in the study, even those who dropped out. That, while telling us something about the tolerability of the intervention, is at risk of leading to an underestimation of the effectiveness of the intervention. In contrast, analyzing only those who completed the study might be biased by including only the most motivated or responsive patients. Papalia et al. (47) suggested that future studies should report on both the results of the intention-to-treat as well as completers samples.

The sample size of most of the studies that we identified was small. That finding might partly explain the large number of non-significant findings among these studies. In most papers the authors did not report a pre-study power analysis. Thus, they could not plan their studies based on this kind of information, which, in turn, makes it difficult for readers to decide how to interpret negative results. Although we focused on SSDs, frequently subjects with other diagnoses were included in these studies. The data were often not reported separately for patients with SSD and other diagnoses. Furthermore, most studies did not use standardized diagnostic instruments, such as the SCID, to confirm diagnoses or illness severity scales.

Assessments

Outcome measures used to quantify the level or risk of violence varied considerably between the studies. While some authors (29) used standardized and validated scales such as the Overt Aggression Scale (40), others simply counted the number of seclusions or aggressive incidents recorded in the patients' hospital files (30, 34). The nature of what constituted aggression and violence also varied. This is particularly true for lower level violent incidents. In some studies the definition of aggression and violence may have been influenced by legal or clinical considerations thus hindering comparability between studies. Similarly, national definitions, legal and clinical rules and considerations may influence how often seclusions are used rather than any study intervention. There are a range of validated instruments to record and quantify violence for clinical and research purposes in mental health settings (49). Where violence is recorded and how that data is accessed is also important. Using multiple sources of information, such as self-report, clinical assessments and patient files will yield the most comprehensive information.

It is also clear, with regard to study outcome, that the duration of the follow-up varied considerably. We assumed that the effect of any non-pharmacological intervention will persist at least for some weeks (29) and possibly for longer (31). Of course, longer follow up periods allow more time for violent incidents to occur, though these will be matched between study groups. However, given that the aim of forensic services in general is to produce long term violence risk reduction and allow discharge to less restrictive settings, better designed studies with longer term follow up is needed.

Findings of This Review

The range of interventions studied was very broad from training in the early recognition of symptoms, cognitive remediation therapy to therapeutic theater and yoga. CBT was the most frequently investigated type of intervention (31, 32, 39). This matches with the finding of Rampling et al. (19) who reported that several studies exist which reported positive effects of CBT in reducing physical aggression among severely mentally ill including SSD patients in general psychiatry. Similar to our review Darmedru et al. (50) reported that in general psychiatry cognitive remediation was effective in the reduction of aggressive behaviors and physical assaults in schizophrenia.

The studies included group programs [e.g., (29)], individual interventions [e.g., (34)] and combinations of group and individual interventions [e.g., (32)]. Papalia et al. (47) reported

from their review of psychological treatments that group-based interventions were associated with greater reductions in violent recidivism relative to treatments that used individual delivery only. Due to the heterogeneity of study designs and interventions in our review, we cannot verify if this holds true for patients with SSD.

Interventions ranged widely in their demands and duration. Some consisted of at least 125 treatment sessions (32) while others had only 8 sessions (37). This wide span place hugely different demands on clinical budgets and staffing levels and training. These considerations will influence what interventions might be implemented in clinical settings, balanced against the evidence of clinical effectiveness.

There was an interesting finding in the observed changes in violent incidents linked to the ratio between medical staff and forensic patients. Violence was less when there were more psychiatric or general medical personnel. This relationship might seem obvious, though the underlying mechanisms are unclear. More medical staff members could lead to more time per patient for treatment planning, evaluation and risk assessment, therefore potentially improving outcomes. On the other hand, it is plausible that the mere presence of staff produces a sense of security and therefore has a preventive effect on aggressive and violent behavior. However, staff numbers can also be having effects by implementing interventions such as the "Early Recognition Method" or preventive strategies like "Positive Behavioral Support"-plans. Reliable violence risk assessment and management takes time and effort, safe staffing levels need to be available.

Limitations

Despite the fact that we used a very comprehensive search strategy we found only a very small number of studies that attempted to provide evidence for the impact of non-pharmacological treatments to patients with SSDs aiming to reduce violence in forensic psychiatry settings. This is striking given the number of patients that could directly benefit but also the wider implications for society. It is also striking given that many forensic services invest so heavily in such therapies without a clear evidence base. Despite applying a very comprehensive search strategy, for practical reasons we excluded some specific forms of aggression such as child abuse, school violence or terrorism. We cannot rule out that we might have overlooked a small number of papers. We limited our search strategy to articles published since 1990 because the forensic psychiatry field has changed so radically over the intervening three decades. Of course, this lack of data could be considered a limitation of this review, but we think that it is of itself a very relevant finding. Forensic psychiatry services invest huge amounts of time and resources in non-pharmacological therapies, yet there is a very poor evidence base to support that expenditure. Furthermore, in some jurisdictions, patients remain detained in forensic hospitals until they engage in such violence reduction treatment and until the treatment is completed. This could be considered unethical if the treatment cannot be shown to offer benefit to the patient or other people.

The second main finding was that although we included only articles published in peer-reviewed journals hoping to yield studies with an adequate level of methodological rigor, the results were very disappointing. In general, even in the published literature the quality of evidence was poor to very poor. There is therefore a pressing and urgent need to conduct methodologically robust studies to test what works, expand what does, and stop what does not.

Since we did not search for book chapters, congress abstracts or unpublished studies, we might have overlooked some studies. Nevertheless, we expect that the large majority of sophisticated studies would have been published in peer-reviewed journals. We did not search for studies published in other languages than English. Thus, we cannot exclude that we have missed a small number of studies.

CONCLUSIONS

Because of the methodological limitations of the studies in our review, it is not possible to draw any firm conclusions about the effectiveness of non-pharmacological interventions to reduce the risk of violence in patients with SSD in forensic settings. Two papers (29, 31) reported of RCTs showing that more ambitious study designs can be realized even in forensic settings with SSD patients. The methodological limitations of those two projects (e.g., mixed samples, diagnostic heterogeneity) could be resolved in future studies. Other review papers reporting on other studies in forensic and correctional settings confirm this conclusion (47, 48).

What should be done in everyday work with SSD patients in forensic services until we have more sophisticated studies? At the moment, we must rely on findings from clinical psychiatry showing that some psychological interventions are effective to reduce violence among patients with SSD (50). Findings from reviews showed that some psychological interventions, mainly cognitive-behavioral, are effective for reducing violence. Other studies among offenders without psychiatric diagnoses support this idea (47, 51). Of course, there are important differences between SSD patients in general psychiatry and in forensic settings, but at the moment forensic psychiatrists must rely to a large extent on research conducted in general psychiatry settings.

This systematic review clearly shows that high quality research in this area is urgently needed. It is important that future studies plan sample sizes that are sufficiently powered to confidently address the research questions. In addition, studies should use standardized diagnostic procedures for SSD, use clear definitions of violence which can easily be compared with other studies and are clinically relevant (e.g., number of violent attacks against hospital staff or other people, criminal violence or incarceration). The use of standardized and validated assessment instruments can improve the description of forensic samples. The consequences of lacking research in this area is currently that people are detained against their wishes in forensic hospitals, and often treated against their wishes using interventions which frequently lack high-quality evidence regarding their effectiveness. This raises serious ethical concerns.

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/s.

AUTHOR CONTRIBUTIONS

AR and RS planned the literature search, selected the abstracts, extracted data from original papers, and wrote the original draft. HW selected the abstracts and reviewed the manuscript. GdG and GC planned the literature search, submitted the grant, and reviewed the manuscript. CC and IM commented the methods and reviewed the manuscript. HF and JH prepared the grant and reviewed the manuscript. HS and MP made suggestions for literature searches and reviewed the manuscript. GdG and GC planned the literature search, prepared the grant, and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by the European Union under grant no PP-2-3-2016.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.618860/full#supplementary-material

REFERENCES

1. World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research*. Geneva: WHO (1993).
2. Rössler W, Kawohl W, Nordt C, Haker H, Rüsch N, Hengartner MP. 'Placement budgets' for supported employment: impact on employment rates in a multicentre randomised controlled trial. *Brit J Psychiatry*. (2020) 216:308–13. doi: 10.1192/bjp.2019.154
3. Killaspy H, Priebe S, McPherson P, Zenasni Z, Greenberg L, McCrone P, et al. Predictors of moving on from mental health supported accommodation in England: national cohort study. *Brit J Psychiatry*. (2020) 216:331–7. doi: 10.1192/bjp.2019.101
4. Fazel S, Gulati G, Linsell L, Geddes JR, Grann M. Schizophrenia and violence: systematic review and meta-analysis. *PLoS Med*. (2009) 6:e1000120. doi: 10.1371/journal.pmed.1000120
5. Glancy GD, Regehr C. The forensic psychiatric aspects of schizophrenia. *Psychiatr Clin North Am*. (1992) 15:575–89. doi: 10.1016/S0193-953X(18)30225-9
6. Heads TC, Taylor PJ, Leese M. Childhood experiences of patients with schizophrenia and a history of violence: a special hospital sample. *Crim Behav Ment Health*. (1997) 7:117–30. doi: 10.1002/cbm.157
7. Arboleda-Florez J. Forensic psychiatry: contemporary scope, challenges and controversies. *World Psychiatry*. (2006) 5:87–91.
8. Salize H-J, Dressing H. Admission of mentally disordered offenders to specialized forensic care in fifteen European Union member states. *Soc Psychiatry Psychiatr Epidemiol*. (2007) 42:336–42. doi: 10.1007/s00127-007-0159-2
9. Leucht S, Leucht C, Huhn M, Chaimani A, Mavridis D, Helfer B, et al. Sixty years of placebo-controlled antipsychotic drug trials in acute schizophrenia: systematic review, bayesian meta-analysis, and meta-regression of efficacy predictors. *Am J Psychiatry*. (2017) 174:927–42. doi: 10.1176/appi.ajp.2017.16121358
10. Ceraso A, Lin JJ, Schneider-Thoma J, Siafis S, Tardy M, Komossa K, et al. Maintenance treatment with antipsychotic drugs for schizophrenia. *Cochrane Database Syst Rev*. (2020) 8:CD008016. doi: 10.1002/14651858.CD008016.pub3
11. Fazel S, Zetterqvist J, Larsson H, Långström N, Lichtenstein P. Antipsychotics, mood stabilisers, and risk of violent crime. *Lancet*. (2014) 384:1206–14. doi: 10.1016/S0140-6736(14)60379-2
12. Jones C, Cormac I, Silveira da Mota Neto JI, Campbell C. Cognitive behaviour therapy for schizophrenia. *Cochrane Database Syst Rev*. (2007). 4:CD000524.
13. Quinn J, Kolla NJ. From clozapine to cognitive remediation: a review of biological and psychosocial treatments for violence in schizophrenia. *Can J Psychiatry*. (2017) 62:94–101. doi: 10.1177/0706743716656830
14. Haddock G, Barrowclough C, Shaw JJ, Dunn G, Novaco RW, Tarrier N. Cognitive–behavioural therapy v. social activity therapy for people with psychosis and a history of violence: randomized controlled trial. *Br J Psychiatry*. (2009) 194:152–7. doi: 10.1192/bjp.bp.107.039859
15. Henning KR, Frueh BC. Cognitive-behavioral treatment of incarcerated offenders: an evaluation of the Vermont Department of Corrections' Cognitive Self-Change Program. *Crim Justice Behav*. (1996) 23:523–41. doi: 10.1177/0093854896023004001
16. Hogan NL, Lambert EG, Barton-Bellessa SM. Evaluation of CHANGE, an involuntary cognitive program for high-risk inmates. *J Offender Rehabil*. (2012) 51:370–88. doi: 10.1080/10509674.2012.664254
17. Davidson K, Tyrer P, Tata P, Cooke D, Gumley A, Ford I, et al. Cognitive behaviour therapy for violent men with antisocial personality disorder in the community: an exploratory randomized controlled trial. *Psychol Med*. (2009) 39:569–77. doi: 10.1017/S0033291708004066
18. Bernstein DP, Nijman HLI, Karos K, Keulen-de Vos M, Vogel V, Lucker TP. Schema therapy for forensic patients with personality disorders: design and preliminary findings of a multicenter randomized clinical trial in the Netherlands. *Int J Forens Ment Health*. (2012) 11:312–24. doi: 10.1080/14999013.2012.746757
19. Rampling J, Furtado V, Winsper C, Marwaha S, Lucca G, Livanou M, et al. Non-pharmacological interventions for reducing aggression and violence in serious mental illness: a systematic review and narrative synthesis. *Eur Psychiatry*. (2016) 34:17–28. doi: 10.1016/j.eurpsy.2016.01.2422
20. Wolf A, Whiting D, Fazel S. Violence prevention in psychiatry: an umbrella review of interventions in general and forensic psychiatry. *J Forens Psychiatry Psychol*. (2017) 28:659–73. doi: 10.1080/14789949.2017.1284886
21. Buckley PF, Hrouda DR, Friedman L, Noffsinger SG, Resnick PJ, Camlin-Shingler K. Insight and its relationship to violent behavior in patients with schizophrenia. *Am J Psychiatry*. (2004) 161:1712–4. doi: 10.1176/appi.ajp.161.9.1712
22. Fazel S, Langström N, Hjern A, Grann M, Lichtenstein P. Schizophrenia, substance abuse, and violent crime. *JAMA*. (2009) 301:2016–23. doi: 10.1001/jama.2009.675
23. Lau S. Challenges in the treatment of schizophrenic offenders. *Forens Psychiatr Psychol Kriminol*. (2017) 11:39–45. doi: 10.1007/s11757-016-0404-1
24. Völlm BA, Clarke M, Herrando VT, Seppänen AO, Gosek P, Heitzman J, et al. European Psychiatric Association (EPA) guidance on forensic psychiatry: evidence based assessment and treatment of mentally disordered offenders. *Eur Psychiatry*. (2018) 51:58–73. doi: 10.1016/j.eurpsy.2017.12.007
25. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. (2009) 6:e1000097. doi: 10.1371/journal.pmed.1000097
26. Allen JJ, Anderson CA. Aggression and violence: definitions and distinctions. In: Sturmey P, editor. *The Wiley Handbook of Violence and Aggression*. Chichester, UK: Wiley (2017). p. 1–14.
27. Cohen J. A coefficient of agreement for nominal scales. *Educ Psychol Meas*. (1960) 20:37–46. doi: 10.1177/001316446002000104

28. Ryan R, Hill S. *How to GRADE the Quality of the Evidence*. Cochrane Consumers and Communication Group, Version 3.0 (2016). Available online at: http://cccrg.cochrane.org/author-resources (accessed September 26, 2019).
29. Ahmed AO, Hunter KM, Goodrum NM, Batten NJ, Birgenheir D, Hardison E, et al. A randomized study of cognitive remediation for forensic and mental health patients with schizophrenia. *J Psychiatr Res*. (2015) 68:8–18. doi: 10.1016/j.jpsychires.2015.05.013
30. Carmel H, Tanke ED, Yesavage JA. Physician staffing and patient violence. *Bull Am Acad Psychiatry Law*. (1991) 19:49–51.
31. Cullen AE, Clarke AY, Kuipers E, Hodgins S, Dean K, Fahy T. A multisite randomized trial of a cognitive skills program for male mentally disordered offenders: violence and antisocial behavior outcomes. *J Consult Clin Psychol*. (2012) 80:1114–20. doi: 10.1037/a0030291
32. Daffern M, Simpson K, Ainslie H, Chu S. The impact of an intensive inpatient violent offender treatment programme on intermediary treatment targets, violence risk and aggressive behaviour in a sample of mentally disordered offenders*. *J Forens Psychiatry Psychol*. (2018) 29:163–88. doi: 10.1080/14789949.2017.1352014
33. Davies BE, Lowe K, Morgan S, John-Evans H, Fitoussi J. An evaluation of the effectiveness of positive behavioural support within a medium secure mental health forensic service. *J Forens Psychiatry Psychol*. (2019) 30:38–52. doi: 10.1080/14789949.2018.1459785
34. Fluttert FA, van Meijel B, Nijman H, Bjorkly S, Grypdonck M. Preventing aggressive incidents and seclusions in forensic care by means of the 'Early Recognition Method'. *J Clin Nurs*. (2010) 19:1529–37. doi: 10.1111/j.1365-2702.2009.02986.x
35. Lohner J, Lauterbach C, Konrad N. Inpatient treatment of mentally ill schizophrenic offenders. Evaluation of an integrative therapy concept at a psychiatric hospital for prisoners. *Krankenhauspsychiatrie*. (2006) 17:148–54. doi: 10.1055/s-2006-944304
36. Reiss D, Quayle M, Brett T, Meux C. Dramatherapy for mentally disordered offenders: changes in levels of anger. *Crim Behav Ment Health*. (1998) 8:139–53. doi: 10.1002/cbm.232
37. Sistig B, Friedman SH, McKenna B, Consedine NS. Mindful yoga as an adjunct treatment for forensic inpatients: a preliminary evaluation. *J Forens Psychiatry Psychol*. (2015) 26:824–46. doi: 10.1080/14789949.2015.1062996
38. Howner K, Andiné P, Bertilsson G, Hultcrantz M, Lindström E, Mowafi F, et al. Mapping systematic reviews on forensic psychiatric care: a systematic review identifying knowledge gaps. *Front. Psychiatry*. (2018) 9:452. doi: 10.3389/fpsyt.2018.00452
39. Yip VC, Gudjonsson GH, Perkins D, Doidge A, Hopkin G, Young S. A non-randomised controlled trial of the RandR2MHP cognitive skills program in high risk male offenders with severe mental illness. *BMC Psychiatry*. (2013) 13:267. doi: 10.1186/1471-244X-13-267
40. Yudofsky SC, Silver JM, Jackson W, Endicott J, Williams D. The Overt Aggression Scale for the objective rating of verbal and physical aggression. *Am J Psychiatry*. (1986) 143:35–9. doi: 10.1176/ajp.143.1.35
41. Porporino F, Fabiano E. *Program Overview of Cognitive Skills Reasoning and Rehabilitation Revised: Theory and Application*. Ottawa, ON: T3 Associates (2000).
42. Walker JS. The Maudsley Violence Questionnaire: initial validation and reliability. *Pers Individ Differ*. (2005) 38:187–201. doi: 10.1016/j.paid.2004.04.001
43. Novaco RW. *The Novaco Anger Scale and Provocation Inventory*. Los Angeles, CA: Western Psychological Services (2003).
44. Harris P, Humphreys J, Thomson G. A checklist of challenging behaviour: the development of a survey instrument. *Ment Handicap Res*. (1994) 7:118–33. doi: 10.1111/j.1468-3148.1994.tb00120.x
45. Waterburton WA, Anderson CA. Social psychology of aggression. In: *International Encyclopedia of the Social and Behavioral Sciences*, 2nd ed, Vol. 1. New York, NY: Elsevier (2015). p. 373–80.
46. Spielberger CD. *State-Trait Anger Expression Inventory, Research Edition Professional Manual*. Odessa, FL: Psychological Assessment Resources (1979).
47. Papalia N, Spivak B, Daffern M, Ogloff JRP. A meta-analytic review of the efficacy of psychological treatments for violent offenders in correctional and forensic mental health settings. *Clin Psychol Sci Pract.* (2019) 26:e12282. doi: 10.1111/cpsp.12282
48. Byrne G, Ghrada AN. The application and adoption of four 'third wave' psychotherapies for mental health difficulties and aggression within correctional and forensic settings: a systematic review. *Aggress Viol Behav*. (2019) 46:45–55. doi: 10.1016/j.avb.2019.01.001
49. Harris ST, Oakley C, Picchioni M. Quantifying violence in mental health research. *Aggress Viol Behav*. (2013) 18:695–701. doi: 10.1016/j.avb.2013.07.022
50. Darmedru C, Demily C, Franck N. Cognitive remediation and social cognitive training for violence in schizophrenia: a systematic review. *Psychiatry Res*. (2017) 251:266–74. doi: 10.1016/j.psychres.2016.12.062
51. Gannon TA, Olver ME, Mallion JS, James M. Does specialized psychological treatment for offending reduce recidivism? A meta-analysis examining staff and program variables as predictors of treatment effectiveness. *Clin Psychol Rev*. (2019) 73:101752. doi: 10.1016/j.cpr.2019.101752

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.

frontiers in Psychiatry

SYSTEMATIC REVIEW
published: 28 May 2021
doi: 10.3389/fpsyt.2021.666988

Acupuncture as an Independent or Adjuvant Management to Standard Care for Perimenopausal Depression: A Systematic Review and Meta-Analysis

Fei-Yi Zhao[1,2,3], *Qiang-Qiang Fu*[4], *Gerard A. Kennedy*[1,5,6], *Russell Conduit*[1], *Wen-Jing Zhang*[2*] and *Zhen Zheng*[1*]

[1] School of Health and Biomedical Sciences, RMIT University, Bundoora, VIC, Australia, [2] Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China, [3] Department of Nursing, School of International Medical Technology, Shanghai Sanda University, Shanghai, China, [4] Yangpu Hospital, Tongji University School of Medicine, Shanghai, China, [5] School of Science, Psychology and Sport, Federation University, Mount Helen, VIC, Australia, [6] Institute for Breathing and Sleep, Austin Health, Heidelberg, VIC, Australia

OPEN ACCESS

Edited by:
Joe Kossowsky,
Harvard Medical School,
United States

Reviewed by:
Irving Kirsch,
Harvard Medical School,
United States
Francesco Monaco,
Azienda Sanitaria Locale Salerno, Italy

***Correspondence:**
Wen-Jing Zhang
1072@szy.sh.cn.com
Zhen Zheng
zhen.zheng@rmit.edu.au

Specialty section:
This article was submitted to Psychosomatic Medicine, a section of the journal Frontiers in Psychiatry

Received: 11 February 2021
Accepted: 06 April 2021
Published: 28 May 2021

Citation:
Zhao F-Y, Fu Q-Q, Kennedy GA, Conduit R, Zhang W-J and Zheng Z (2021) Acupuncture as an Independent or Adjuvant Management to Standard Care for Perimenopausal Depression: A Systematic Review and Meta-Analysis. Front. Psychiatry 12:666988. doi: 10.3389/fpsyt.2021.666988

Background: Many women with perimenopausal depression (PMD) have sought alternative therapies such as acupuncture because of concerns about risks associated with antidepressant and hormone replacement therapy (HRT). This systematic review aimed to clarify if acupuncture is effective for PMD compared with waitlist control or placebo/sham acupuncture, and if acupuncture alone or combined with standard care (antidepressant and/or HRT) is more effective in ameliorating PMD in comparison with standard care alone.

Methods: Randomized controlled trials (RCTs) of PMD treatment *via* acupuncture vs. waitlist control or placebo/sham acupuncture, and RCTs of PMD treatment *via* acupuncture alone or combined with Western pharmacotherapy vs. Western pharmacotherapy were searched for from seven databases from inception to December 2020. Cochrane criteria were followed.

Results: Twenty-five studies involving 2,213 women were analyzed. Meta-analyses indicated that acupuncture significantly reduced the global scores of Hamilton Depression Scale (HAMD) [standardized mean difference (SMD) = −0.54, 95% CI (−0.91, −0.16), $p < 0.01$], compared with standard care. The therapeutic effect of acupuncture maintained at 2-, 4-, and 12-week follow-ups. Acupuncture combined with standard care was more effective than standard care alone in decreasing HAMD scores [SMD = −0.82, 95% CI (−1.07, −0.58), $p < 0.01$]. Too few RCTs were available to assess the clinical efficacy differences between acupuncture and placebo/sham acupuncture or HRT alone. Acupuncture also showed better effects in decreasing Kupperman index (KI) scores, whether compared with antidepressant alone [MD = −4.55, 95% CI (−8.46, −0.65), $p = 0.02$] or antidepressant combined with HRT [MD = −0.89, 95% CI (−1.34, −0.43), $p < 0.01$].

Conclusions: In comparison with standard care, acupuncture alone or combined with standard care was associated with significant improvements in PMD and reductions of other menopausal symptoms. This finding suggests that acupuncture may be a useful addition to treatment for PMD.

Keywords: acupuncture, perimenopausal depression, standard care, systematic review, meta-analysis

BACKGROUND

Women are twice as likely to suffer from depression in their lifetime as men, and depression is also one of the major causes of disease-related disabilities in women (1). Menopausal transition, also called perimenopause, refers to a critical stage of dynamic hormonal flux (2) that occurs at midlife in women and is defined as a specific period in the final years of reproductive life (3–5). Experiencing a range of significant endocrine and other biological changes (6), women are usually affected by a variety of physical and psychological complaints, including vasomotor symptoms (hot flashes and night sweats); sleep disturbance; vaginal, urinary, and sexual symptoms (e.g., vaginal dryness, dyspareunia, bleeding, etc.), as well as adverse mood states (e.g., depression, anxiety, mood swings, etc.) (1, 5, 6). Perimenopause is defined as a "window" of vulnerability for the development of depression (7), with prevalence rates of depression ranging up to 20–40% (8, 9). A number of cross-sectional investigations have shown that in comparison with premenopause, women in perimenopause are at a higher risk for depression and present a higher prevalence of depressive symptoms (7). Diagnosis and treatment of perimenopausal depression (PMD) is challenging because it commonly co-occurs with other menopausal symptoms (7). PMD is associated with the impaired functional outcomes, decreased social supports, increased complaints of disability, and lower quality of life, which are not widely reported by perimenopausal women without depression (9–11). Untreated PMD can increase medical morbidity after menopause, including risks of cardiovascular disease, diabetes, and osteoporosis (12). Effective management strategies are therefore required to reduce the negative impact of depression in this vulnerable group (10).

Perimenopausal syndrome including mild-to-moderate and non-long-standing PMD symptoms are often managed with hormone replacement therapy (HRT) (3, 5, 6, 13). Despite its positive effect on mood, HRT is linked with the increased risk of ovarian cancer (14), breast cancer (15), and cardiovascular diseases (16). Furthermore, estrogen therapy has not been approved by the Food and Drug Administration (FDA) to treat PMD and/or other mood disturbances (7). Antidepressant treatment [e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and mirtazapine, etc.] is another pharmacological option for PMD (7). However, women tend not to use antidepressants due to potential side effects such as weight gain (17), gastrointestinal symptoms (18, 19), and sexual dysfunction (17–19).

The limitations of conventional therapies have driven women to seek relief from complementary and alternative medicine (CAM) treatments (20). Acupuncture as part of Traditional Chinese Medicine (TCM) is one of the most popular and safest CAM therapies (21). It is a traditional healing technique involving the insertion of fine, solid, metallic needles into targeted sites called "acupoints" on the body wall to achieve therapeutic outcomes (22–24). After insertion, the needles are usually stimulated manually with slight twisting and with gentle movements up and down [manual acupuncture (MA)] or are stimulated with the electrical impulses delivered by an electric microcurrent device [electroacupuncture (EA)] (22, 24, 25).

Several randomized controlled trials (RCTs) regarding the use acupuncture for the treatment of PMD have been published (26–29). Conflicting findings (30, 31) and differences in research design among those RCTs hinder a firm conclusion regarding the use of acupuncture for PMD (27), as either an independent or adjuvant therapy to standard care (antidepressant and/or HRT). This systematic review aimed to address the following research questions: (1) Can acupuncture be used as an independent therapy for PMD?; (2) how effective is acupuncture for the management of PMD in comparison with standard care; and (3) when acupuncture is used as an adjuvant therapy to standard care, could it further enhance the therapeutic effect or reduce the side effects of Western pharmacotherapy? This systematic review was carried out in accordance with Cochrane Handbook for Systematic Reviews and was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.

MATERIALS AND METHODS

Study Registration

The protocol for this systematic review was registered in the Prospective Register of Systematic Reviews (PROSPERO): No. CRD42021227015.

Eligibility Criteria

Studies included were published RCTs with parallel designs. Women in the perimenopausal period with a clinical diagnosis of depression as per standard diagnostic criteria were included. Any trial without a standard diagnostic guideline was excluded even it mentioned that the patient was diagnosed with PMD or it provided brief information regarding women's complaints of depressed mood. Participants in a pre- or post-menopausal status, or with comorbid cardiovascular disease, cerebrovascular disease, endocrine diseases, cancer, other psychiatric or gynecological disorders, or other severe disorders were excluded. Interventions were restricted to traditional needle acupuncture (TNA) including MA and EA, or TNA

combined with standard care for PMD (antidepressant and/or HRT). Comparator interventions were restricted to waitlist control, placebo/sham acupuncture, or standard care. The primary outcome was validated depression scales [e.g., Hamilton Depression Scale (HAMD) and Self-rating Depression Scale (SDS)]. There are several versions of HAMD, such as HAMD-6, HAMD-17, HAMD-21, HAMD-23, HAMD-24, and HAMD-27 (32). There was no restriction on HAMD version for searching and including studies. Papers were excluded if they did not report the global scores of any validated depression scale, even though they reported the clinical effectiveness rates based on the scale or reported partial items of the scale. Secondary outcomes included menopausal symptoms assessed with validated scales [e.g., Kupperman index (KI) and Menopause-Specific Quality of Life (MENQOL)], sleep/anxiety symptoms, serum hormone levels [e.g., follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2)], and adverse events (AEs).

Search Strategy and Data Extraction

Four Chinese and three English electronic databases—China biomedical literature service system (SinoMed), Wanfang database, China National Knowledge Infrastructure (CNKI), Chongqing VIP database (CQVIP), Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (*via* PubMed), and EMBASE—with language restrictions of Chinese and English were searched from the inception date of each database until December 2020. Additional studies were also identified from other sources, including the online trial registries such as US ClinicalTrials.gov and WHO International clinical trials registry platform search portal, the reference lists of the included papers, existing systematic reviews, and gray literatures (**Appendix 1**).

For each study, the following data for demographic and clinical characteristics were extracted: the last name of the first author, publication year, grouping methods and number of patients in each group, duration of PMD, diagnostic criteria used, TCM syndrome type of patients, protocols including timing, frequency, and dosage in acupuncture, the acupoints selected, prescription in control group (timing, frequency, and dosage in placebo/sham acupuncture or type, dosage, and oral frequency of Western medication), outcome measures, results, follow-up, and AEs. Additionally, GetData software (Version 2.25) was used to measure the data if the outcomes were only shown graphically.

Study Quality and Risk of Bias Assessment

Two assessors carried out independent evaluations (including determining risk of bias and assessing the internal validity) of all the included RCTs using Cochrane Collaboration's risk of bias tool (33). The revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) checklist (revised version, published in 2010) was used to evaluate and describe the details of acupuncture procedure including completeness and reporting quality in each RCT (34).

DATA ANALYSIS

The meta-analysis was performed *via* Cochrane Collaboration Review Manager Software (RevMan Version 5.3). The inverse-variance method in RevMan was used to assign weight to each included study. Given that the major outcome measures (e.g., global scores of depression/perimenopause scales and hormone levels) were continuous variables, mean differences (MDs) were analyzed. When the depression in different studies was assessed *via* different scales or different versions of the same scale (e.g., 17-item HAMD, 21-item HAMD, and 2-item HAMD, etc.) or when serum hormonal levels were presented in the different units of measurement, standardized MDs (SMDs) were used. Confidence intervals (CIs) were established at 95%. Level of heterogeneity across studies was tested using the Q- and I^2-test. Statistically significance was set at two-tailed probability (p) value < 0.05. The results were pooled using a fixed-effects model when the p-value was >0.10 in the Q-test and the I^2-value was $\leq$50%, which was considered be to an acceptable level of heterogeneity. Otherwise, a random-effects model was applied. When significant heterogeneity existed, subgroup analyses were carried out based on different acupuncture stimulations (MA or EA), different prescriptions in the controls (antidepressant, HRT, or antidepressant + HRT), and different versions of HAMD used. Sensitivity analysis and meta-regression analysis were also adopted to explore sources of heterogeneity and check robustness of the conclusions. Publication bias was investigated *via* Egger's test and Begg's test.

RESULTS ANALYSIS

The initial search yielded 572 potentially eligible studies. After removing the duplicates and further screening, 25 studies (involving 2,213 participants) met the predefined criteria (**Figure 1**). All included studies were qualitatively analyzed, and 24 of them underwent quantitative synthesis (meta-analysis).

Description of Studies

Among the 25 RCTs, two RCTs (35, 36) employed sham-acupuncture control [one RCT (36) was a three-arm trial with both sham acupuncture and antidepressant as controls], 20 RCTs (30, 31, 37–54) employed standard care (antidepressant or antidepressant combined with HRT) control, and the remaining three (55–57) compared the clinical effectiveness between standard care (antidepressant or antidepressant combined with HRT) alone and acupuncture combined with standard care. None of the RCTs included a waitlist control. In the studies with standard care as control, the frequency of use of antidepressant drugs from high to low were fluoxetine (10/24), fluoxetine combined with HRT (5/24), escitalopram (4/24), Deanxit (3/24), sertraline (1/24), and paroxetine (1/24). None of the trials addressed the comparison between acupuncture and HRT alone. Seven out of the 25 RCTs (36, 37, 45, 46, 48, 52, 55) investigated the clinical effectiveness of EA, while the remaining 18 RCTs investigated the effectiveness of MA. Acupuncture treatment was provided daily to three times per week for 10 days−12 weeks (**Table 1**).

Table 2 and **Appendix 2** show the assessment time-points and results of each outcome in each trial. Except for one study (35) that adopted SDS as the primary outcome, the remaining studies adopted HAMD to assess the changes in depression at

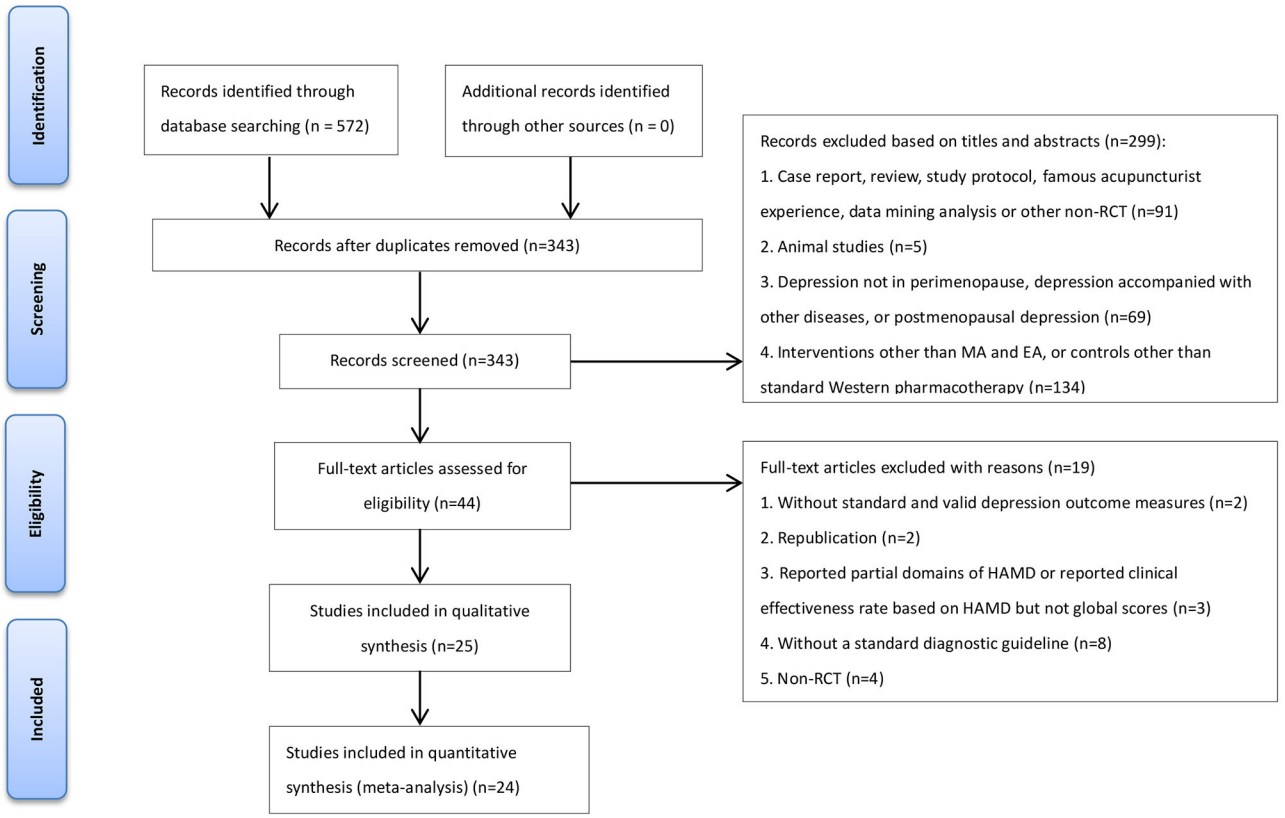


FIGURE 1 | Flow diagram of the study selection process. MA, manual acupuncture; EA, electroacupuncture; RCT, randomized controlled trial.

pre- and post-treatment. HAMD-17 was used in 11 RCTs (36–38, 40, 43–45, 47, 50, 52, 53), HAMD-24 in seven (30, 39, 48, 49, 51, 54, 55), and HAMD-21 in one (31). The remaining five studies (41, 42, 46, 56, 57) did not report which version of HAMD was used. KI (38, 40, 48, 50, 51) and MENQOL (35–37) were used to evaluate patients' perimenopausal symptoms and quality of life during perimenopause, respectively. In addition, serum FSH (36, 37, 48–50, 56), E2 (36, 37, 48–50, 56), and LH (36, 37, 48–50) were assessed in some RCTs to explore the association between the effect of acupuncture and the modulation of reproductive hormone levels.

Eight studies (35–38, 45, 47, 50, 53) reported follow-up data from 2 to 24 weeks after the end of treatment (**Appendix 2**).

Thirteen studies (30, 36–38, 40–43, 47–50, 55) reported AEs. AEs associated with acupuncture treatment were hematoma (16/146), feeling pain when inserting needle (4/154), dizziness (8/147), palpitation (4/83), dry mouth (1/41), nausea and/or vomiting (6/85), changes of character of stool (4/50), and sweating (5/44); AEs associated with standard (antidepressant or antidepressant combined with HRT) included fatigue (17/30), palpitation (25/206), headache (3/62), dizziness (40/472), sleep disturbance (25/250), sweating (10/30), dry mouth and/or halitosis (41/229), indigestion (1/32), loss of appetite (5/60), stomachache (18/105), nausea and/or vomiting (18/303), constipation (14/76), diarrhea (4/92), changes of character of stool (6/29), dysphoria (14/96), for excitation and agitation (2/30), akathisia (1/30), spasmus (1/60), breast distending pain (16/156), leukorrhagia (2/60), skin symptom (1/30), and elevated blood pressure (2/50). No sham-acupuncture-related AEs were reported (**Table 1**).

Study Quality Evaluation

Fifteen out of 25 trials provided an adequate description of the process and method of randomization (31, 35–38, 42–44, 47, 48, 50, 52, 54, 56, 57), while 10 trials (30, 39–41, 45, 46, 49, 51, 53, 55) only mentioned that the RCT design was employed in the trial but did not clarify the specific randomization procedure. All except for two trials were judged as being unclear in risk of bias in the domain of allocation concealment (30, 31, 35, 38–57). Only two trials (36, 37) reported blinding of outcome assessment. Incomplete outcome data were judged as low risk of bias in 24 studies. Amongst them, 16 studies (30, 37, 39, 41, 42, 44–46, 49–54, 56, 57) reported no withdrawal of patients. In the remaining eight studies (31, 35, 36, 38, 40, 43, 47, 55), the dropout cases in each study were <10% of

TABLE 1 | Study characteristics of 25 included studies.

References	Group/size	Age (year)	Depression duration (m = month, y = year)	Diagnostic system	TCM Syndrome Type	Acupuncture interventions	Acupoints	Prescription in control group (placebo or Western medication)	Outcome measure tool	Acupuncture/ Acupuncture + Western medication compared with control (waitlist, placebo-/ sham-acupuncture, Western medication)	Follow-up	Adverse events
Wang et al. (35)	- MA/n = 33 - Sham-MA/ n = 33	- MA/48.72 ± 4.21 - Sham-MA/47.82 ± 4.35	- MA/NR - Sham-MA/NR	CCMD-3	NR	30 min/day, 3 days/week for 8 weeks	KI6, LU7, PC6, SP4	sham-MA 30 min/day, 3 days/week for 8 weeks	(i) SDS (ii) MENQOL	(i) compared with sham-MA $P < 0.05$ (ii) compared with sham-MA $P < 0.05$	Lower SDS in MA in 4-week follow-up (ii) no difference in MENQOL between MA and sham-MA in 4-week follow-up	NR
Li (36)	- EA/n = 30 - Sham-EA/ n = 30 - Escitalopram/ n = 30	- EA/49.80 ± 3.39 - Sham-EA/49.83 ± 4.10 - Escitalopram/ 49.90 ± 2.98	- EA/30.73 ± 18.57 m - Sham-EA/30.43 ± 22.15 m - Escitalopram/ 26.43 ± 17.86 m	ICD-10	NR	- 30 min/day, 3 days/week for 12 weeks - dense-sparse waves, 10/50 Hz, 0.5–1 mA	CV4, EX-CA1, EX-HN3, GV20, LI4, LR3, SP6, ST25	- sham-EA 30 min/day, 3 days/week for 12 weeks - Escitalopram 10 mg/day for 12 weeks	(i) HAMD (ii) MENQOL (iii) FSH (iv) E2 (v) LH	(i-i) compared with sham-EA $P < 0.05$ (i-ii) compared with Escitalopram $P > 0.05$ (ii-i) compared with sham-EA $P < 0.05$ (ii-ii) compared with Escitalopram $P > 0.05$ (iii) compared with sham-EA or Escitalopram $P > 0.05$ (iv) compared with sham-EA or Escitalopram $P > 0.05$ (v) compared with sham-EA or Escitalopram $P > 0.05$	(i) Lower HAMD in EA in 4- and 12-week follow-up (ii) Lower MENQOL in acupuncture in 4-, 8-, and 12-week follow-up	- EA/n = 2 [hematoma] - sham-EA/n = 0 - - Escitalopram/ n = 25 [fatigue (17); headache (2); sleep disturbance (7); dizziness (7); palpitation (4); sweating (10); dry mouth (14); constipation (8)]
Li et al. (37)	- EA/n = 116 - Escitalopram/n = 105	- EA/49.83 ± 3.10 - Escitalopram/ 49.93 ± 3.10	- EA/20.60 ± 16.20 m - Escitalopram/ 20.20 ± 16.50 m	DSM-V, ICD-10	NR	- 30 min/day, 3 days/week for 12 weeks - dilatational wave wave, 50 Hz, 0.5–1 mA	CV4, EX-CA1, EX-HN3, GV20, LI4, LR3, SP6, ST25	- Escitalopram 10 mg/day for 12 weeks	(i) HAMD (ii) MENQOL (iii) FSH (iv) E2 (v) LH	(i) compared with Escitalopram $P > 0.05$ (ii) compared with Escitalopram $P > 0.05$ (iii) compared with Escitalopram $P > 0.05$ (iv) compared with Escitalopram $P > 0.05$ (v) compared with Escitalopram $P > 0.05$	(i) Lower HAMD in EA in 4- and 12- week follow-up (ii) Lower MENQOL in acupuncture in 4-, 8- and 12-week follow-up	- EA/n = 14 [hematoma] - Escitalopram/n = 18 [dizziness, palpitation, stomachache]
Chi and Zou (30)	- MA/n = 30 - Fluoxetine/n = 30	- MA/51.63 ± 1.72 - Fluoxetine/51.43 ± 1.62	- MA/10.61 ± 6.10 m - Fluoxetine/11.12 ± 5.58 m	CCMD-3	NR	30 min/day for 4 weeks	EX-HN1, EX-HN3, GV20, KI3, LR3, LR14, SP6, ST36	- Fluoxetine 20 mg/day for 4 weeks	(i) HAMD	(i) compared with Fluoxetine $P < 0.05$	No follow-up	- MA/n = 0 - Fluoxetine/n = 3 [dizziness (1); nausea (2)]
Deng (38)	- MA/n = 29 - Deanxit/n = 29	- MA/50.03 ± 4.43 - Deanxit/48.70 ± 4.93	- MA/6.25 ± 2.31 m - Deanxit/5.77 ± 3.64 m	ICD-10	NR	20–30 min/day, after 3 consecutive days of treatment, once treatment every 3 days for total 4 weeks	CV3, CV4, CV6, CV10, CV12, KI17, Qipang (0.5 *Cun* beside CV6), Xiafengshidian (1 *Cun* below and beside ST26)	- Deanxit 20 mg/day for 4 weeks	(i) HAMD (ii) KI (iii) 5-HT	(i) compared with Deanxit $P > 0.05$ (ii) compared with Deanxit $P > 0.05$ (iii) compared with Deanxit $P > 0.05$	(i) Lower HAMD in MA in 2-week follow-up (ii) no difference in HAMD between MA and Deanxit in 4-week follow-up (iii) no difference in KI between MA and Deanxit in 2- and 4-week follow-up	- MA/n = 3 [changes of character of stool (2); palpitation (1)] - Deanxit/n = 32 [changes of character of stool (6); dry mouth and halitosis (9); dysphoria (6); dreaminess (6); breast distending pain (5)]

(Continued)

TABLE 1 | Continued

References	Group/size	Age (year)	Depression duration (m = month, y = year)	Diagnostic system	TCM Syndrome Type	Acupuncture interventions	Acupoints	Prescription in control group (placebo or Western medication)	Outcome measure tool	Acupuncture/ Acupuncture + Western medication compared with control (waitlist, placebo-/ sham-acupuncture, Western medication)	Follow-up	Adverse events
Dong (39)	- MA/*n* = 30 - Nilestriol + Fluoxetine/*n* = 30	- MA/55.00 - Nilestriol + Fluoxetine/53.00	- MA/24.00 m - Nilestriol + Fluoxetine/26.00 m	CCMD-3, CDTE-TCM	NR	30 min/day for 30 days	BL13, BL15, BL17, BL18, BL20, BL21, BL23	Nilestriol 2 mg/15 days for 30 days + Fluoxetine 20 mg/day for 30 days	(i) HAMD	(i) compared with Nilestriol + Fluoxetine $P < 0.05$	No follow-up	NR
Li (40)	- MA/*n* = 32 - Fluoxetine/*n* = 32	- MA/50.59 ± 2.94 - Fluoxetine/50.25 ± 2.71	- MA/20.63 ± 7.49 m - Fluoxetine/20.31 ± 7.45 m	CCMD-3	*Liver* stagnation and *Kidney* deficiency	30 min/day, 6 days/week for 12 weeks	BL15, BL18, BL23, EX-HN1, EX-HN3, GV20, GV24, PC6	20 mg/day for 12 weeks	(i) HAMD (ii) KI	(i) compared with Fluoxetine $P < 0.05$ (ii) compared with Fluoxetine $P < 0.05$	follow-up for 12 weeks; no data of HAMD and KI total scores for follow-up	- MA/*n* = 0 - Fluoxetine/ *n* = 8 [nausea or vomiting (2); dry mouth (1); indigestion (1); diarrhea (1); dizziness (1); headache (1)]
Ma and Liu (41)	- MA/*n* = 30 - Fluoxetine/*n* = 30	- MA/53.45 ± 4.82 - Fluoxetine/52.74 ± 5.17	- MA/8.24 ± 4.76 m - Fluoxetine/7.65 ± 4.52 m	CCMD-3, CDTE-TCM	NR	30 min/day, 5 days/week for 8 weeks	EX-HN1, EX-HN3, GV20, HT7, PC6, PC7, SP6, ST36	20 mg/day for 8 weeks	(i) HAMD	(i) compared with Fluoxetine $P > 0.05$	No follow-up	- MA/*n* = 0 - Fluoxetine/ *n* = 6 [nausea (2); dizziness (2)]
Niu and Wang (42)	- MA/*n* = 41 - Fluoxetine/*n* = 41	- MA/54.10 ± 2.00 - Fluoxetine/54.20 ± 2.10	- MA/7.70 ± 1.20 m - Fluoxetine/7.70 ± 1.30 m	CCMD-3	Stagnation of *Liver*-Qi	30 min/day, 5 days/week for 6 weeks	BL13, BL15, BL17, BL18, BL20, BL23	20 mg/day for 6 weeks	(i) HAMD	(i) compared with Fluoxetine $P < 0.05$	No follow-up	- MA/*n* = 7 [dizziness (2); palpitation (1); dry mouth (1); nausea (3)] - Fluoxetine/*n* = 6 [dizziness (1); palpitation (2); dry mouth (2); nausea (1)]
Qian et al. (43)	- MA/*n* = 33 - Fluoxetine/*n* = 30	- MA/54.00 - Fluoxetine/ 55.00	- MA/7.00 m - Prozac/8.00 m	CCMD-3	NR	25 min/day, 5 days/week for 6 weeks	BL13, BL15, BL17, BL18, BL20, BL23	20 mg/day for 6 weeks	(i) HAMD	(i) compared with Fluoxetine $P > 0.05$	No follow-up	- MA/*n* = 2 [dizziness (1); palpitation (1)] - Fluoxetine/*n* = 9 [insomnia (1); akathisia (1); dry mouth (1); nausea (1); palpitation (1); skin symptom (1); forexcitation and agitation (2)]

(Continued)

TABLE 1 | Continued

References	Group/size	Age (year)	Depression duration (m = month, y = year)	Diagnostic system	TCM Syndrome Type	Acupuncture interventions	Acupoints	Prescription in control group (placebo or Western medication)	Outcome measure tool	Acupuncture/ Acupuncture + Western medication compared with control (waitlist, placebo-/ sham-acupuncture, Western medication)	Follow-up	Adverse events
Qiang (44)	- MA/*n* = 30 - Fluoxetine/*n* = 30	- MA/54.32 ± 3.29 - Fluoxetine/54.00 ± 4.62	- MA/11.32 ± 6.25 m - Fluoxetine/12.12 ± 4.58 m	CCMD-3	NR	25 min/day, 5 days/week for 6 weeks	BL15, BL18, BL23,EX-HN1, GB20	20 mg/day for 6 weeks	(i) HAMD	(i) compared with Prozac $P > 0.05$	No follow-up	NR
Shi et al. (45)	- EA/*n* = 30 - Escitalopram/*n* = 30	- EA/48.70 ± 1.99 - Escitalopram/ 49.43 ± 1.87	- EA/14.17 ± 4.99 m - Escitalopram/ 14.23 ± 5.58 m	DSM-V	NR	- 30 min/day, 3 days/week for 12 weeks - dense-sparse waves, 10/50 Hz, 0.5–1.0 mA	CV4, EX-CA1, EX-HN3, GV20, LI4, LR3, SP6, ST25	10 mg/day for 12 weeks	(i) HAMD	(i) compared with Escitalopram $P < 0.05$	(i) Lower HAMD in EA in 4- and 12- week follow-up	NR
Sun et al. (46)	- EA/*n* = 21 - Escitalopram/*n* = 21	- EA/50.29 ± 2.59 - Escitalopram/ 49.86 ± 3.83	- EA/1.94 ± 0.68 m - Citalopram/1.56 ± 0.94 m	DSM-V	NR	- 30 min/day, 3 days/week for 12 weeks - dense-sparse waves, 10/50 Hz, 0.5–1.0 mA	CV4, EX-CA1, EX-HN3, GV20, LI4, LR3, SP6, ST25	10 mg/day for 12 weeks	(i) HAMD	(i) compared with Escitalopram $P < 0.05$	No follow-up	NR
Wang et al. (47)	- MA/*n* = 21 - Deanxit/*n* = 21	- MA/49.60 ± 4.30 - Deanxit/48.30 ± 4.70	NR	CCMD-3	NR	- 30 min/day, after 3 consecutive days of treatment, once treatment every 3 days for total 4 weeks	CV3, CV4, CV6, CV10, CV12, KI17	10 mg/day for 4 weeks	(i) HAMD	(i) compared with Prozac $P > 0.05$	(i) Lower HAMD in MA in 2- and 4- week follow-up	- MA/*n* = 3 [changes of character of stool (2); palpitation (1)] - Deanxit/*n* = 15 [dry mouth and halitosis (9); dysphoria, dreaminess or breast distending pain (6)]
Zhang (48)	- EA/*n* = 44 - Nilestriol+ Fluoxetine/*n* = 46	- EA/48.48 ± 5.39 - Nilestriol+ Fluoxetine/48.16 ± 4.15	- EA/29.15 ± 25.90 m - Nilestriol+ Fluoxetine/27.45 ± 28.83 m	CCMD-3	NR	- 30 min/day, 5 days/week for 12 weeks - dilatational wave wave, 8–9 mA, 6 V	BL13, BL15, BL17, BL20, BL23, GV20, KI3, LR3, PC6, SP6	Nilestriol 2 mg/14 days for 30 days + Fluoxetine 20 mg/day for 12 weeks	(i) HAMD (ii) KI (iii) FSH (iv) E2 (v) LH	(i) compared with Nilestriol+ Fluoxetine $P > 0.05$ (ii) compared with Nilestriol+ Fluoxetine $P > 0.05$ (iii) compared with Nilestriol+ Fluoxetine $P > 0.05$ (iv) compared with Nilestriol+ Fluoxetine $P > 0.05$ (v) compared with Nilestriol+ Fluoxetine $P > 0.05$	No follow-up	- EA/*n* = 5 [sweating, dizziness, vomiting] - Nilestriol+ Fluoxetine/*n* = 23 [dry mouth and halitosis (5); nausea (6); dysphoria (2); constipation (6); dreaminess (2); breast distending pain (2)]

(Continued)

TABLE 1 | Continued

References	Group/size	Age (year)	Depression duration (m = month, y = year)	Diagnostic system	TCM Syndrome Type	Acupuncture interventions	Acupoints	Prescription in control group (placebo or Western medication)	Outcome measure tool	Acupuncture/ Acupuncture + Western medication compared with control (waitlist, placebo-/ sham-acupuncture, Western medication)	Follow-up	Adverse events
Zhang (49)	- MA/*n* = 94 - Premarin + Provera + Fluoxetine/*n* = 94	- MA/50.10 ± 2.70 - Premarin + Provera + Fluoxetine/49.80 ± 2.60	- MA/1.40 ± 0.50y - Premarin + Provera + Fluoxetine/1.30 ± 0.40y	CCMD-3	NR	30 min/day, 7 days/week for 12 weeks	EX-HN1, GB13, GV20, GV24, HT7	Premarin 0.625 mg/day and Provera 6 mg/day + Fluoxetine 20 mg/day for 12 weeks	(i) HAMD (ii) FSH (iii) E2 (iv) LH	(i) compared with Premarin + Provera + Fluoxetine $P < 0.05$ (ii) compared with Premarin + Provera + Fluoxetine $P > 0.05$ (iii) compared with Premarin + Provera + Fluoxetine $P > 0.05$ (iv) compared with Premarin + Provera + Fluoxetine $P > 0.05$	No follow-up	- MA/*n* = 2 [feeling pain when inserting needle] - Premarin + Provera + Fluoxetine/*n* = 12 [dizziness (5); nausea and vomiting (4); hypersomnia (3)]
Zheng et al. (50)	- MA/*n* = 60 - Premarin + Provera + Fluoxetine/*n* = 60	- MA/52.27 ± 3.45 - Premarin + Provera + Fluoxetine/51.98 ± 3.14	- MA/1.22 ± 0.87y - Premarin + Provera + Fluoxetine/1.34 ± 0.92y	CCMD-3	NR	30 min/day, 7 days/week for 12 weeks (needle retaining time for 8 h in BL8, GV19, GV21 per session)	BL8, BL18, BL23, GV19, GV21, KI3, LR3, SP6	Premarin 0.625 mg/day for 20 days + and Provera 6 mg/day + Fluoxetine 20 mg/day for 12 weeks	(i) HAMD (ii) KI (iii) FSH (iv) E2 (v) LH	(i) compared with Premarin + Provera + Fluoxetine $P > 0.05$ (ii) compared with Premarin + Provera + Fluoxetine $P > 0.05$ (iii) compared with Premarin + Provera + Fluoxetine $P > 0.05$ (iv) compared with Premarin + Provera + Fluoxetine $P < 0.05$ (v) compared with Premarin + Provera + Fluoxetine $P > 0.05$	(i) Lower HAMD and KI in MA in 24- week follow-up	- MA/*n* = 2 [feeling pain when inserting needle] - Premarin + Provera + Fluoxetine/*n* = 18 [loss of appetite (5); dizziness (4); diarrhea (3); breast distending pain (3); leukorrhagia (2); spasmus (1)]
Ding and Liu (51)	- MA/*n* = 39 - Fluoxetine/*n* = 39	- MA/49.68 ± 3.90 - Fluoxetine/49.50 ± 3.51	NR	CCMD-2-R	NR	30 min/day, 6 days/week for 4 weeks	BL15, BL18, BL20, BL23, GV20, HT7, LR3, SP6	20 mg/day for 4 weeks	(i) HAMD (ii) KI	(i) compared with Fluoxetine $P > 0.05$ (ii) compared with Fluoxetine $P < 0.05$	No follow-up	NR
Li and Dai (52)	- EA/*n* = 30 - Fluoxetine/*n* = 30	NR	NR	CDTE-TCM	NR	- 25 min/day, 3 days/week for 6 weeks - dilatational wave, 15 Hz, 1 mA	EX-HN1, EX-HN3, GV20, HT7, LI4, PC6, SP6, ST36	20 mg/day for 6 weeks	(i) HAMD (ii) HAMA	(i) compared with Fluoxetine $P > 0.05$ (ii) compared with Fluoxetine $P < 0.05$	No follow-up	NR
Zhang (53)	- MA/*n* = 29 - Deanxit/*n* = 29	NR	NR	CCMD-3	NR	30 min/day, after 3 consecutive days of treatment, once treatment every 3 days for total 4 weeks	CV3, CV4, CV6, CV10, CV12, KI17	20 mg/day for 4 weeks	(i) HAMD	(i) compared with Deanxit $P > 0.05$	(i) Lower HAMD in MA in 2- and 4- week follow-up	NR

(Continued)

TABLE 1 | Continued

References	Group/size	Age (year)	Depression duration (m = month, y = year)	Diagnostic system	TCM Syndrome Type	Acupuncture interventions	Acupoints	Prescription in control group (placebo or Western medication)	Outcome measure tool	Acupuncture/ Acupuncture + Western medication compared with control (waitlist, placebo-/ sham-acupuncture, Western medication)	Follow-up	Adverse events
Xing (54)	- MA/*n* = 120 - Fluoxetine/*n* = 120	- MA/51.20 ± 5.40 - Fluoxetine/49.50 ± 6.80	- MA/11.60 ± 7.30 m - Fluoxetine/10.50 ± 8.60 m	CCMD-3	Stagnation of *Liver*-Qi, *Heart* and *Spleen* deficiency; *Liver* depression and phlegm-heat	20 min/day, 7 days/week for 6 weeks	GV26, PC5	20 mg/day for 6 weeks	(i) HAMD	(i) compared with Fluoxetine $P > 0.05$	No follow-up	NR
Zhou and Wu (31)	- MA/*n* = 30 - Fluoxetine/*n* = 28	- MA/51.80 ± 4.20 - Fluoxetine/48.90 ± 3.80	- MA/30.63 ± 10.12 m - Prozac/26.33 ± 9.65 m	CCMD-3	*Liver* and *kidney Yin* deficiency, *Spleen* and *Kidney* Yang deficiency, stagnated Qi transforming into fire, stagnation of phlegm and Qi	30 min/day, 6 days/week for 6 weeks	BL15, BL18, BL23, EX-HN1, GB13, GV24, SP6, ST36	20 mg/day for 6 weeks	(i) HAMD (ii) 5-HIAA (iii) NE (iv) DA	(i) compared with Fluoxetine $P < 0.05$ (ii) compared with Fluoxetine $P > 0.05$ (iii) compared with Fluoxetine $P > 0.05$ (iv) compared with Fluoxetine $P < 0.05$	No follow-up	NR
Ma et al. (55)	- EA + Paroxetine/*n* = 55 - Paroxetine/*n* = 50	- EA + Paroxetine /52.95 ± 5.86 - Paroxetine / 51.49 ± 6.03	- EA + Paroxetine/5.49 ± 4.86 m - Paroxetine/4.98 ± 4.75 m	CCMD-3	NR	- 45 min/day, 7 days/week for 6 weeks - dilatational wave wave, 8–9 mA	EX-HN3, GV20, LI4, PC6, ST36	- 10 mg/day for 6 weeks	(i) HAMD	(i) compared with Paroxetine $P > 0.05$	No follow-up	- EA + Paroxetine/ *n* = 2 [dizziness (1); nausea (1)] - Paroxetine/*n* = 3 [dizziness (1); elevated blood pressure (2)]
Liu and Chen (56)	- MA + Sertraline/*n* = 40 - Sertraline/*n* = 40	- MA + Sertraline/ 51.50 ± 3.40 - Sertraline/52.10 ± 3.30	- MA + Sertraline/ 2.58 ± 2.18y - Sertraline/2.67 ± 1.73y	- CCMD-3, - ICD-10	NR	30 min/day, 3 days/week for 12 weeks	BL23, CV4, HT7, KI3, LI4, LR3, SP6	50 mg/day for 6 weeks	(i) HAMD (ii) FSH (iii) E2 (iv) 5-HT (v) GABA	(i) compared with Sertraline $P < 0.05$ (ii) compared with Sertraline $P < 0.05$ (iii) compared with Sertraline $P < 0.05$ (iv) compared with Sertraline $P < 0.05$ (v) compared with Sertraline $P < 0.05$	No follow-up	NR
Ning (57)	- MA + Nilestriol + Fluoxetine/*n* = 45 - Nilestriol + Fluoxetine/*n* = 45	NR	NR	Psychiatry textbook	NR	30 min/day, 7 days/week for 12 weeks	BL13, BL15, BL18, BL20, BL23, GV20, HT7, KI3, LI4, LR3	Nilestriol 2 mg/15 days + Fluoxetine 20 mg/day for 12 weeks	(i) HAMD (ii) TESS	(i) compared with Nilestriol + Fluoxetine $P < 0.05$ (ii) compared with Nilestriol + Fluoxetine $P < 0.05$	No follow-up	NR

TABLE 2 | Trends of major outcomes for depression and perimenopausal symptoms in acupuncture (OR acupuncture + antidepressant/HRT) and comparison with controls in each study.

References	Comparison		Outcome measures for depression	Outcome measures for perimenopausal symptoms	Sex hormone levels		
			HAMD/SDS	KI/MENQOL	FSH	E2	LH
Wang et al. (35)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	↓	/	/	/
		4-week follow-up vs. pre-treatment	↓	↓	/	/	/
	Acup vs. sham Acup at same time-point	Post-treatment	<	<	/	/	/
		4-week follow-up	<	(–)	/	/	/
Li (36)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	↓	(–)	↓	(–)
		4-week follow-up vs. pre-treatment	↓	↓	/	/	/
		8-week follow-up vs. pre-treatment	/	↓	/	/	/
		12-week follow-up vs. pre-treatment	↓	↓	/	/	/
	Acup vs. sham Acup at same time-point	Post-treatment	<	<	(–)	(–)	(–)
		4-week follow-up	<	<	/	/	/
		8-week follow-up	/	<	/	/	/
		12-week follow-up	<	<	/	/	/
	Acup vs. antidepressant at same time-point	Post-treatment	(–)	(–)	(–)	(–)	(–)
		4-week follow-up	(–)	<	/	/	/
		8-week follow-up	/	<	/	/	/
		12-week follow-up	(–)	<	/	/	/
Li et al. (37)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	↓	(–)	(–)	(–)
	Acup vs. antidepressant at same time-point	Post-treatment	(–)	(–)	(–)	(–)	(–)
		4-week follow-up	<	<	/	/	/
		8-week follow-up	/	<	/	/	/
		12-week follow-up	<	<	/	/	/
Chi and Zou (30)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	/	/	/	/
	Acup vs. antidepressant at same time-point	Post-treatment	<	/	/	/	/
Deng (38)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	↓	/	/	/
	Acup vs. antidepressant at same time-point	Post-treatment	(–)	(–)	/	/	/
		2-week follow-up	<	(–)	/	/	/
		4-week follow-up	(–)	(–)	/	/	/
Dong (39)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	/	/	/	/
	Acup vs. HRT + antidepressant at same time-point	Post-treatment	<	/	/	/	/
Li (40)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	↓	/	/	/
	Acup vs. antidepressant at same time-point	Post-treatment	<	<	/	/	/
Ma and Liu (41)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	/	/	/	/
	Acup vs. antidepressant at same time-point	Post-treatment	(–)	/	/	/	/
Niu and Wang (42)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	/	/	/	/
	Acup vs. antidepressant at same time-point	Post-treatment	<	/	/	/	/
Qian et al. (43)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	/	/	/	/
	Acup vs. antidepressant at same time-point	Post-treatment	(–)	/	/	/	/
Qiang (44)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	/	/	/	/
	Acup vs. antidepressant at same time-point	Post-treatment	(–)	/	/	/	/
Shi et al. (45)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	/	/	/	/
	Acup vs. antidepressant at same time-point	Post-treatment	<	/	/	/	/

(Continued)

TABLE 2 | Continued

References	Comparison		Outcome measures for depression	Outcome measures for perimenopausal symptoms	Sex hormone levels		
			HAMD/SDS	KI/MENQOL	FSH	E2	LH
		4-week follow-up	<	/	/	/	/
		12-week follow-up	<	/	/	/	/
Sun et al. (46)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	/	/	/	/
	Acup vs. antidepressant at same time-point	Post-treatment	<	/	/	/	/
Wang et al. (47)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	/	/	/	/
	Acup vs. antidepressant at same time-point	Post-treatment	(–)	/	/	/	/
		2-week follow-up	<	/	/	/	/
		4-week follow-up	<	/	/	/	/
Zhang (48)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	↓	↓	↑	↓
	Acup vs. HRT + antidepressant at same time-point	Post-treatment	(–)	(–)	(–)	(–)	(–)
Zhang (49)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	/	↓	↑	↓
	Acup vs. HRT + antidepressant at same time-point	Post-treatment	<	/	(–)	(–)	(–)
Zheng et al. (50)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	↓	↓	↑	↓
	Acup vs. HRT + antidepressant at same time-point	Post-treatment	(–)	(–)	(–)	<	(–)
		24-week follow-up	<	<	/	/	/
Ding and Liu (51)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	↓	/	/	/
	Acup vs. antidepressant at same time-point	Post-treatment	(–)	<	/	/	/
Li and Dai (52)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	/	/	/	/
	Acup vs. antidepressant at same time-point	Post-treatment	(–)	/	/	/	/
Zhang (53)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	/	/	/	/
	Acup vs. antidepressant at same time-point	Post-treatment	(–)	/	/	/	/
		2-week follow-up	<	/	/	/	/
		4-week follow-up	<	/	/	/	/
Xing (54)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	/	/	/	/
	Acup vs. antidepressant at same time-point	Post-treatment	(–)	/	/	/	/
Zhou and Wu (31)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	/	/	/	/
	Acup vs. antidepressant at same time-point	post-treatment	(–)	/	/	/	/
Ma et al. (55)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	/	/	/	/
	Acup + antidepressant vs. antidepressant at same time-point	Post-treatment	(–)	/	/	/	/
Liu and Chen (56)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	/	↓	↑	/
	Acup + antidepressant vs. antidepressant at same time-point	Post-treatment	<	/	<	<	/
Ning (57)	Vs. same group at different time-points	Post- vs. pre-treatment	↓	/	/	/	/
	Acup + antidepressant vs. antidepressant at same time-point	Post-treatment	<	/	/	/	/

↑, statistically increase; ↓, statistically decrease; >, statistically higher/longer/more; <, statistically lower/shorter/less; (–), no statistical difference/no statistical changes; Acup, acupuncture; HRT, hormone replacement therapy; HAMD, Hamilton Depression Scale; SDS, Self-Rating Depression Scale; KI, Kupperman index; MENQOL, Menopause-Specific Quality of Life; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, estradiol.

the initial samples, which is within the controllable range. For the item of selective outcome reporting, one RCT (37) was assessed as low risk of bias, as its protocol was registered in the ChiCTR. The remaining studies were rated as unclear risk of bias because of unavailable protocols or there was insufficient evidence and information to permit a clear judgment. "Blinding

of personnel (acupuncturist)" in all studies was rated as a high risk of bias due to the nature of acupuncture. Acupuncture techniques require manipulation by a qualified professional to perform; thus, it is not feasible to blind the trial acupuncturists. In two studies with sham acupuncture as control, participants (patients) were blinded and clearly described in one study (36). All RCTs addressed baseline balance adequately (**Figure 2**, **Appendices 3, 4**).

Appendix 5 summarizes the details about acupuncture per STRICTA guideline. Traditional Chinese acupuncture was used in all 25 studies, and treatment was provided in accordance with TCM theory. As the core part of acupuncture therapy, the needling details were not clearly reported in all RCTs. For instance, the depth of insertion was presented in detail in only 16 trials (30, 31, 36, 40–46, 49–52, 54, 57), and four studies did not show the needle type used (35, 49, 53, 55). All trials gave the information of the needle retention time ranging from 20 to 45 min. Setting of treatment was not illustrated in any included trial. Only one RCT (37) introduced acupuncturist's background.

Analysis of Outcome Measures

The qualitative and quantitative analyses for outcome measures in the 25 included studies were divided into three parts: (1) acupuncture vs. sham acupuncture ($n = 2$); (2) acupuncture vs. Western medicine (antidepressant or antidepressant combined with HRT) ($n = 21$); and (3) acupuncture combined with Western medicine vs. Western medicine ($n = 3$). One RCT had three arms with acupuncture vs. sham acupuncture vs. antidepressant (**Appendix 6**).

Acupuncture vs. Sham Acupuncture

Two studies (35, 36) ($n = 126$) were under this category and used HAMD and SDS as the primary outcome, respectively. Both studies found that acupuncture significantly reduced the global scores of HAMD/SDS and MENQOL, in comparison with sham acupuncture. These findings suggest that acupuncture can improve both the depressed mood and quality of life in women with PMD.

During the follow-up, one study (36) found that the HAMD score continued to decline, and another study (35) found SDS score slightly increased but was still significantly lower than baseline data in the acupuncture group. Both studies found HAMD/SDS of the sham-acupuncture group almost returned to the baseline level during the follow-up. One of the studies (36) investigated the impacts of acupuncture on sex hormone levels but did not find any statistically significant difference between pre- and post-treatment (**Table 2**).

Acupuncture vs. Antidepressant/Antidepressant + HRT

Twenty-one trials ($n = 1{,}842$) were included in this comparison. Meta-analyses were performed for five indicators, namely, HAMD, KI, FSH, E2, and LH. We did not carry out the meta-analysis for other outcome measures because there were fewer than three studies for each of them (**Appendix 2**).

Depression Symptoms

(1) Post-Treatment

All 21 trials employed HAMD as an outcome measure. Due to the high heterogeneity ($p < 0.01$, $I^2 = 93\%$), a random-effects model was used. The results favored acupuncture in reducing HAMD global scores [SMD = −0.54, 95% CI (−0.91, −0.16), $p < 0.01$] (**Figure 3**).

(2) Follow-Up

2-Week Follow-Up. Three (38, 47, 53) out of 21 trials compared antidepressants (Deanxit). Due to no evident heterogeneity ($p = 0.99$, $I^2 = 0$), a fixed-effects model was used. At 2-week follow-up, the results favored acupuncture in reducing HAMD global scores [SMD = −0.64, 95% CI (−0.95, −0.33), $p < 0.01$] (**Figure 3**).

4-Week Follow-Up. Six (36–38, 45, 47, 53) out of 21 trials compared antidepressants (escitalopram or Deanxit). Due to the high heterogeneity ($p < 0.01$, $I^2 = 97\%$), a random-effects model was used. At 4-week follow-up, no significant difference was identified between acupuncture and antidepressant in reducing HAMD global scores [SMD = −1.36, 95% CI (−2.72, 0.00), $p = 0.05$] (**Figure 3**).

12-Week Follow-Up. *Three* (36, 37, 45) out of 21 trials compared antidepressants (escitalopram). A random-effects model was used due to the high heterogeneity ($p < 0.01$, $I^2 = 99\%$). At 12-week follow-up, there was no significant difference between acupuncture and antidepressant in reducing HAMD global scores [SMD = −2.73, 95% CI (−6.14, 0.67), $p = 0.12$] (**Figure 3**).

Perimenopausal Symptoms and Hormonal Levels

Five trials (38, 40, 48, 50, 51) ($n = 275$) employed KI as an outcome measure. No significant differences were identified between acupuncture and antidepressant/antidepressant + HRT in reducing KI scores [MD = −2.80, 95% CI (−5.60, −0.01), $p = 0.05$] (**Figure 4**).

Serum hormonal levels (FSH, E2, and LH) were reported in five studies (36, 37, 48–50) with contradictory results. When all data were combined, no statistically significant differences were identified between acupuncture and antidepressant/antidepressant + HRT in regulating FSH [SMD = −0.02, 95% CI (−0.17, 0.13), $p = 0.82$], E2 [SMD = −0.30, 95% CI (−0.77, 0.17), $p = 0.22$], or LH [SMD = 0.04, 95% CI (−0.11, 0.19), $p = 0.59$] (**Figure 4**).

Subgroup Analysis

Based on different acupuncture methods (MA or EA), or different standard care in control groups (antidepressant alone or antidepressant + HRT), we conducted subgroup analyses on HAMD (at post-treatment), HAMD (at 4-week follow-up), and KI scores, as well as serum E2 levels. However, the heterogeneity could not be fully explained. No interaction was identified in any subgroup. There was an interesting discovery about KI. When all five RCTs were pooled for analysis, there was no significant difference between acupuncture and standard care in reducing KI scores [MD = −2.80, 95% CI (−5.60, −0.01), $p = 0.05$]. However, in subgroup analysis, acupuncture showed better effects in decreasing KI scores, whether compared with antidepressant alone [MD = −4.55, 95% CI (−8.46, −0.65), p

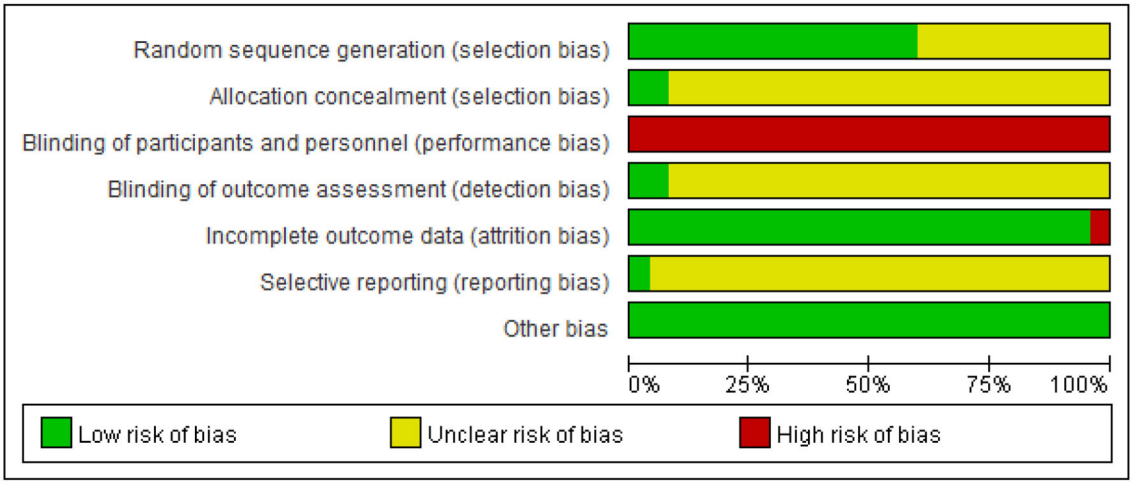


FIGURE 2 | Risk of bias summary. Other biases are assessed based on baseline balance.

= 0.02] or antidepressant combined with HRT [MD = −0.89, 95% CI (−1.34, −0.43), $p < 0.01$]. We could not conduct subgroup analysis based on HAMD version, as three of 21 trials did not report which version of HAMD was used for assessment (**Appendix 7**).

Sensitivity Analysis

In an attempt to address the high heterogeneity, sensitivity analysis was performed based on the outcome of HAMD (at post-treatment) to ensure the results were not due to one or two studies. We chose influence analysis, by removing one study at a time and recalculating the combined estimate on the remaining studies to evaluate the stability of the results. We did not perform sensitivity analysis for the other outcome measures because of the small number of studies (<10).

The results indicated that except for one study (37), each single study had little impact on the pooled estimate effects of HAMD, and the overall robustness and reliability of our study results were relatively high (**Figure 5**). That study (37) was thereby removed, and pooled estimate effects were recalculated. However, there were no significant changes in forest plots, and results still favored acupuncture in reducing HAMD global scores [SMD = −0.36, 95% CI (−0.54, −0.17), $p < 0.01$]. Heterogeneity was not completely explained with I^2 only decreased from 93 to 70% (**Appendix 8**). These findings suggested that the study did not fully explain the heterogeneity. It may be one of the sources of heterogeneity.

Meta-Regression Analysis

Using HAMD (at post-treatment) as the outcome measure, we conducted univariate meta-regressions to investigate the sources of heterogeneity by treating publication year, study sample size, acupuncture stimulation (MA or EA), and standard care in control groups (antidepressant alone or antidepressant + HRT) as covariates. However, the heterogeneity across the 21 included studies could not be substantially explained by publication year (I^2 = 91.02%, Tau2 = 0.54, $p = 0.02$), study sample size (I^2 = 93.36%, Tau2 = 0.63, $p = 0.10$), acupuncture stimulation (I^2 = 92.25%, Tau2 = 0.63, $p = 0.12$), and standard care in control groups (I^2 = 93.47%, Tau2 = 0.72, $p = 0.73$) (**Appendix 9**, **Supplementary Figures 1–4**).

Acupuncture Combined With Antidepressant/Antidepressant + HRT vs. Antidepressant/Antidepressant + HRT

Three trials (55–57) were included (n = 275). Meta-analysis was only carried out for HAMD but not for other outcomes because there were fewer than three included trials for each of them.

Depression Symptoms

HAMD was employed as an outcome in all three trials. The results favored acupuncture combined with antidepressant/antidepressant + HRT [SMD = −0.82, 95% CI (−1.07, −0.58), $p < 0.01$] (**Figure 6**).

Perimenopausal Symptoms and Hormonal Levels

None of the trials included an outcome related to perimenopausal symptoms, which hinder the judgment of difference between standard care alone and standard care combined with acupuncture in improving perimenopausal symptoms. However, one (56) of the three trials investigated the sex hormone levels of patients at pre- and post-treatment and found that standard care combined with acupuncture was more effective in down-regulating FSH levels and up-regulating E2 levels.

Acupuncture vs. Waitlist Control

No studies were identified under this comparison.

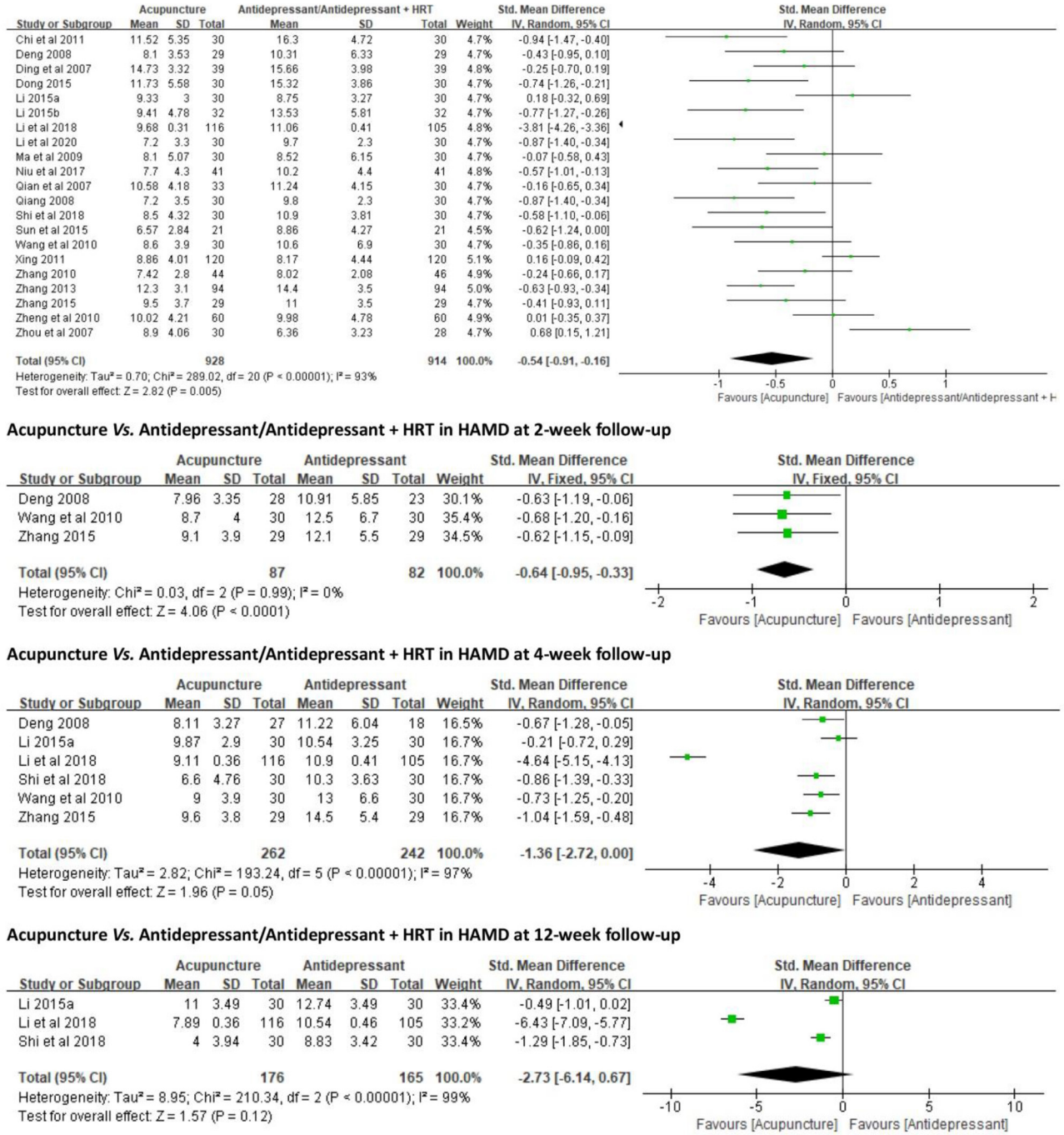


FIGURE 3 | Forest plots of acupuncture vs. antidepressant/antidepressant + HRT in HAMD. HRT, hormone replacement therapy; HAMD, Hamilton Depression Scale.

Publication Bias Test

We used linear regression analysis (Egger's test) to detect the publication bias based on HAMD in 25 included studies, and we found no statistically significant effect ($p = 0.261$) (**Figure 7**). Publication bias tests were not conducted for the other outcome measures because of the small number of studies (<10).

DISCUSSION

Summary of Findings

Acupuncture appears to have better effects in reducing PMD than sham acupuncture. Acupuncture alone or combined with standard care (antidepressant/antidepressant + HRT) is

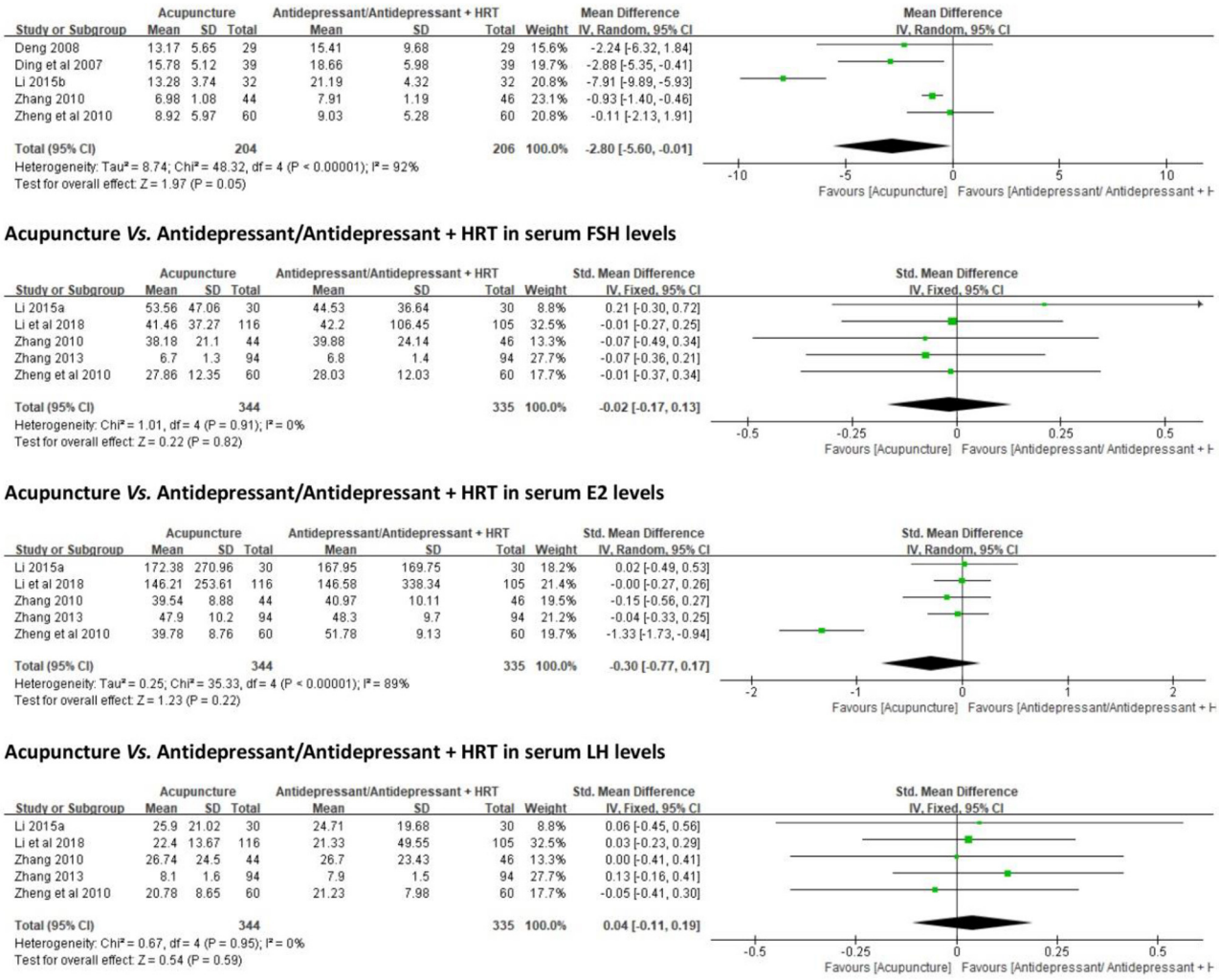


FIGURE 4 | Forest plots of acupuncture vs. antidepressant/antidepressant + HRT in KI and serum hormone levels. HRT, hormone replacement therapy; KI, Kupperman index.

superior to standard care alone in improving depressed mood in perimenopausal women. The reduction of HAMD global score varied from 1.4 to 3.6 points, and the reduction is of clinical relevance. Acupuncture showed better effects than or equivalent effects to antidepressants (escitalopram or Deanxit) in decreasing HAMD global scores at 2-, 4-, and 12-week follow-ups, suggesting that acupuncture may have intermediate- and long-term therapeutic effects on PMD, and its short-term effect was superior to antidepressants. Not enough data were reported on whether acupuncture also has intermediate- and long-term effects on perimenopausal symptoms other than depression in women with PMD. Whether or not the benefits of acupuncture were mediated *via* regulating serum hormone levels, such as FSH, E2, and LH, remains unclear because there were insufficient data. Not enough studies reported if acupuncture could reduce the side effects of HRT or antidepressants, as only one study (55) with a small sample size addressed this comparison. Acupuncture appeared to be well-tolerated and safe, as the AEs were only mild and far less than those for standard care. The most frequent AE was hematoma, which usually healed quickly after the needles were removed. Overall, the quality of the studies was low to moderate due to a lack of blinding of patients and outcome assessors.

Strengths, Limitations, and Comparison With Previous Systematic Reviews

To the best of our knowledge, this was the first systematic review and meta-analysis comprehensively investigating if acupuncture can be recommended as an independent or adjuvant management to standard care for PMD.

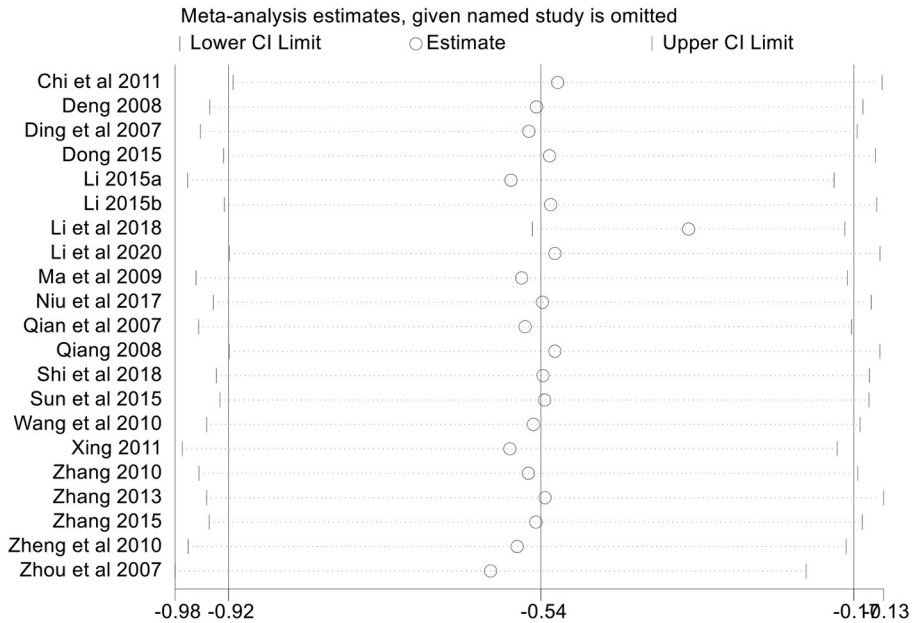


FIGURE 5 | Sensitivity analysis based on HAMD. HAMD, Hamilton Depression Scale.

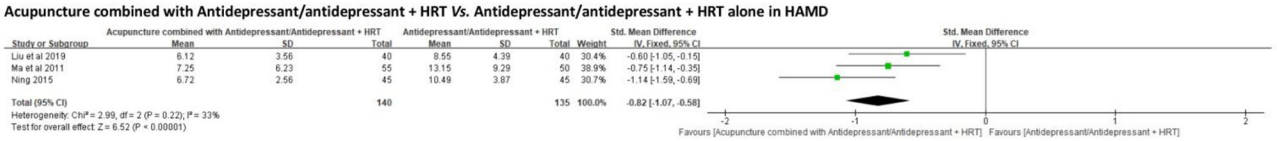


FIGURE 6 | Forest plots of acupuncture combined with antidepressant/antidepressant + HRT vs. antidepressant/antidepressant + HRT in HAMD. HRT, hormone replacement therapy; HAMD, Hamilton Depression Scale.

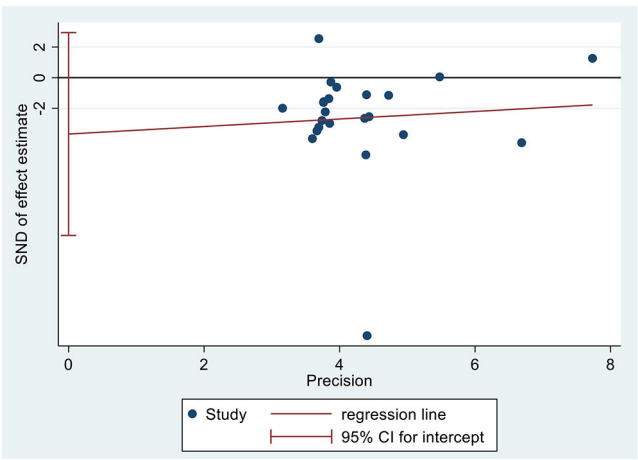


FIGURE 7 | Publication bias test based on HAMD. HAMD, Hamilton Depression Scale.

Women in Western countries are not likely to immediately give up Western medicine and choose acupuncture. However, they may be more willing to adopt acupuncture as adjuvant therapy to Western medication as part of a comprehensive management program (58, 59). Our review specifically addresses this question and supports a better effect of acupuncture alone or when combined with standard care.

We are aware of five previous systematic reviews (two in Chinese and three in English) that addressed a similar topic (26–29, 60). However, three of them were carried out more than 5 years ago (27–29). Three of the five reviews included many different forms of acupoint-based therapies, such as moxibustion (28, 29, 60), intradermal needling (28), acupoint catgut implantation (60), and/or even psychotherapy (60) and Chinese herbal medicine (60). Such practice introduces extra variability and makes it difficult to interpret the results. We only focused on common forms of acupuncture (MA or EA) to reduce variability and to better reflect the real clinical practice. It is worth mentioning that an incomplete retrieval issue was identified in one of the five reviews published in a peer-reviewed journal in 2020 (26). The review that reported no available RCT with acupuncture vs. placebo/sham acupuncture was retrieved (searching time: October 2018). However, two RCTs (35, 36) with this design (published in 2015) were identified and included in our review. Another issue with that review (26) was an RCT that

was mistakenly included. The interventions of that review (26) were limited to only MA or EA like ours, but it included an RCT that used both acupuncture and moxibustion (61). Finally, these five reviews did not consider/mention the different versions of HAMD used in the included RCTs. MD but not SMD therefore was inappropriately used for pooling the estimated effect size, which reduced the reliability of their results.

In addition to the stricter selection criteria, usage of widely accepted analyses tools as mentioned above, the advantages of our review also included the following: (1) we conducted meta-analysis on HAMD at post-treatment as well as at 2-, 4-, and 12-week follow-ups; (2) we included the comparison of acupuncture + standard care vs. stand care alone and found acupuncture combined with standard care showed a better antidepressant effect than standard care alone, indicating that acupuncture can be considered as an adjuvant management in future treatment program; (3) we carried out meta-analysis and subgroup analysis for sex hormonal levels to elucidate the potential factors mediating the effect of acupuncture in perimenopausal women; (4) we employed STRICTA checklist to assess the reporting quality of acupuncture. These merits were not identified in any of previous systematic review.

This review has a few limitations. First, the meta-analysis was limited by the number of studies and small sample sizes despite our comprehensive search. Second, the quality of included studies was less than satisfactory. Third, the heterogeneity was high among the studies. We employed subgroup, sensitivity, and meta-regression analyses but could not identify the sources. Fourth, there were insufficient studies (<3) comparing acupuncture with placebo/sham acupuncture supporting a meta-analysis. Furthermore, there are potential flaws of design in these two RCTs (35, 36), which restricts us from more confidently recommending acupuncture as an independent remedy in the management of PMD. Fifth, some included studies did not clearly describe acupuncture details including depth of insertion and/or needle type used. Acupuncture is a complex intervention, and the skills of operators are important. However, only one study (37) explained the background of the trial acupuncturist. Those limitations impact the reproducibility and assessment of the real contribution. Finally, all the included RCTs were conducted in China. It is unknown if the results could be replicated in women outside of China. Further rigorous and well-designed RCTs with larger sample sizes and a multicenter design were required to build stronger evidence. The reporting quality of acupuncture should also be more detailed in order to improve the reproducibility of the treatment procedure as well as to facilitate the usage of this remedy by clinical practitioners.

Considering the consistency in findings and deficiency in study quality, we rate the strength of evidence being low to moderate, supporting the positive effect of acupuncture.

Interpretation of Findings

Thousands of years ago, Chinese medical practitioners had realized the concept of perimenopause, and the etiology and pathogenesis of perimenopausal syndrome, as well as put forward the principles of diagnosis and treatment (e.g., herbal medicine and acupuncture) (62). Different from interpretation of hypothalamic–pituitary–gonadal axis in Western medicine, TCM believes perimenopausal disorders including PMD are caused by imbalance/disharmony of *Yin* and *Yang*, and *Zang-Fu*, which is expected to be balanced/harmonized with the intervention of acupuncture (62). Until now, acupuncture is still widely used in China to manage various physical and mental symptoms associated with menopause (63). Despite the promising results, the evidence quality of two included trials comparing acupuncture vs. sham acupuncture was poor (35, 36). Neither of these two studies carried out sample size calculation or intention-to-treat (ITT) analysis, which may partially weaken the reliability of the results. Sham acupuncture in these two trials used the same acupoints as those in the real-acupuncture group, with shallow insertion. Based on advanced medical imaging technology (laser Doppler blood-flow imaging), Huang et al. reported that deep or shallow acupuncture at acupoints caused decline in the ratio of blood-flow perfusion, while this phenomenon was not found in acupuncture at non-acupoints or in placebo-acupuncture (non-invasive) intervention (64), suggesting that deep or shallow needling on acupoints can trigger the desired physiological effects. Shallow acupuncture on acupoints is thereby not an appropriate placebo control (65). Future research should include effective sample size calculation, appropriate sham acupuncture control, which is near non-acupoints or acupoints unrelated to depression/menopausal symptoms with shallow needling and without *De-qi* sensation, an ITT analysis for outcomes, and more comprehensive follow-ups.

A three-point difference on HAMD is regarded as the "minimal improvement" (66). Our review found that acupuncture was better than standard care alone in reducing HAMD score by 1.4–3.6, which is of clinical significance—acupuncture is better than or at least equivalent to antidepressant in improving perimenopausal women's depression. In addition to the satisfactory short-term effects, the intermediate- and long-term benefits of acupuncture against PMD outlast those of antidepressants. Long-term clinical efficacy is crucial in the management of depressive symptoms, as depression is characterized by a high recurrence rate (67). Frequent relapse of depression (67) and withdrawal symptoms of antidepressants (68) are also two major reasons for numerous patients reject psychotropic agents and seek help from CAM therapy (36).

It is interesting to note that acupuncture also improved perimenopausal symptoms (decreased KI scores), better than either antidepressant alone or antidepressant combined with HRT, reflecting different underlying mechanisms of the two interventions (acupuncture vs. *p*harmacotherapy). A strong association between depression and changes in hormonal milieu has been widely established (69–71). Previous studies demonstrated that increased FSH and LH are linked to the depressed mood in women with no history of depression during their menopause transition (69); decreased E2 enhanced the risk for menopause-related depression and anxiety (70). Another study that reported contradictory results that PMD was associated with increased variability of E2 (69). Animal studies further explained the pathway on how hormonal fluctuations trigger the development of menopause-related depression. Gu et al. reported that increased FSH and LH contributed to the lower neurotransmitter release, such as 5-hydroxytryptamine (5-HT), norepinephrine (NE), and dopamine (DA), which might

in turn cause the depression syndromes in menopause (71). Based on the PMD mouse model, Guo and colleagues reported EA significantly reduced mice's depressed performance, reflected by decreased time of forced swimming and tail suspension, increased number of spontaneous activities, etc. They also observed increased 5-HT, NE, and DA in mice's cerebral tissue, as well as increased serum E2 and decreased serum FSH and LH (72). However, in our review, the changes in those hormones in the acupuncture group did not differ from those in antidepressant/antidepressant + HRT group. Whether hormonal regulation mediates the effect of acupuncture on PMD thereby requires further investigation. For neurotransmitters, only one included study (56) reported that compared with sertraline, MA + sertraline was more effective in increasing serum 5-HT and γ-aminobutyric acid (GABA) levels, which are the major neurotransmitters involved in depression (73, 74). Therefore, this potential "cascade" phenomenon of acupuncture affecting sex hormones, which in turn affects neurotransmitter regulation, could be further investigated. In addition, KI score was also improved. KI measures both somatic and mental perimenopausal symptoms, including vasomotor symptoms, anxiety, and insomnia (75); all of these could contribute to depression in perimenopausal women (7).

The second aim of this systematic review was to investigate if acupuncture could further enhance the clinical efficacy and/or reduce the adverse reactions caused by these Western medications. While three RCTs (55–57) in this category showed that the combined therapy was more significantly effective in improving PMD than standard care, only one trial reported AEs in EA combined paroxetine was slightly less than paroxetine alone (2/55 vs. 3/50). Future studies are thereby needed to further explore the safety of a combined therapy of acupuncture and standard care for PMD.

According to the "Guidelines for the Evaluation and Treatment of Perimenopausal Depression" issued by Board of Trustees for the North American Menopause Society (NAMS), sleep disturbance, particularly insomnia, should be a part of PMD management (7). Depression comorbid insomnia is very common in perimenopausal women (76). However, we did not identify any study including the assessment for sleep. To understand the relationship between PMD and insomnia as well as the comprehensiveness of acupuncture's effects, future studies need to include validated sleep measures such as Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), or actigraphy for sleep assessment in women with PMD.

CONCLUSIONS

This review has provided a low-to-moderate level of evidence supporting acupuncture as a safe and effective alternative to or adjuvant to standard care (antidepressant/antidepressant + HRT) in improving depressed mood as well as other menopause-related symptoms among women with PMD. Future studies need to include appropriate sham/placebo acupuncture and patient-assessor blinding methods in the trial designs, clarify whether acupuncture could also be an adjuvant to HRT, observe the intermediate- and long-term effects of acupuncture on perimenopausal symptoms other than depression in women with PMD, and understand if the improvement is associated with reproductive hormone changes induced by acupuncture. The assessment of sleep index should also be included.

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-JZ and ZZ designed this review. Q-QF and F-YZ performed database search, data extraction, and statistical analyses. ZZ was involved in the quality assessment and bias risk analysis. F-YZ drafted the manuscript. GK, RC, and ZZ provided critical comments for revising the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was sponsored by RMIT Research Stipend Scholarship, RMIT University, Australia, and University's scientific research project, Shanghai Sanda University [2021zz02-yj] to F-YZ; and Three-year Action Plan for Public Health 2020–2022 (Key discipline construction—TCM psychology/TCM psychiatry), Shanghai Municipal Health Commission (GWV-10.1-XK20), Project Management and Technical Specifications of Insomnia Treatment Service Key Promotion, Shanghai Municipal Health Commission [ZY(2018–2020)-ZWB-1001-FWB-07], and Cognitive Behavior Therapy combined with "Shugan Anshen Decoction" in the Treatment of Insomnia, Shanghai Municipal Health Commission (201940058) to W-JZ.

ACKNOWLEDGMENTS

The authors would like to extend their gratitude to Yan Xu, the chair of Nursing Department, School of International Medical Technology, Shanghai Sanda University, as well as Hong Xu (chief physician) and Huiru Wang (associate chief physician) from the Department of Psychiatry, Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, for providing general support.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.666988/full#supplementary-material

REFERENCES

1. Sassarini J. Depression in midlife women. *Maturitas.* (2016) 94:149–54. doi: 10.1016/j.maturitas.2016.09.004
2. Bromberger JT, Epperson CN. Depression during and after the perimenopause: impact of hormones, genetics, and environmental determinants of disease. *Obstet Gynecol Clin North Am.* (2018) 45:663–78. doi: 10.1016/j.ogc.2018.07.007
3. Santoro N. Perimenopause: from research to practice. *J Women's Health.* (2016) 25:332–9. doi: 10.1089/jwh.2015.5556
4. Guo T, Jia M, Jin Y, Xu N, Peng T. Acupuncture for perimenopausal insomnia: a systematic review and meta-analysis protocol. *Medicine.* (2018) 97:e11083. doi: 10.1097/MD.0000000000011083
5. Delamater L, Santoro N. Management of the perimenopause. *Clin Obstetrics Gynecol.* (2018) 61:419–32. doi: 10.1097/GRF.0000000000000389
6. Di YM, Yang L, Shergis JL, Zhang AL, Li Y, Guo X, et al. Clinical evidence of Chinese medicine therapies for depression in women during perimenopause and menopause. *Complement Ther Med.* (2019) 47:102071. doi: 10.1016/j.ctim.2019.03.019
7. Maki PM, Kornstein SG, Joffe H, Bromberger JT, Freeman EW, Athappilly G, et al. Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations. *Menopause.* (2018) 25:1069–85. doi: 10.1097/GME.0000000000001174
8. Süss H, Ehlert U. Psychological resilience during the perimenopause. *Maturitas.* (2020) 131:48–56. doi: 10.1016/j.maturitas.2019.10.015
9. Wariso BA, Guerrieri GM, Thompson K, Koziol DE, Haq N, Martinez PE, et al. Depression during the menopause transition: impact on quality of life, social adjustment, and disability. *Arch Women's Mental Health.* (2017) 20:273–82. doi: 10.1007/s00737-016-0701-x
10. Zeng LN, Yang Y, Feng Y, Cui X, Wang R, Hall BJ, et al. The prevalence of depression in menopausal women in China: a meta-analysis of observational studies. *J Affect Disord.* (2019) 256:337–43. doi: 10.1016/j.jad.2019.06.017
11. Kulkarni J. Perimenopausal depression - an under-recognised entity. *Austral Prescriber.* (2018) 41:183–5. doi: 10.18773/austprescr.2018.060
12. Miller LJ, Girgis C, Gupta R. Depression and related disorders during the female reproductive cycle. *Women's Health.* (2009) 5:577–87. doi: 10.2217/WHE.09.44
13. Toffol E, Heikinheimo O, Partonen T. Hormone therapy and mood in perimenopausal and postmenopausal women: a narrative review. *Menopause.* (2015) 22:564–78. doi: 10.1097/GME.0000000000000323
14. Greiser CM, Greiser EM, Dören M. Menopausal hormone therapy and risk of ovarian cancer: systematic review and meta-analysis. *Human Reprod Update.* (2007) 13:453–63. doi: 10.1093/humupd/dmm012
15. Greiser CM, Greiser EM, Dören M. Menopausal hormone therapy and risk of breast cancer: a meta-analysis of epidemiological studies and randomized controlled trials. *Human Reprod Update.* (2005) 11:561–73. doi: 10.1093/humupd/dmi031
16. Lowe GD. Hormone replacement therapy and cardiovascular disease: increased risks of venous thromboembolism and stroke, and no protection from coronary heart disease. *J Internal Med.* (2004) 256:361–74. doi: 10.1111/j.1365-2796.2004.01400.x
17. Soares CN. Menopausal transition and depression: who is at risk and how to treat it? *Expert Rev Neurother.* (2007) 7:1285–93. doi: 10.1586/14737175.7.10.1285
18. Anderson IM, Ferrier IN, Baldwin RC, Cowen PJ, Howard L, Lewis G, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines. *J Psychopharmacol.* (2008) 22:343–96. doi: 10.1177/0269881107088441
19. Worsley R, Davis SR, Gavrilidis E, Gibbs Z, Lee S, Burger H, et al. Hormonal therapies for new onset and relapsed depression during perimenopause. *Maturitas.* (2012) 73:127–33. doi: 10.1016/j.maturitas.2012.06.011
20. Deligiannidis KM, Freeman MP. Complementary and alternative medicine for the treatment of depressive disorders in women. *Psychiatric Clin North Am.* (2010) 33:441–63. doi: 10.1016/j.psc.2010.01.002
21. Yeung WF, Chung KF, Zhang SP, Yap TG, Law AC. Electroacupuncture for primary insomnia: a randomized controlled trial. *Sleep.* (2009) 32:1039–47. doi: 10.1093/sleep/32.8.1039
22. Chon TY, Lee MC. Acupuncture. *Mayo Clin Proc.* (2013) 88:1141–6. doi: 10.1016/j.mayocp.2013.06.009
23. Ernst E. Acupuncture. *Lancet Oncol.* (2010) 11:20. doi: 10.1016/S1470-2045(09)70399-7
24. Hong SH, Ding SS, Wu F, Xi Q, Li Q, Liu YY, et al. Strong manual acupuncture manipulation could better inhibit spike frequency of the dorsal horn neurons in rats with acute visceral nociception. *Evid Based Complement Alternative Med.* (2015) 2015:675437. doi: 10.1155/2015/675437
25. Li ZQ, Zhang Y, Wang YP, Yan X, Xie PC. Electroacupuncture for primary insomnia: protocol for a systematic review and meta-analysis. *Medicine.* (2018) 97:e11063. doi: 10.1097/MD.0000000000011063
26. Xiao X, Zhang J, Jin Y, Wang Y, Zhang Q. Effectiveness and safety of acupuncture for perimenopausal depression: a systematic review and meta-analysis of randomized controlled trials. *Evid Based Complement Alternative Med.* (2020) 2020:5865697. doi: 10.1155/2020/5865697
27. Quan XH, Ma H, Li Y, Wu C, Chen XH. Acupuncture compares with Western medicine for climacteric depression. *Bangladesh J Pharmacol.* (2016) 11:S144–53. doi: 10.3329/bjp.v11iS1.26799
28. Li ZF, Wu Q, Fu WB, Chen JY. Systematic review on effectiveness and safety of acupuncture-moxibustion for perimenopausal depression. *CJTCMP.* (2014) 29:1746–52.
29. Huang YF, Fu WB, Wu TX, Zhang GC, Su LR, Chen YF. A systematic review on effect and safety of acupuncture for perimenopausal depression. *CJTCMP.* (2011) 26:908–14.
30. Chi H, Zou W. Yishen-tiaoan acupuncture therapy in the treatment of perimenopausal depression: an observation of 30 cases. *JCAM.* (2011) 27:4–7.
31. Zhou SH, Wu FD. Therapeutic effect of acupuncture on perimenopausal depression and its effects on DA, NE and 5-HIAA contents. *Chin Acup Moxib.* (2007) 27:317–21.
32. Carrozzino D, Patierno C, Fava GA, Guidi J. The hamilton rating scales for depression: a critical review of clinimetric properties of different versions. *Psychother Psychosomatics.* (2020) 89:133–50. doi: 10.1159/000506879
33. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. *Cochrane Handbook for Systematic Reviews of Interventions.* 2nd ed. Chichester: John Wiley & Sons (2019). p. 205–88.
34. MacPherson H, Altman DG, Hammerschlag R, Youping L, Taixiang W, White A, et al. Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement. *J Evid Based Med.* (2010) 3:140–55. doi: 10.1111/j.1756-5391.2010.01086.x
35. Wang C, Bai YF, Fu WB, He YH. Clinical effect of acupuncture at four acupoints of Qijing on perimenopausal depression. *Chin J Gerontol.* (2015) 35:3390–2. doi: 10.5005/jp/books/12591_10
36. Li ZF. *Clinical study on the effect of electroacupuncture on patients with mild to moderate depression in perimenopausal period* (Dissertation/Ph.D. thesis). Guangzhou University of Chinese Medicine, Guangzhou, China (2015a).
37. Li S, Li ZF, Wu Q, Guo XC, Xu ZH, Li XB, et al. A multicenter, randomized, controlled trial of electroacupuncture for perimenopause women with mild-moderate depression. *BioMed Res Int.* (2018) 2018:5351210. doi: 10.1155/2018/5351210
38. Deng AJ. *A randomized controlled clinical study of Bo's abdominal acupuncture in treatment of perimenopausal depression* (Dissertation/Master thesis). Guangzhou University of Chinese Medicine, Guangzhou, China (2008).
39. Dong Y. Clinical observation of acupuncture of beishu point in treatment of perimenopausal depression. *Jilin J Traditional Chin Med.* (2015) 35:306–8. doi: 10.13463/j.cnki.jlzyy.2015.03.028
40. Li HB. *Clinical observation on the treatment of kidney deficiency and liver stagnation of perimenopausal depression by acupuncture* (Dissertation/Master thesis). Heilongjiang University of Traditional Chinese Medicine, Harbin, China (2015b).
41. Ma J, Liu Z. A clinical study of the acupuncture treatment in the treatment of perimenopausal depression. *J Psychiatry.* (2009) 22:276–8.
42. Niu XS, Wang P. Clinical study on acupuncture Wangshi Wuzangshu combined Geshu in the treatment of perimenopausal depression with stagnation of Liver-Qi syndrome. *Int J Trad Chin Med.* (2017) 39:999–1002. doi: 10.3760/cma.j.issn.1673-4246.2017.11.010
43. Qian J, Zhang J, Pei Y, Cheng J. Clinical observation of Wangshi Wuzangshu combined Geshu for perimenopausal depression. *Beijing J TCM.* (2007) 26:491–2.

44. Qiang BQ. Acupuncture treatment 30 cases of perimenopause depression. *J Shaanxi TCM.* (2008) 29:871–2.
45. Shi J, Huang DM, Feng QF, Tang NL. Clinical observation on electroacupuncture treatment for mild to moderate depression in perimenopausal period. *China J Modern Med.* (2018) 28:52–6. doi: 10.3969/j.issn.1005-8982.2018.20.009
46. Sun YJ, Tan Z, Jiang CY, Li SY. Clinical observation of electroacupuncture in the treatment of mild and moderate depressionr in perimenopausal period. *J Guangxi Univ Chin Med.* (2015) 18:13–5.
47. Wang XY, Li XY, Deng AJ. Comparative study on abdominal acupuncture and western medicine for treatment of perimenopause depression. *Chin Acup Moxib.* (2010) 30:913–7. doi: 10.13703/j.0255-2930.2010.11.026
48. Zhang YL. *Effect of electroacupuncture on Hamilton score and sex hormone levels in patients with perimenopausal depression* (Dissertation/Master thesis). Shaanxi University of Chinese Medicine, Xianyang, China (2010).
49. Zhang YQ. Clinical study of acupuncture treatment on 94 cases of perimenopausal depression. *Inner Mongol J Traditional Chin Med.* (2013) 32:41–2.
50. Zheng SH, Wu YT, Liao JR, Xu MZ, Hu ZN, Chen LH. Clinical study of treatment of perimenopausal depression with Sishen needle *Liaoning J Traditional Chin Med.* (2010) 37:726–8. doi: 10.13192/j.ljtcm.2010.04.155
51. Ding L, Liu B. Treatment of perimenopausal depression by acupuncture with Nourishing-Kidney-Regulating-Liver-Strengthening-Spleen-Tranquilizing-Heart method. *Chin Arch Traditional Chin Med.* (2007) 25:1066–7.
52. Li P, Dai W. Clinical observation of electroacupuncture in the treatment of perimenopause depression. *Clin J Traditional Chin Med.* (2020) 32:555—8. doi: 10.16448/j.cjtcm.2020.0344
53. Zhang J. Comparative study on the efficacy of abdominal acupuncture and Western medicine in treating perimenopause depression. *World Latest Med Information.* (2015) 64:145. doi: 10.3969/j.issn.1671-3141.2015.64.107
54. Xing K. Clinical observation of 120 cases of perimenopausal depression by Xingshen-Jieyu acupuncture. *Maternal Child Health Care China.* (2011) 26:5373–5.
55. Ma YB, Guo YM, Li XJ. Therapeutic effect of electroacupuncture combined with paroxetine on 55 cases of perimenopausal depression. *Medical J Chin People's Health.* (2011) 23:1426–8.
56. Liu HF, Chen GZ. Effect of acupuncture combined with Sertraline on hormone levels and neurotransmitters in women with perimenopausal depression–clinical data of 40 cases. *Jiangsu J Traditional Chin Med.* (2019) 51:70–2.
57. Ning Y. Clinical study on acupuncture treatment of perimenopausal depression. *J Sichuan Traditional Chin Med.* (2015) 33:154–5.
58. Hui KK. *Harmonizing Traditional Chinese and Modern Western Medicine: A Perspective From the US.* (1999). Available online at: https://cewm.med.ucla.edu/wp-content/uploads/1999HuiKHarmonizingTCM-MWMPerspectiveUS.pdf (accessed February 11, 2021).
59. Courbasson CM, de Sorkin AA, Dullerud B, Van Wyk L. Acupuncture treatment for women with concurrent substance use and anxiety/depression: an effective alternative therapy? *Family Commun Health.* (2007) 30:112–20. doi: 10.1097/01.FCH.0000264408.36013.03
60. Li S, Luo D, Ma R, Ning BL, Guo XC, Zhou JH, et al. Meta-analysis of acupuncture versus Western medicine in the treatment of perimenopausal depression. *Chin J Gerontol.* (2019) 39:1891–6. doi: 10.3969/j.issn.1005-9202.2019.08.034
61. Lin GQ, Sun PF. Clinical observation of acupuncture in the treatment of perimenopausal depression. *Sichuan J Traditional Chin Med.* (2008) 26:115–6.
62. Eisenhardt S, Fleckenstein J. Traditional Chinese medicine valuably augments therapeutic options in the treatment of climacteric syndrome. *Arch Gynecol Obstetrics.* (2016) 294:193–200. doi: 10.1007/s00404-016-4078-x
63. Qin Y, Ruan X, Ju R, Pang J, Zhao G, Hu X. Acupuncture for menopausal symptoms in Chinese women: a systematic review. *Climact J Int Menopause Soc.* (2021) 24:68–73. doi: 10.1080/13697137.2020.1795115
64. Huang T, Wang RH, Zhang WB, Han B, Wang GJ, Tian YY, et al. The influence of different methods of acupuncture on skin surface perfusion. *J Traditional Chin Medicine.* (2012) 32:40–4. doi: 10.1016/S0254-6272(12)60029-6
65. Yang HY, Wang DY, Dong X, He L, Lu SY, Jiao ML. Status of placebo acupuncture control research. *Chin Acup Moxib.* (2020) 40:337—41. doi: 10.13703/j.0255-2930.20190311-0002
66. Moncrieff J, Kirsch I. Empirically derived criteria cast doubt on the clinical significance of antidepressant-placebo differences. *Contemp Clin Trials.* (2015) 43:60–2. doi: 10.1016/j.cct.2015.05.005
67. Dionisie V, Filip GA, Manea MC, Manea M, Riga S. The anti-inflammatory role of SSRI and SNRI in the treatment of depression: a review of human and rodent research studies. *Inflammopharmacology.* (2021) 29:75–90. doi: 10.1007/s10787-020-00777-5
68. Guy A, Brown M, Lewis S, Horowitz M. The 'patient voice': patients who experience antidepressant withdrawal symptoms are often dismissed, or misdiagnosed with relapse, or a new medical condition. *Ther Adv Psychopharmacol.* (2020) 10:2045125320967183. doi: 10.1177/2045125320967183
69. Freeman EW, Sammel MD, Lin H, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. *Arch General Psychiatry.* (2006) 63:375–82. doi: 10.1001/archpsyc.63.4.375
70. Estrada CM, Ghisays V, Nguyen ET, Caldwell JL, Streicher J, Solomon MB. Estrogen signaling in the medial amygdala decreases emotional stress responses and obesity in ovariectomized rats. *Hormones Behav.* (2018) 98:33–44. doi: 10.1016/j.yhbeh.2017.12.002
71. Gu S, Jing L, Li Y, Huang JH, Wang F. Stress induced hormone and neuromodulator changes in menopausal depressive rats. *Front Psychiatry.* (2018) 9:253. doi: 10.3389/fpsyt.2018.00253
72. Guo X, Pan F, Wang B, Li W, Xia C, Ju Z. Effect of electroacupuncture on mice model of permenopausal depressive disorder. *Saudi J Biol Sci.* (2019) 26:2030–6. doi: 10.1016/j.sjbs.2019.08.007
73. Bhatt S, Devadoss T, Manjula SN, Rajangam J. 5-HT3 receptor antagonism a potential therapeutic approach for the treatment of depression and other disorders. *Curr Neuropharmacol.* (2020). doi: 10.2174/1570159X18666201015155816. [Epub ahead of print].
74. Liao J, Wang S, Yang H, Ma P, Li C, Huang Q, et al. The mRNA expression levels of GABA(A) receptor α1 and α2 subunits in patients with major depressive disorder during onset and remission. *Int J Neurosci.* (2021) 1–7. doi: 10.1080/00207454.2020.1829618. [Epub ahead of print].
75. Xi S, Mao L, Chen X, Bai W. Effect of health education combining diet and exercise supervision in Chinese women with perimenopausal symptoms: a randomized controlled trial. *Climact J Int Menopause Soc.* (2017) 20:151–6. doi: 10.1080/13697137.2017.1281903
76. Terauchi M, Obayashi S, Akiyoshi M, Kato K, Matsushima E, Kubota T. Insomnia in Japanese peri- and postmenopausal women. *Climacteric J Int Menopause Soc.* (2010) 13:479–86. doi: 10.3109/13697130903353478

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.

frontiers | Frontiers in Psychiatry

MINI REVIEW
published: 21 April 2022
doi: 10.3389/fpsyt.2022.874128

A Literature Mini-Review of Transcranial Direct Current Stimulation in Schizophrenia

Zuzana Stuchlíková[1,2,3] *and Monika Klírová*[1,2]*

[1] National Institute of Mental Health, Klecany, Czechia, [2] Third Faculty of Medicine, Charles University, Prague, Czechia, [3] Hospital České Budějovice, a.s., České Budějovice, Czechia

Transcranial direct current stimulation (tDCS) is a non-invasive neurostimulation method that utilizes the effect of low-current on brain tissue. In recent years, the effect of transcranial direct current stimulation has been investigated as a therapeutic modality in various neuropsychiatric indications, one of them being schizophrenia. This article aims to provide an overview of the potential application and effect of tDCS in treating patients with schizophrenia. A literature search was performed using the PubMed, Web of Science, and Google Scholar databases for relevant research published from any date until December 2021. Eligible studies included those that used randomized controlled parallel-group design and focused on the use of transcranial direct current stimulation for the treatment of positive, negative, or cognitive symptoms of schizophrenia. Studies were divided into groups based on the focus of research and an overview is provided in separate sections and tables in the article. The original database search yielded 705 results out of which 27 randomized controlled trials met the eligibility criteria and were selected and used for the purpose of this article. In a review of the selected trials, transcranial direct current stimulation is a safe and well-tolerated method that appears to have the potential as an effective modality for the treatment of positive and negative schizophrenic symptoms and offers promising results in influencing cognition. However, ongoing research is needed to confirm these conclusions and to further specify distinct application parameters.

Keywords: review, neurostimulation, direct current stimulation, tDCS, schizophrenia, schizophrenic

OPEN ACCESS

Edited by:
Mirko Manchia,
University of Cagliari, Italy

Reviewed by:
Thorsten Rudroff,
The University of Iowa, United States
Vanteemar Sreeraj,
National Institute of Mental Health and Neurosciences (NIMHANS), India

***Correspondence:**
Monika Klírová
monika.klirova@nudz.cz

Specialty section:
This article was submitted to Public Mental Health, a section of the journal Frontiers in Psychiatry

Received: *11 February 2022*
Accepted: *14 March 2022*
Published: *21 April 2022*

Citation:
Stuchlíková Z and Klírová M (2022) A Literature Mini-Review of Transcranial Direct Current Stimulation in Schizophrenia. Front. Psychiatry 13:874128. doi: 10.3389/fpsyt.2022.874128

INTRODUCTION

Schizophrenia is a serious mental illness with an average lifetime prevalence of 6.35 per 1,000 persons (1). Symptoms of schizophrenia may be divided into separate clusters in three main domains that are represented by positive, negative, and cognitive symptoms. Whereas the pharmacological approach is effective mainly in the treatment of positive symptoms, it shows only small benefits in treating negative and cognitive symptoms (2). This is one of the reasons why the scientific focus remains on researching and improving new treatment options and therapeutic modalities. Attenuated cortical activity in prefrontal regions, i.e., hypofrontality (3, 4), and altered inter and intrahemispheric connectivity were described in individuals diagnosed with schizophrenia (5). Frontotemporal and frontoparietal disconnectivity is associated with negative (3, 6) and positive

symptoms (3, 7). Hypoactivity of the prefrontal cortex and the disruption of its connection with temporoparietal and contralateral regions were described in relation to the cognitive symptoms (8–10). One of the treatment methods researched for schizophrenia is transcranial direct current stimulation (tDCS) due to its possible effects on the described disrupted cortical mechanisms.

Transcranial direct current stimulation is a non-invasive neuromodulation method based on the use of low-intensity direct current (usually 1–2 mA) and its effect on brain tissue (11). The direct current generated between the surface of electrodes (anode and cathode) placed on the scalp creates cortical changes dependent on the polarity of the applied current. During anodal tDCS (located under the anode), the depolarization of neuronal membranes occurs and thus the cortical excitability rises, meanwhile cathodal tDCS (under the cathode) has the opposite effect (12). Albeit the precise mechanism of the post-modulatory effect of tDCS remains not fully clarified, studies show that direct current stimulation may influence synaptic plasticity and affect remote brain regions by acting on non-synaptic axonal levels (13). The post-modulatory effect on the synaptic level is mediated through the alteration of Ca^{2+}- dependent channels of N-methyl-D-aspartate (NMDA) and amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) receptors and also through modulating GABA and its interaction with the glutamatergic system (12). These processes further influence brain-derived neutotrophic factor (BDNF) production leading to long-term potentiation (anodal tDCS) or depression (cathodal tDCS) (14, 15), and produce post-modulatory synaptic changes, with long-term potentiation strengthening connections between neurons and long-term depression weakening them (16). Recent research shows BDNF polymorphism to have an impact on the subject sensitivity to tDCS effects (17, 18). Other studies demonstrate a non-synaptic mechanism of tDCS after-effects based on changes in neuronal membrane function (19). tDCS also shows the ability to interfere with functional connectivity, synchronization, and oscillatory action of different cortical and subcortical neuronal networks (16, 17). Additional line of research focuses on possible immunomodulatory effects of tDCS and their importance in overall outcomes (20, 21). Furthermore, tDCS is considered to is considered to also act through induced epigenetic changes, such as histone acetylation and methylation (22, 23).

In recent years, tDCS has been explored as a possible treatment modality for a number of neurological and neuropsychiatric disorders (16, 24). Some of the areas of focus for tDCS application include neurodegenerative diseases such as Parkinson's disease (25), motor rehabilitation (26), or cognitive improvement (27). One of the investigated disorders in connection to tDCS is also schizophrenia. Previous reviews mainly focused on tDCS efficacy in separate schizophrenic symptom groups such as auditory hallucinations (AH) (28), negative and cognitive symptoms (29, 30). This literature review focuses specifically on the therapeutic application of tDCS in patients with schizophrenia and aims to provide a comprehensive review of tDCS application and its effect on all schizophrenic symptom clusters. Contrary to recent guidelines (24), studies focusing on cognitive function in patients with schizophrenia were also included in this review.

MATERIALS AND METHODS

For the purpose of this review, a systematic literature search was performed using electronic databases, namely PubMed and Web of Science, and the Google Scholar search engine. The database search was performed on August 4th and on December 14th, 2021. The second search was performed to identify as recently published trials as possible, providing one additionally selected study. With the use of Boolean operators *(tdcs OR "transcranial direct current stimulation" OR "direct current stimulation") AND (schizophrenia OR "schizophrenic disorder" OR schizophrenic)* the search yielded 318 results in the Pubmed database and 381 results in the Web of Science database. The filter to exclude meeting abstracts was used in the search. Subsequently, the Google Scholar search engine was used to identify six more sources from the last year not yet available in the databases.

Inclusion criteria were determined based on the population, intervention, control group, study design, and language used for publication. The population included adults diagnosed with schizophrenia or schizoaffective disorder. The intervention was defined as the use of tDCS for the treatment of positive, negative, or cognitive symptoms of schizophrenia. The control group was set as a sham tDCS application. The study design included randomized blinded studies with parallel arms, therefore excluding any open-label or cross-over trials. Only trials published in English were included. A total of 705 search results were screened based on the titles and/or abstracts. If a trial met inclusion criteria, the full text of the article was retrieved. Full texts were read and reviewed by the first investigator (ZS) with supervision by the senior investigator (MK) who provided subsequent clarification if necessary. Twenty-seven clinical trials were selected following the previously described procedure. A PRISMA flow diagram is available in the **Supplementary Material**.

Selected trials underwent qualitative analysis. Trials were divided into three groups based on the primary focus on positive, negative, or cognitive symptoms. Studies were categorized into the positive symptom group if the outcomes focused on changes in AH or PANSS total and positive scores. The negative symptom group included outcomes measured by SANS or PANSS negative score. Trials in the cognitive symptom group focused on changes in at least one observed cognitive outcome. Specific stimulation parameters such as total number and frequency of tDCS applications, electrode positioning, and intensity of the electrical current were assessed for each trial. The number of participants in both active and sham stimulation was identified. And primary and secondary clinical outcomes were highlighted. All the information was recorded in comprehensive tables.

The risk of bias was assessed for each of the included trials using the revised Cochrane risk of bias assessment tool (31).

RESULTS

Selected studies focused on the possible effect of tDCS application on the frontotemporal and bifrontal disconnectivity in schizophrenia and on ameliorating schizophrenic symptoms. Different positioning of the electrodes and stimulation protocols

were explored. Most of the randomized controlled trials (RCTs) focused on the clinical effect of the stimulation, some of the research also focused on functional changes in distinct brain areas.

Positive Symptoms

Treatment in schizophrenia is often focused on reducing AH as they are frequently present in patients and are often refractory to antipsychotic drugs. Eight of the identified RCTs focused on the reduction of AH as the primary outcome. Two additional trials investigated the effect of tDCS on the reduction of AH in relation to possible modulation of the disrupted neuronal processes in schizophrenia. All 10 studies used similar electrode placement with the anode positioned over the left prefrontal cortex and the cathode over the temporoparietal area. In addition, one study used a bilateral form of stimulation with the second pair of electrodes placed over corresponding contralateral positions (32). All of the studies used the current intensity of 2 mA.

Most of the studies applied tDCS twice daily on five consecutive days (33–39). Two protocols chose to apply stimulation only once per day (32, 40), and two protocols continued to administer stimulation for several weeks (32, 41).

The selected RCT studies do not provide consistent results regarding the efficacy of tDCS on AH intensity. A 2012 study (33) was one of the first to show a significant effect of tDCS in this indication. The effect on AH was also documented in five other studies (34–36, 39, 41). As a secondary outcome, the stimulation protocols reduced the Positive and Negative Syndrome Scale (PANSS) scores (33), and an improvement in working memory was described (41).

Four of the selected studies failed to demonstrate a significant effect of active tDCS stimulation on AH, despite a sufficient sample size and statistical significance being reached (32, 37, 38, 40). Furthermore, two of these RCT studies failed to confirm a significant effect in favor of active stimulation over placebo on any other of the observed symptoms (38, 40). The largest negative study in influencing AH, however, documents improvement in the observed PANSS score and in the level of insight (37). Data from this study were additionally analyzed in two subsequent publications (42, 43). The first paper commented on a trend-level improvement in planning ability, and further specified the positive trends in PANSS score change, where the amelioration of total and general psychopathology did not reach statistical significance compared to sham stimulation (42). The publication in the following year focused on the observed temporary improvement in insight, treatment adherence, and psychological domain of quality of life (43).

Increased activity in the frontal and temporoparietal cortex was previously described in relation to AH (44). A 2016 study (35) showed the effect of tDCS on the resting-state functional connectivity between the frontal and temporoparietal cortex. The reduction of aberrant connectivity positively correlated with the reduction of AH severity (35). These findings may help clarify the positive effect of the preferred frontotemporal stimulation used to improve AH. Subsequent analysis of brain activity in a selected sample from the previous study suggested that the strength of the tDCS-induced electric field reaching the left transverse temporal gyrus may have an important influence on the outcome of frontotemporal stimulation (45).

Impairment of the ability to distinguish between self-generated events and external stimuli was also described in relation to AH in patients with schizophrenia (46). One of the studies showed frontotemporal stimulation to be effective in improving the source-monitoring ability and the improvement positively correlated with a reduction in AH severity (34). A study published in 2019 (47) also explored tDCS application and its ability to influence source-monitoring deficits in a sample of subjects from the 2018 study (36), the findings documented improvement in corollary discharge.

An overview of the selected RCT studies, stimulation parameters, and observed effects is provided in **Table 1**.

Negative Symptoms

Key negative symptoms of schizophrenia include blunted affect, alogia, anhedonia, asociality, and avolition (48). Negative symptoms may present as one of the first symptoms of schizophrenia (49) and most antipsychotic drugs have a limited effect on their treatment (50). The search yielded five RCT studies mainly focusing on tDCS application as a possible treatment for negative symptoms. All of the trials demonstrated active stimulation to be at least partially effective in improving the observed outcomes. Based on the assumed association between negative symptoms and neurobiological correlates in the prefrontal cortex (51), the anode was positioned over the corresponding area in all of the studies. One trial protocol placed the cathode over the ipsilateral temporoparietal cortex (52), two over the contralateral prefrontal cortex (53, 54), one protocol used bi-anodal stimulation of the prefrontal cortex bilaterally with cathodes placed on the forearms (55), and one trial used high definition tDCS (HD-tDCS) with four return electrodes positioned around the anode (56). This was the only study using HD-tDCS to be included in this review. All of the selected studies used current intensity of 2 mA for stimulation.

The study using bi-anodal stimulation presented positive outcomes in psychosocial functioning and ameliorated disorganization and cognitive symptoms as measured by PANSS (55). This study showed a rapid reduction in negative symptoms with the beneficial effect lasting up to 3 months (55). Further data analysis, published 1 year later, also documented a significant enhancement of insight and beliefs about medication compliance (57).

In terms of the amelioration of negative symptoms, a 36% reduction in the SANS score (54) and a 45% reduction in the PANSS negative score (53) was described in trials using electrode montage with the cathode placed over the right prefrontal cortex. A significant SANS and PANSS reduction were also documented in a study with HD-tDCS stimulation (56).

A study with frontotemporal electrode montage presented a significantly greater reduction in negative symptoms and the total PANSS score after active stimulation compared to the sham (52). As a secondary outcome, the effect of tDCS on cognitive performance was evaluated in the majority of participants, and no beneficial effect was shown in favor of active stimulation over placebo (58).

TABLE 1 | Effects of tDCS on positive symptoms.

Studies	Design	Inclusion criteria, diagnosis	Number of subjects (*n*)	Electrode placement Size of electrodes	Stimulation parameters *(duration, course, total number, intensity used)*	Sham parameters	Outcomes
Brunelin et al. 2012 (33)	RDBS, SH	SZ + TR AH	$n = 30$ (15 active, 15 sham)	Anode – F3/FP1 cathode – T3/P3 size: 7 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 40 s +110 μA pulse over 15 ms every 550 ms	Robust AH reduction (mean improvement of 31% in AHRS score) lasting up to 3 months. Amelioration of schizophrenia symptoms as assessed by total PANSS, with significant effect on the negative dimension. Medium effect size on the positive and depressive dimension short of statistical significance.
Fitzgerald et al. 2014 (32)	2x RDBS, SH	SZ/SZA + persistent AH and negative symptoms	$n = 24$ (11 bilateral, 13 unilateral)	Unilateral: anode – F3 cathode – TP3 Bilateral: + anode – F4 + cathode – TP4 size: 35 cm^2	20 min 1x/day, 3 weeks, weekdays (15) 2 mA	2 mA for 30 s with ramp-up	No substantial change in AH, PANSS or SANS score after neither unilateral nor bilateral stimulation.
Mondino et al. 2015 (34)[a]	RDBS, SH	SZ + TR AH	$n = 28$ (15 active, 13 sham)	Anode – F3/FP1 cathode- T3/P3 size: 7 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 30 s	Medium effect on covert/overt speech misattributions in the active group. A large effect on AH frequency in the active group. The reduction in covert/overt speech misattributions positively correlated with the reduction in AH frequency.
Fröhlich et al. 2016 (40)	RDBS, SH	SZ/SZA + AH	n = 26 (13 active, 13 sham)	anode - F3/FP1 cathode - T3/P3 (+ return electrode Cz). size: 7 × 5cm	20 min 1x/day, 5 days (5) 2 mA	2 mA for 40 s	Lack of efficacy of active tDCS. A significant reduction in AH not specific to the treatment group. No significant change in PANSS.
Mondino et al. 2016 (35)[b]	RDBS, SH	SZ + TR AH	$n = 23$ (11 active, 12 sham)	Anode – F3/FP1 cathode – T3/P3 size: 7 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 30 s	Significant reduction of AH as well as negative symptoms after active tDCS. Reduced resting state functional connectivity (rs-FC) of the left temporoparietal junction with the left anterior insula and the right inferior gyrus, and increased rs-FC of the left TPJ with the left angular gyrus, the left DLPFC and the precuneus after active tDCS.
Bose et al. 2018 (36)	RDBS, SH + open label extension (OLE)	SZ + TR AH	$n = 25$ (12 active, 13 sham)	Anode – F3/FP1 cathode – T3/P3 size: 7 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 40 s + 110 μA pulse over 15 ms every 550 ms	RDBS phase: Significant tDCS-type X time-point interaction with significantly greater reduction of AHRS score in active tDCS (30.22%). OLE phase: Significant greater reduction in AH severity in sham-to-verum crossed over patients.
Chang et al. 2018 (37)	RDBS, SH	SZ/SZA + TR AH	$n = 60$ (30 active, 30 sham)	Anode – F3/FP1 cathode – T3/P3 size: 7 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 30 s	No significant changes in the severity of AH or in PANSS after active tDCS. Improvement in the level of insight into illness and into positive symptoms lasting 1 month after active tDCS.
Koops et al. 2018 (38)	RDBS, SH	TR AH (several diagnostic categories)	$n = 54$ (28 active, 26 sham)	Anode – FP1/F3 cathode – T3/P3 size: 7 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 40 s +110 μA pulse over 15 ms every 550 ms	Active tDCS was not more effective than placebo on any of the main outcomes *(AHRS, PANSS, the Stroop, and the Trail Making Test)*.
Kantrowitz et al. 2019 (39)	RDBS, SH	SZ/SZA + TR AH	$n = 89$ (47 active, 42 sham)	Anode – F3/FP1 cathode – T3/P3 size: 6.75 × 5.75 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 40 s ramp-up/ramp-down	Significant reduction in AHRS total score (>30%) across 1-week and 1-month. (Greatest change observed on the AHRS loudness item.) No significant change in PANSS negative.

(Continued)

TABLE 1 | (Continued)

Studies	Design	Inclusion criteria, diagnosis	Number of subjects (*n*)	Electrode placement Size of electrodes	Stimulation parameters *(duration, course, total number, intensity used)*	Sham parameters	Outcomes
Lindenmayer et al. 2019 (41)	RDBS, SH	Ultra-TR SZ +persistent AH	$n = 28$ (15 active, 13 sham)	Anode – F3/FP1 cathode – T3/P3 size: 7 × 5 cm	20 min 2x/day, 4 weeks, weekdays (40) 2 mA	2 mA for 40 s +110 μA pulse over 15 ms every 550 ms	Small but meaningful AHRS reduction (21.9%). Significant change in working memory and PANSS total in the active tDCS group. No significant changes in PANSS subscales.
Gomes et al. 2015 (53)	RDBS, SH	SZ	$n = 15$ (7 active, 8 sham)	Anode – F3 cathode – F4 size: not specified	20 min 1x/day, 2 weeks, weekdays (10) 2 mA	Not specified	PANSS reduction (total score 42.3%, negative score 45.4%, general score 29%) after active tDCS. No effects for CDSS, GAF and PANSSpositive score.
Smith et al. 2015 (66)	RDBS, SH	SZ/SZA + current smokers	$n = 37$ (19 active, 18 sham)	Anode – F3 cathode – FP2 size: 5.08 cm^2	20 min 1x/day, 5 days (5) 2 mA	2 mA for 40 s	Significant improvements in MCCB Composite score and the domain scores for Working Memory and Attention Vigilance with large effect sizes. (MCCB Composite score and domain score for Working Memory remained significant with corrected significance levels). No statistically significant effects on secondary outcome measures (PANSS scores, hallucinations, cigarette craving, or cigarettes smoked).
Palm et al. 2016 (54)	RDBS, SH	SZ with predominantly negative symptoms	$n = 20$ (10 active, 10 sham)	Anode – F3 cathode – FP2 size: 7 × 5 cm	20 min 1x/day, 2 weeks, weekdays (10) 2 mA	Not specified	Significantly greater decrease in SANS score (36.1%) and PANSS sum scores (23.4%) after active tDCS compared to sham (0.7%, 2.2% respectively). Explorative analysis of fcMRI data revealed changes in subgenual cortex and DLPFC connectivity within fontal-thalamic-temporo-parietal networks. No significant effect of active tDCS on CDSS score or cognitive outcomes.
Shiozawa et al. 2016 (70)	RDBS, SH	SZ	$n = 10$ (5 active, 5 sham)	anode – left DLPFC cathode – right DLPFC size: 35 cm^2	20 min 2x/day, 5 days 1x "online" tDCS (10) 2 mA *+ cognitive training randomly applied during one of the tDCS sessions*	2 mA for 60 s	Failed to demonstrate effect of "online tDCS" on improvement in clinical outcomes (N-back and sequence learning task, PANSS).
Gomes et al. 2018 (69)	RDBS, SH	SZ	$n = 24$ (12 active, 12 sham)	Anode– left DLPFC cathode – right DLPFC size: 25 cm^2	20 min 1x/day, 2 weeks, weekdays (10) 2 mA	2 mA for 30 s	Without improvement in working memory. Therapeutic effects of tDCS for treatment of persistent symptoms in schizophrenia, with reduction of negative symptoms.
Jeon et al. 2018 (68)	RDBS, SH	SZ	$n = 56$ (28 active, 28 sham)	Anode – F3 cathode – F4 size: 25 cm^2	30 min 1x/day, 2 weeks, weekdays (10) 2 mA	2 mA for 30 s ramp-up + 30 s ramp-down	MCCB working memory and overall scores improved over time after active tDCS. Depressive symptoms decreased after tDCS. Improvement of PANSS score (did not reach statistical significance).
Bose et al. 2019 (47)[c]	RDBS, SH *ancillary study*	SZ + TR AH	$n = 13$ (7 active, 6 sham)	Anode –left DLPFC cathode – left TPJ (no further specification)	20 min 2x/day, 5 days (10) 2 mA	2 mA for 40 s +110 μA pulse over 15 ms every 550 ms	Improvements in corollary discharge with concurrent reduction in AH scores after active tDCS. Change in corollary discharge correlated with change in AH severity.

(Continued)

TABLE 1 | (Continued)

Studies	Design	Inclusion criteria, diagnosis	Number of subjects (*n*)	Electrode placement Size of electrodes	Stimulation parameters *(duration, course, total number, intensity used)*	Sham parameters	Outcomes
Weickert et al. 2019 (74)	RDBS, SH	SZ/SZA	*n* = 12 (6 active, 6 sham)	Anode – F4 cathode – T3/P3 size: 7 × 5 cm	20 min 1x/day, 4 weeks, weekdays "online" tDCS (20) 2 mA + 2-back test	2 mA for 15 s ramp-up + 15 s ramp-down	Significant improvement in language-based working memory after 2 weeks and verbal fluency after 2 and 4 weeks. No significant effect on any other cognitive assessment. No significant effects on AHRS score.
Chang et al. 2020 (55)	RDBS, SH	SZ/SZA	*n* = 60 (30 active, 30 sham)	Bilateral: anode 1 – F3/FP1 anode 2 – F4/FP2 reference electrodes – ipsilateral forearm size: 7 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 30 s +110 μA pulse over 15 ms every 550 ms	Rapid reduction of negative symptoms measured by PANSS, with the beneficial effect lasting up to 3 months. Improvement of psychosocial functioning. Improvement of psychopathological symptoms especially for disorganization and cognitive symptoms as measured by the PANSS. No effects on other schizophrenia symptom dimensions or on the performance in neurocognitive tests.
Smith et al. 2020 (65)	RSBS, SH	SZ + significant cognitive deficit	*n* = 49 (24 active, 25 sham) **45 evaluated*	Anode – F3 cathode – FP2 size: 5,08 cm^2	20 min 1x/day, 2 weeks, weekdays (10) 2 mA	2 mA for 40 s	Significant pro-cognitive effects on some aspects of cognitive testing at 2 and 4 weeks after the final tDCS session (MATRICS Speed of Processing domain). No immediate pro-cognitive effects. No significant effects on other psychiatric outcomes.
Valiengo et al. 2020 (52)	RDBS, SH	SZ	*n* = 100 (50 active, 50 sham)	Anode – F3 cathode – T3/P3 size: 7 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 30 s + 40 s ramp-up + 40 s ramp-down	Significantly greater improvement in PANSS scores after active tDCS. Higher response rates for negative symptoms in the active group.
Dharani et al. 2021 (56)	RDBS, SH	SZ	*n* = 14 (7 active, 7 sham)	Anode – F3 4 return electrodes (FC1, F7, FC5, AF3) size: 1 cm radius ring electrodes	20 min 2x/day, 5 days (10) 2 mA	1 mA for 30 s	Significant reduction in PANSS, SANS, and CGI-S.
Meiron et al. 2021 (71)	RDBS, SH	SZ/SZA	*n* = 19 (11 active, 8 sham, +12 healthy controls for baseline and post-tDCS comparison)	Anode – F3/AF3 cathode – vertex size: 5 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 30 s ramp-up + 30 s ramp-down	Improvement in working memory performance in the active tDCS group. Post-tDCS scores were comparable to healthy control scores. Significant alleviation of symptom severity maintained for four weeks.
Mondino et al. 2021 (45)[d]	RDBS, SH *Electrical field modeling using baseline structural MRI scans*	SZ + TR AH	*n* = 17 subjects with active tDCS (6 responders, 11 non-responders)	Anode – F3/FP1 cathode – T3/P3 size: 7 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 30 s	Higher electric field strength in the left transverse temporal gyrus at baseline in responders to tDCS (at least a 50% decrease of AH 1 month after the last tDCS session) compared to non-responders.

Studies placed below the double line did not explore positive symptoms as the primary outcome.

AH, auditory hallucinations; AHRS, Auditory Hallucinations Rating Scale; DLPFC, dorsolateral prefrontal cortex; MCCB, MATRICS Consensus Cognitive Battery; OL, open label; PANSS, Positive and Negative Syndrome Scale; RDBS, randomized double blind study; RSBS, randomized single blind study; SH, sham controlled; SZ, schizophrenia; SZA, schizoaffective disorder; TPJ, temporoparietal junction; TR, treatment resistant.

[a] *The sample partially overlaps (n = 15) with an already published study (34).*

[b] *Clinical data from 7 patients of the sham group and 8 of the active group were already used (35).*

[c] *A random subset of a previous clinical study (47).*

[d] *Data from 11 patients were used in a previously published study (45).*

Detailed information on the studies mentioned in this section is provided in **Table 2**.

Cognitive Symptoms

Cognitive impairment is one of the main intervention targets in the treatment of schizophrenia. Cognitive impairment evolves even before the onset of schizophrenia (prodromal phase), is observable in most patients in the first episode, often persists during symptomatic remissions, and is relatively stable across time (59). Important domains of cognitive deficit in schizophrenia include deficits in working memory, executive functions, attention, and speech (60). However, generalized impairment of various cognitive functions has been described (61). The search identified twelve RTCs with the primary focus on influencing cognitive functions. The selected studies do not provide entirely consistent results, two-thirds of them, nonetheless, reported at least partial improvement in the observed cognitive domains. Anodal tDCS over the left prefrontal cortex appears to be a promising method for improving cognition in neuropsychiatric disorders (11). Most of the studies chose this type of stimulation with the cathode located above the contralateral orbitofrontal area (62–67), contralateral prefrontal area (68–70), or vertex (71). One study placed the anode over the right prefrontal cortex, and one protocol used bi-anodal and bi-cathodal stimulation in the prefrontal area (72). The current intensity of 2 mA was used in all of the studies, except for one trial which applied a lower current intensity of 1 mA (64).

Three studies investigated the cognitive outcomes after a single application of tDCS (63, 67, 72). Only one of them, using bi-anodal stimulation, reported a positive effect on one of the observed parameters, which was emotion identification (72). A second study remained without any positive effect of tDCS on initially significantly reduced visual processing speed and visual short-term memory storage capacity in patients with schizophrenia, and even considered the possibility that tDCS may interfere with practice-dependent improvements in the rate of visual information uptake (67). A third study described a possible impairment of response inhibition after a single tDCS session (63).

Likewise, two of the protocols with multiple tDCS applications – specifically with bi-frontal electrode placement – did not find a significant effect on cognition (69, 70). However, one of the trials reported therapeutic effects of tDCS for the treatment of persistent symptoms in schizophrenia, with a reduction of negative symptoms (69). The applied electrode positioning was the same as in a similar study from 2015 that was reported previously in the section on negative symptoms (53).

The remaining studies with multiple tDCS applications yielded positive results in affecting cognitive functions. Other positive effects of repeated stimulation regimens included a reduction in the PANSS score (68, 71) and alleviation of depressive symptoms (68). Functional magnetic resonance imaging was acquired during tDCS stimulation from some of the participants in a study with a positive effect on working memory (62). Increased activity in the medial prefrontal cortex below the anode was positively correlated with improved working memory, and decreased activity in the anterior cingulate cortex was associated with improved performance on the executive function task, further suggesting the procognitive effects of tDCS applied over the frontal area (73).

A total of four studies used "online" tDCS application, where stimulation is applied at the time of ongoing cognitive training (62, 64, 70, 74). In two cases, "online" tDCS took place during all (74) or more than half of the cognitive training sessions (64).The remaining studies applied stimulation only during one (70) or two appointments (62). By activating the prefrontal cortex, the trials anticipated augmentation of the cognitive training.

An overview of the tDCS use for cognitive symptoms in schizophrenia is provided in **Table 3**.

Transcranial Direct Current Stimulation Tolerability and Side Effects

None of the studies reported any serious adverse effects. The most common side effects (SE) documented in the trials included skin redness, tingling or itching sensation under the electrodes, moderate fatigue, tiredness, and headache, all of which were usually well-tolerated and of a mild and transient character. Mostly, there was no significant difference in frequency of SE between active and sham tDCS groups, except for skin redness and a burning sensation under the electrodes with higher frequency in the active tDCS group, which was documented in some of the papers (38, 52, 65). According to recent reviews, there is no evidence for irreversible injury produced by conventional tDCS protocols within a wide range of stimulation parameters (75) and within standard protocols, tDCS is considered a safe method (76).

Risk of Bias

The Cochrane risk of bias assessment tool was used to evaluate the methodological quality of each trial. Study quality assessment included randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain was scored as "low risk," "some concerns," or "high risk." The level of the risk of bias varied across studies. The most common potential causes of bias were the insufficient description of the randomization and blinding process, dealing with missing data, and unavailability of pre-specified analysis plan (i.e., study protocol) which led to scoring as "some concerns." A significant number of studies did not provide a sufficient description of blinding of staff delivering intervention and assessors of outcome measures, or did not describe the method used for randomization other than stating the participants were randomized (33–35, 37, 41, 53, 62, 64, 70–72). One of the studies reported only partial effectiveness of blinding since both subjects and testers could correctly guess that the sham group received sham stimulation in most of their guesses (65). There was also missing outcome data in a larger part of the trials mainly due to discontinuation of participants, leading to scoring as "some concerns" in the domain (37, 38, 41, 53, 56, 62, 64–66, 68–72, 74). None of the reviewed studies scored "high" in the overall risk of bias.

TABLE 2 | Effects of tDCS on negative symptoms.

Studies	Design	Inclusion criteria, diagnosis	Number of subjects	Electrode placement	Stimulation parameters *(duration, course, total number, intensity used)*	Sham parameters	Outcomes
Gomes et al. 2015 (53)	RDBS, SH	SZ	$n = 15$ (7 active, 8 sham)	Anode – F3 cathode – F4 size: not specified	20 min 1x/day, 2 weeks, weekdays (10) 2 mA	Not specified	PANSS reduction (total score 42.3%, negative score 45.4%, general score 29%) after active tDCS. No effects for CDSS, GAF and PANSSpositive score.
Palm et al. 2016 (54)	RDBS, SH	SZ with predominantly negative symptoms	$n = 20$ (10 active, 10 sham)	Anode – F3 cathode – FP2 size: 7 × 5 cm	20 min 1x/day, 2 weeks, weekdays (10) 2 mA	Not specified	Significantly greater decrease in SANS score (36.1%) and PANSS sum scores (23.4%) after active tDCS compared to sham (0.7, 2.2% respectively). Explorative analysis of fcMRI data revealed changes in subgenual cortex and DLPFC connectivity within fontal-thalamic-temporo-parietal networks. No significant effect of active tDCS on CDSS score or cognitive outcomes.
Chang, et al. 2020 (55)	RDBS, SH	SZ/SZA	$n = 60$ (30 active, 30 sham)	Bilateral: anode 1 – F3/FP1 anode 2 – F4/FP2 reference electrodes – ipsilateral forearm size: 7 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 30 s +110 μA pulse over 15 ms every 550 ms	Rapid reduction of negative symptoms measured by PANSS, with the beneficial effect lasting up to 3 months. Improvement of psychosocial functioning. Improvement of psychopathological symptoms especially for disorganization and cognitive symptoms as measured by the PANSS. No effects on other schizophrenia symptom dimensions or on the performance in neurocognitive tests.
Valiengo et al. 2020 (52)	RDBS, SH	SZ	$n = 100$ (50 active, 50 sham)	Anode – F3 cathode – T3/P3 size: 7 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 30 s + 40 s ramp-up + 40 s ramp-down	Significantly greater improvement in PANSS scores after active tDCS. Higher response rates for negative symptoms in the active group.
Dharani et al. 2021 (56)	RDBS, SH	SZ	$n = 14$ (7 active, 7 sham)	Anode – F3 4 return electrodes (FC1, F7, FC5, AF3) size: 1 cm radius ring electrodes	20 min 2x/day, 5 days (10) 2 mA	1 mA for 30 s	Significant reduction in PANSS, SANS, and CGI-S.
Brunelin et al. 2012 (33)	RDBS, SH	SZ + TR AH	$n = 30$ (15 active, 15 sham)	Anode – F3/FP1 cathode - T3/P3 size: 7 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 40 s +110 μA pulse over 15 ms every 550 ms	Robust AH reduction (mean improvement of 31% in AHRS score) lasting up to 3 months. Amelioration of schizophrenia symptoms as assessed by total PANSS, with significant effect on the negative dimension. Medium effect size on the positive and depressive dimension short of statistical significance.
Fitzgerald et al. 2014 (32)	2x RDBS, SH	SZ/SZA + persistent AH and negative symptoms	$n = 24$ (11 bilateral, 13 unilateral)	Unilateral: anode – F3 cathode – TP3 Bilateral: + anode – F4 + cathode – TP4 size: 35cm^2	20 min 1x/day, 3 weeks, weekdays (15) 2 mA	2 mA for 30 s with ramp-up	No substantial change in AH, PANSS or SANS score after neither unilateral nor bilateral stimulation.

(Continued)

TABLE 2 | (Continued)

Studies	Design	Inclusion criteria, diagnosis	Number of subjects	Electrode placement	Stimulation parameters *(duration, course, total number, intensity used)*	Sham parameters	Outcomes
Smith et al. 2015 (66)	RDBS, SH	SZ/SZA + current smokers	$n = 37$ (19 active, 18 sham)	Anode – F3 cathode – FP2 size: 5,08 cm^2	20 min 1x/day, 5 days (5) 2 mA	2 mA for 40 s	Significant improvements in MCCB Composite score, and the domain scores for Working Memory and Attention Vigilance with large effect sizes. (MCCB Composite score and domain score for Working Memory remained significant with corrected significance levels). No statistically significant effects on secondary outcome measures (PANSS scores, hallucinations, cigarette craving, or cigarettes smoked).
Fröhlich et al. 2016 (40)	RDBS, SH	SZ/SZA + AH	$n = 26$ (13 active, 13 sham)	Anode – F3/FP1 cathode – T3/P3 (+ return electrode Cz). size: 7 × 5cm	20 min 1x/day, 5 days (5) 2 mA	2 mA for 40 s	A lack of efficacy of active tDCS. A significant reduction in AH not specific to the treatment group. No significant change in PANSS.
Mondino et al. 2016 (35)[b]	RDBS, SH	SZ + TR AH	$n = 23$ (11 active, 12 sham)	Anode – F3/FP1 cathode – T3/P3 size: 7 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 30 s	Significant reduction of AH as well as negative symptoms after active tDCS. Reduced resting state functional connectivity (rs-FC) of the left temporoparietal junction with the left anterior insula and the right inferior gyrus, and increased rs-FC of the left TPJ with the left angular gyrus, the left DLPFC and the precuneus after active tDCS.
Shiozawa et al. 2016 (70)	RDBS, SH	SZ	$n = 10$ (5 active, 5 sham)	anode – left DLPFC cathode – right DLPFC size: 35 cm^2	20 min 2x/day, 5 days 1x "online" tDCS (10) 2 mA *+ cognitive training randomly applied during one of the tDCS sessions*	2 mA for 60 s	Failed to demonstrate effect of "online tDCS" on improvement in clinical outcomes (N-back and sequence learning task, PANSS).
Gomes et al. 2018 (69)	RDBS, SH	SZ	$n = 24$ (12 active, 12 sham)	Anode– left DLPFC cathode – right DLPFC size: 25 cm^2	20 min 1x/day, 2 weeks, weekdays (10) 2 mA	2 mA for 30 s	Without improvement in working memory. Therapeutic effects of tDCS for treatment of persistent symptoms in schizophrenia, with reduction of negative symptoms.
Chang et al. 2018 (37)	RDBS, SH	SZ/SZA + TR AH	$n = 60$ (30 active, 30 sham)	Anode – F3/FP1 cathode – T3/P3 size: 7 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 30 s	No significant changes in the severity of AH or in PANSS after active tDCS. Improvement in the level of insight into illness and into positive symptoms lasting 1 month after active tDCS.
Jeon et al. 2018 (68)	RDBS, SH	SZ	$n = 56$ (28 active, 28 sham)	Anode – F3 cathode – F4 size: 25 cm^2	30 min 1x/day, 2 weeks, weekdays (10) 2 mA	2 mA for 30 s ramp-up + 30 s ramp-down	MCCB working memory and overall scores improved over time after active tDCS. Depressive symptoms decreased after tDCS. Improvement of PANSS score (did not reach statistical significance).

(Continued)

TABLE 2 | (Continued)

Studies	Design	Inclusion criteria, diagnosis	Number of subjects	Electrode placement	Stimulation parameters *(duration, course, total number, intensity used)*	Sham parameters	Outcomes
Koops et al. 2018 (38)	RDBS, SH	TR AH (several diagnostic categories)	$n = 54$ (28 active, 26 sham)	Anode – FP1/F3 cathode – T3/P3 size: 7 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 40 s + 110 μA pulse over 15 ms every 550 ms	Active tDCS was not more effective than placebo on any of the main outcomes (AHRS, PANSS, the Stroop, and the Trail Making Test)
Kantrowitz, J. T. et al. 2019 (39)	RDBS, SH	SZ/SZA + TR AH	$n = 89$ (47 active, 42 sham)	Anode – F3/FP1 cathode – T3/P3 size: 6.75 × 5.75 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 40 s ramp-up/ramp-down	Significant reduction in AHRS total score (>30%) across 1-week and 1-month. (Greatest change observed on the AHRS loudness item.) No significant change in PANSS negative.
Lindenmayer et al. 2019 (41)	RDBS, SH	Ultra-TR SZ + persistent AH	$n = 28$ (15 active, 13 sham)	Anode – F3/FP1 cathode – T3/P3 size: 7 × 5 cm	20 min 2x/day, 4 weeks, weekdays (40) 2mA	2 mA for 40 s + 110 μA pulse over 15 ms every 550 ms	Small but meaningful AHRS reduction (21.9%). Significant change in working memory and PANSS total in the active tDCS group. No significant changes in PANSS subscales.
Weickert et al. 2019 (74)	RDBS, SH	SZ/SZA	$n = 12$ (6 active, 6 sham)	Anode – F4 cathode – T3/P3 size: 7 × 5 cm	20 min 1x/day, 4 weeks, weekdays "online" tDCS (20) 2 mA + 2-back test	2 mA for 15 s ramp-up + 15 s ramp-down	Significant improvement in language-based working memory after 2 weeks and verbal fluency after 2 and 4 weeks. No significant effect on any other cognitive assessment. No significant effects on AHRS score.
Smith et al. 2020 (65)	RSBS, SH	SZ + significant cognitive deficit	$n = 49$ (24 active, 25 sham) **45 evaluated*	Anode – F3 cathode – FP2 size: 5.08 cm^2	20 min 1x/day, 2 weeks, weekdays (10) 2 mA	2 mA for 40 s	Significant pro-cognitive effects on some aspects of cognitive testing at 2 and 4 weeks after the final tDCS session (MATRICS Speed of Processing domain). No immediate pro-cognitive effects. No significant effects on other psychiatric outcomes.
Chang et al. 2021 (57)[a]	RDBS, SH *ancillary investigation*	SZ/SZA	$n = 60$ (30 active, 30 sham)	Bilateral: anode 1 – F3/FP1 anode 2 – F4/FP2 reference electrodes – ipsilateral forearm size: 7 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 30 s + 110 μA pulse over 15 ms every 550 ms	Significant enhancement of insight levels and beliefs about medication compliance after active tDCS.
Meiron et al. 2021 (71)	RDBS, SH	SZ/SZA	$n = 19$ (11 active, 8 sham, +12 healthy controls for baseline and post-tDCS comparison)	Anode – F3/AF3 cathode – vertex size: 5 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 30 s ramp-up + 30 s ramp-down	Improvement in working memory performance in the active tDCS group. Post-tDCS scores were comparable to healthy control scores. Significant alleviation of symptom severity maintained for 4 weeks.

Studies placed below the double line did not explore negative symptoms as the primary outcome.

AH, auditory hallucinations; AHRS, Auditory Hallucinations Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; CGI-S, Clinical Global Impression Scale; DLPFC, dorsolateral prefrontal cortex; GAF, Global Assessment of Functioning; MCCB, MATRICS Consensus Cognitive Battery; PANSS, Positive and Negative Syndrome Scale; RDBS, randomized double blind study; RSBS, randomized single blind study; SH, sham controlled; SZ, schizophrenia; SZA, schizoaffective disorder; TPJ, temporoparietal junction; TR, treatment resistant.

[a]*Ancillary investigation of secondary outcomes from a previously published study (55).*

TABLE 3 | Effects of tDCS on cognitive symptoms.

Studies	Design	Inclusion criteria, diagnosis	Number of subjects (n)	Electrode placement Size of electrodes	Stimulation parameters *(duration, course, total number, intensity used)*	Sham parameters	Outcomes
Rassovsky et al. 2015 (72)	RSBS, SH	SZ	$n = 36$ (12 anodal, 12 cathodal, 12 sham)	Bilateral anodal/cathodal: active electrodes - FP1, FP2 reference electrodes – right arm Size: 7 × 5 cm	20 min anodal/cathodal/sham (1) 2 mA	2 mA for 30 s	Significant improvement in one of the four social cognitive tasks – emotion identification – after anodal stimulation.
Smith et al. 2015 (66)	RDBS, SH	SZ/SZA + current smokers	$n = 37$ (19 active, 18 sham)	Anode – F3 cathode – FP2 size: 5.08 cm^2	20 min 1x/day, 5 days (5) 2 mA	2 mA for 40 s	Significant improvements in MCCB Composite score and the domain scores for Working Memory and Attention Vigilance with large effect sizes. (MCCB Composite score and domain score for Working Memory remained significant with corrected significance levels). No statistically significant effects on secondary outcome measures (PANSS scores, hallucinations, cigarette craving, or cigarettes smoked).
Nienow et al. 2016 (64)	RSBS, SH	SZ/SZA	$n = 10$	Anode – F3 cathode – right SO size: 7 × 5 cm	20 min 2x/week from 3rd week "online" tDCS (28) 1 mA *Cognitive training 1 h 3x/week for 16 weeks*	Not specified	Suggests "online tDCS" enhances cognitive performance.
Shiozawa et al. 2016 (70)	RDBS, SH	SZ	$n = 10$ (5 active, 5 sham)	Anode – left DLPFC cathode – right DLPFC size: 35 cm^2	20 min 2x/day, 5 days 1x "online" tDCS (10) 2 mA *+ cognitive training randomly applied during one of the tDCS sessions*	2 mA for 60 s	Failed to demonstrate effect of "online tDCS" on improvement in clinical outcomes (N-back and sequence learning task, PANSS).
Gögler et al. 2017 (67)	RDBS, SH	SZ/SZA	$n = 20$ patients (10 active, 10 sham) $n = 20$ healthy controls (10 active, 10 sham)	Anode – F3 cathode –FP2 size: 35 cm^2	20 min (1) 2 mA	2 mA for 30 s + 15 s ramp-up + 15 s ramp-down	Prefrontal tDCS may interfere with practice-dependent improvements in the rate of visual information uptake.
Orlov et al. 2017 (62)	RDBS, SH	SZ/SZA	$n = 49$ (24 active, 25 sham)	Anode – F3 cathode – FP2 size: 35 cm^2	30 min on days 1 and 14 "online" tDCS (2) 2 mA *Cognitive training 2x/day on days 1, 2, 14, 56*	2 mA for 30 s	Significant long-term effect of tDCS on working memory (suggested effect on consolidation of learning, no significant benefit during the acute stimulation on working memory).

(Continued)

TABLE 3 | (Continued)

Studies	Design	Inclusion criteria, diagnosis	Number of subjects (n)	Electrode placement Size of electrodes	Stimulation parameters *(duration, course, total number, intensity used)*	Sham parameters	Outcomes
Gomes et al. 2018 (69)	RDBS, SH	SZ	*n* = 24 (12 active, 12 sham)	Anode– left DLPFC cathode – right DLPFC size: 25 cm^2	20 min 1x/day, 2 weeks, weekdays (10) 2 mA	2 mA for 30 s	Without improvement in working memory. Therapeutic effects of tDCS for treatment of persistent symptoms in schizophrenia, with reduction of negative symptoms.
Jeon et al. 2018 (68)	RDBS, SH	SZ	n = 56 (28 active, 28 sham)	anode – F3 cathode – F4 size: 25 cm^2	30 min 1x/day, 2 weeks, weekdays (10) 2 mA	2 mA for 30 s ramp-up + 30 s ramp-down	MCCB working memory and overall scores improved over time after active tDCS. Depressive symptoms decreased after tDCS. Improvement of PANSS score (did not reach statistical significance).
Weickert et al. 2019 (74)	RDBS, SH	SZ/SZA	*n* = 12 (6 active, 6 sham)	anode – F4 cathode – T3/P3 size: 7 × 5 cm	20 min 1x/day, 4 weeks, weekdays "online" tDCS (20) 2 mA + 2-back test	2 mA for 15 s ramp-up + 15 s ramp-down	Significant improvement in language-based working memory after 2 weeks and verbal fluency after 2 and 4 weeks. No significant effect on any other cognitive assessment. No significant effects on AHRS score.
Smith et al. 2020 (65)	RSBS, SH	SZ + significant cognitive deficit	*n* = 49 (24 active, 25 sham) **45 evaluated*	Anode – F3 cathode – FP2 size: 5.08 cm^2	20 min 1x/day, 2 weeks, weekdays (10) 2 mA	2 mA for 40 s	Significant pro-cognitive effects on some aspects of cognitive testing at 2 and 4 weeks after the final tDCS session (MATRICS Speed of Processing domain). No immediate pro-cognitive effects. No significant effects on other psychiatric outcomes.
Meiron et al. 2021 (71)	RDBS, SH	SZ/SZA	*n* = 19 (11 active, 8 sham, +12 healthy controls for baseline and post-tDCS comparison)	Anode – F3/AF3 cathode – vertex size: 5 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 30 s ramp-up + 30 s ramp-down	Improvement in working memory performance in the active tDCS group. Post-tDCS scores were comparable to healthy control scores. Significant alleviation of symptom severity maintained for 4 weeks.
Schilling et al. 2021 (63)	RDBS, SH	SZ/SZA/ATPD	*n* = 48 (24 active, 24 sham)	Anode – F3 cathode – FP2 size: 5 × 5 cm	20 min (1) 2 mA	2 mA for 40 s	No acute enhancement of executive functions. Impaired performance in the response inhibition task within 20 min after the stimulation.
Palm et al. 2016 (54)	RDBS, SH	SZ with predominantly negative symptoms	*n* = 20 (10 active, 10 sham)	Anode – F3 cathode – FP2 size: 7 × 5 cm	20 min 1x/day, 2 weeks, weekdays (10) 2 mA	Not specified	Significantly greater decrease in SANS score (36.1%) and PANSS sum scores (23.4%) after active tDCS compared to sham (0.7, 2.2% respectively). Explorative analysis of fcMRI data revealed changes in subgenual cortex and DLPFC connectivity within fontal-thalamic-temporo-parietal networks. No significant effect of active tDCS on CDSS score or cognitive outcomes.
Orlov et al. 2017 (73)[a]	RDBS, SH *fMRI study as a part of a larger behavioral study*	SZ/SZA	n = 49 (24 active, 25 sham)	anode – F3 cathode – FP2 size: 35 cm^2	30 min on days 1 and 14 "online" tDCS (2) 2 mA *Cognitive training 2x/day on days 1, 2, 14, 56*	2 mA for 30 s	Modulation of functional activation in local task-related regions and in more distal nodes in the network with active tDCS.

(Continued)

TABLE 3 | (Continued)

Studies	Design	Inclusion criteria, diagnosis	Number of subjects (n)	Electrode placement Size of electrodes	Stimulation parameters *(duration, course, total number, intensity used)*	Sham parameters	Outcomes
Chang, et al. 2018 (37)	RDBS, SH	SZ/SZA + TR AH	$n = 60$ (30 active, 30 sham)	Anode – F3/FP1 cathode – T3/P3 size: 7 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 30 s	No significant changes in the severity of AH or in PANSS after active tDCS. Improvement in the level of insight into illness and into positive symptoms lasting 1 month after active tDCS.
Koops et al. 2018 (38)	RDBS, SH	TR AH (several diagnostic categories)	$n = 54$ (28 active, 26 sham)	anode - FP1/F3 cathode - T3/P3 size:7 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 40 s + 110 μA pulse over 15 ms every 550 ms	Active tDCS was not more effective than placebo on any of the main outcomes (AHRS, PANSS, the Stroop, and the Trail Making Test)
Chang et al. 2019 (42)[b]	RDBS, SH *ancillary analysis*	SZ/SZA + TR AH	$n = 60$ (30 active, 30 sham)	Anode – F3/FP1 cathode – T3/P3 size: 7 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 30 s	Significant trends in PANSS total and general scores after active tDCS, does not reach statistical significance compared to sham stimulation. No significant effects on other psychopathological symptoms and psychosocial functioning. A trend-level improvement of planning ability.
Lindenmayer et al. 2019 (41)	RDBS, SH	Ultra-TR SZ + persistent AH	$n = 28$ (15 active, 13 sham)	Anode – F3/FP1 cathode – T3/P3 size: 7 × 5 cm	20 min 2x/day, 4 weeks, weekdays (40) 2mA	2 mA for 40 s + 110 μA pulse over 15 ms every 550 ms	Small but meaningful AHRS reduction (21.9%). Significant change in working memory and PANSS total in the active tDCS group. No significant changes in PANSS subscales.
Chang et al. 2020 (55)	RDBS, SH	SZ/SZA	$n = 60$ (30 active, 30 sham)	Bilateral: anode 1 – F3/FP1 anode 2 – F4/FP2 reference electrodes – ipsilateral forearm size: 7 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 30 s + 110 μA pulse over 15 ms every 550 ms	Rapid reduction of negative symptoms measured by PANSS, with the beneficial effect lasting up to 3 months. Improvement of psychosocial functioning. Improvement of psychopathological symptoms especially for disorganization and cognitive symptoms as measured by the PANSS. No effects on other schizophrenia symptom dimensions or on the performance in neurocognitive tests.
Kao et al. 2020 (43)[c]	RDBS, SH *ancillary analysis*	SZ/SZA + TR AH	$n = 60$ (30 active, 30 sham)	Anode – F3/FP1 cathode – T3/P3 size: 7 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 30 s + 110 μA pulse over 15 ms every 550 ms	Brief optimization of self-reported insight levels, beliefs about treatment adherence, and psychological domain of life quality after active tDCS.
Bulubas et al. 2021 (58)[d]	RDBS, SH *ancillary analysis*	SZ	$n = 100$ (50 active, 50 sham) *90 patients included in ancillary analysis (48 active, 42 sham)*	anode – F3 cathode – T3/P3 size: 7 × 5 cm	20 min 2x/day, 5 days (10) 2 mA	2 mA for 30 s + 40 s ramp-up + 40 s ramp-down	No beneficial effects of active tDCS over sham in any of the cognitive tests. Improvements of executive functions and delayed memory in favor of sham stimulation.

Studies placed below the double line did not explore cognitive symptoms as the primary outcome.
AH, auditory hallucinations; AHRS, Auditory Hallucinations Rating Scale; ATPD, acute transient psychotic disorder; DLPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; MCCB, MATRICS Consensus Cognitive Battery; PANSS, Positive and Negative Syndrome Scale; RDBS, randomized double blind study; RSBS, randomized single blind study; SH, sham controlled; SO, supraorbital; SZ, schizophrenia; SZA, schizoaffective disorder; TR, treatment resistant.
[a] *Part of a larger behavioral study (73).*
[b] *Ancillary analysis of secondary outcomes from a previously published study (42).*
[c] *Ancillary analysis of secondary outcomes from a previously published study (43).*
[d] *Ancillary data analysis of part of the subjects from a previously published study (58).*

DISCUSSION

This is an up-to-date review article offering a cross-section of current research with a focus on tDCS application in schizophrenia. Following a standardized literature search, we identified 27 randomized controlled trials. A total of 966 patients diagnosed with schizophrenia or schizoaffective disorder participated in these clinical trials. As a primary aim, ten trials examined the effects of tDCS on positive symptoms with six of them yielding positive results. All five trials focusing primarily on negative symptoms showed some improvement in the measured outcomes. Twelve trials explored the impact of tDCS on cognitive functions and out of those, eight trials report beneficial effects in at least one measured aspect of cognition. Overall, we could not establish a reporting bias.

The reviewed studies differed considerably in the experimental design and stimulation protocols. However, all of the clinical trials selected the anode placement to be over the prefrontal cortex. This may be explained by the effort to positively influence the aforementioned attenuated prefrontal activity that is seen in patients with schizophrenia. Nonetheless, the differences between the cortical activity in early-course and chronic schizophrenia may be of consideration in connection to the anode placement. A previous study suggests a difference in the activity of the prefrontal cortex among early-course schizophrenic patients in contrast to attenuation of the activity that is commonly described in patients with chronic illness (77). In such cases, the activation of prefrontal regions by the anodal transcranial stimulation may not be beneficial. None of the reviewed studies reported using neuronavigation for exact electrode positioning, most of them referred to the 10-20 EEG system frequently used for tDCS electrode montage. Nonetheless, due to inter-personal brain variability this method leads to limited targeting accuracy (78). Although neuronavigation methods are not commonplace outside highly specialized research centers, their future implementation could mean achieving more effective stimulation and consequently better clinical outcomes. Another element of tDCS application to consider is the duration of active stimulation. The vast majority of the selected trials used 20 min of stimulation, and only three of them chose to prolong the stimulation up to 30 min. Current research suggests that the effect of anodal tDCS may not be directly proportional to the duration of the active stimulation, and may on the contrary decrease or even reverse with prolonged stimulation (79, 80). However, the studies included in the review that used a 30-min protocol provided positive outcomes with all of them focusing on cognitive measures. Further exploration of the exact electrode placement and duration of the stimulation should be considered in future studies. Additionally, number of sessions in repeated tDCS application protocols and the repetition interval is an important factor to examine. Studies included in this review used stimulation protocols with tDCS applied once or twice daily, usually separating the two stimulation sessions by 2–3 h. Twice-a-day stimulation is used in order to strengthen the effect. Repeated application protocols offer significant opportunities for induction of long-lasting and significant neuroplastic change (81). However, specific timing of repetition intervals is important for optimizing cumulative effects of tDCS (82). Previously published studies indicate that short repetition interval (<30 min) can lead to prolongation of tDCS after-effects (81–83), whereas longer repetition interval (3 or 24 h) result in no excitability-enhancing after effects or can nullify them (83, 84). Current research focuses on accelerated tDCS protocols (85, 86), and future RCT protocols using tDCS as a treatment option for schizophrenia might benefit from their implementation.

In recent years, the emphasis is also placed on gender differences. Brain anatomy, chemistry, and function differ in relation to sex, leading to differences in response to neurostimulation methods in men and women (87, 88). These issues have been addressed and explored in recent studies (89–91). Some of the studies included in this review controlled for potential confounding effects of male to female ratio in trial groups, however, none of them specifically focused on the various effects of tDCS in connection to gender. There was also no consideration of altering stimulation protocols according to sex-related brain differences or examining response to tDCS in women and men separately. In the future, closer exploration of gender-tailored stimulation protocols might be of interest.

The clinical trials included in the review considerably differ in sample size. As the outcomes are not consistent, this makes it difficult to offer clear recommendations for future research. The differences in methodologies, experimental design, and protocols are considerable limitations for selecting an appropriate and most effective design for future trials. More studies with a clear design and robust sample size are needed to better evaluate the clinical effects and possible application of tDCS in treating patients with schizophrenia.

This review has several limitations. Firstly, only randomized controlled double-blind parallel trials were included, which decreased the total number of reviewed studies. Open-label and cross-over studies may play an important role in an overall assessment of tDCS efficacy, and future reviews may consider their inclusion. Secondly, we did not perform a meta-analysis of the selected research, as this article only brings a qualitative overview, and therefore statistical data are not offered for the overall assessment.

CONCLUSION

This review provides a summary of current research on tDCS application in patients suffering from schizophrenia. Albeit the 2017 guidelines (16) exclude some of the sources on the use of tDCS in schizophrenia as poor evidence, current guidelines list tDCS as a Level B (Probably effective) therapeutic method for the treatment of AH and positive/negative symptoms (24). This review also focused on tDCS application as a treatment for cognitive schizophrenic symptoms, where tDCS appears to be a promising therapeutic method. However, ongoing research is needed to confirm these conclusions and to further specify distinct application parameters.

AUTHOR CONTRIBUTIONS

ZS: conceptualization, methodology, investigation, and writing—original draft preparation. MK: conceptualization, methodology, investigation, supervision, writing—reviewing, and editing. Both authors: contributed to the article and approved the submitted version.

FUNDING

This review was supported by the grant PharmaBrain No. CZ.02.1.01/0.0/0.0/16_0250007444.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.874128/full#supplementary-material

Supplementary Figure 1 | PRISMA 2020 flow diagram for new systematic reviews, which included searches of databases, registers, and other sources [A LiteratureMini-Review of Transcranial Direct Current Stimulation (tDCS) in Schizophrenia]. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit http://www.prisma-statement.org/.

REFERENCES

1. Simeone JC, Ward AJ, Rotella P, Collins J, Windisch R. An evaluation of variation in published estimates of schizophrenia prevalence from 1990-2013: a systematic literature review. *BMC Psychiatry.* (2015) 15:193. doi: 10.1186/s12888-015-0578-7
2. McCutcheon RA, Reis Marques T, Howes OD. Schizophrenia – an overview. *JAMA Psychiatry.* (2020) 77:201–10.
3. Andreasen NC, O'Leary DS, Flaum M, Nopoulos P, Watkins GL, Boles Ponto LL, et al. Hypofrontality in schizophrenia: distributed dysfunctional circuits in neuroleptic-naive patients. *Lancet.* (1997) 349:1730–4. doi: 10.1016/s0140-6736(96)08258-x
4. Weinberger DR, Egan MF, Bertolino A, Callicott JH, Mattay VS, Lipska BK, et al. Prefrontal neurons and the genetics of schizophrenia. *Biol Psychiatry.* (2001) 50:825–44. doi: 10.1016/s0006-3223(01)01252-5
5. Schmitt A, Hasan A, Gruber O, Falkai P. Schizophrenia as a disorder of disconnectivity. *Eur Arch Psychiatry Clin Neurosci.* (2011) 261(SUPPL. 2):150–4. doi: 10.1007/s00406-011-0242-2
6. Galderisi S, Merlotti E, Mucci A. Neurobiological background of negative symptoms. *Eur Arch Psychiatry Clin Neurosci.* (2015) 265:543–58. doi: 10.1007/s00406-015-0590-4
7. Ford JM, Mathalon DH. Corollary discharge dysfunction in schizophrenia: can it explain auditory hallucinations? *Int J Psychophysiol.* (2005) 58:179–89. doi: 10.1016/j.ijpsycho.2005.01.014
8. Glahn DC, Ragland JD, Abramoff A, Barrett J, Laird AR, Bearden CE, et al. Beyond hypofrontality: a quantitative meta-analysis of functional neuroimaging studies of working memory in schizophrenia. *Hum Brain Mapp.* (2005) 25:60–9. doi: 10.1002/hbm.20138
9. Adhikari BM, Hong LE, Sampath H, Chiappelli J, Jahanshad N, Thompson PM, et al. Functional network connectivity impairments and core cognitive deficits in schizophrenia. *Hum Brain Mapp.* (2019) 40:4593–605. doi: 10.1002/hbm.24723
10. Lesh TA, Niendam TA, Minzenberg MJ, Carter CS. Cognitive control deficits in schizophrenia: mechanisms and meaning. *Neuropsychopharmacology.* (2011) 36:316–8. doi: 10.1038/npp.2010.156
11. Hoy KE, Fitzgerald PB. Brain stimulation in psychiatry and its effects on cognition. *Nat Publ Gr.* (2010) 6:267–75. doi: 10.1038/nrneurol.2010.30
12. Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul.* (2012) 5:175–95. doi: 10.1016/j.brs.2011.03.002
13. Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, et al. Transcranial direct current stimulation: state of the art 2008. *Brain Stimul.* (2008) 1:206–2. doi: 10.1016/j.brs.2008.06.004
14. Fritsch B, Reis J, Martinowich K, Schambra HM, Ji Y, Cohen LG, et al. Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. *Neuron.* (2010) 66:198–204. doi: 10.1016/j.neuron.2010.03.035
15. Medeiros LF, de Souza ICC, Vidor LP, de Souza A, Deitos A, Volz MS, et al. Neurobiological effects of transcranial direct current stimulation: a review. *Front Psychiatry.* (2012) 3:110. doi: 10.3389/fpsyt.2012.00110
16. Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol.* (2017) 128:56–92. doi: 10.1016/j.clinph.2016.10.087
17. Polanía R, Nitsche MA, Ruff CC. Studying and modifying brain function with non-invasive brain stimulation. *Nat Neurosci.* (2018) 21:174–87. doi: 10.1038/s41593-017-0054-4
18. Fridriksson J, Elm J, Stark BC, Basilakos A, Rorden C, Sen S, et al. BDNF genotype and tDCS interaction in aphasia treatment. *Brain Stimul.* (2018) 11:1276–81. doi: 10.1016/j.brs.2018.08.009
19. Ardolino G, Bossi B, Barbieri S, Priori A. Non-synaptic mechanisms underlie the after-effects of cathodal transcutaneous direct current stimulation of the human brain. *J Physiol.* (2005) 568:653–3. doi: 10.1113/jphysiol.2005.088310
20. Pelletier SJ, Cicchetti F. Cellular and molecular mechanisms of action of transcranial direct current stimulation: evidence from in vitro and in vivo models. *Int J Neuropsychopharmacol.* (2015) 18:1–13. doi: 10.1093/ijnp/pyu047
21. Rabenstein M, Unverricht-Yeboah M, Keuters MH, Pikhovych A, Hucklenbroich J, Vay SU, et al. Transcranial current stimulation alters the expression of immune-mediating genes. *Front Cell Neurosci.* (2019) 13:461. doi: 10.3389/fncel.2019.00461
22. Podda MV, Cocco S, Mastrodonato A, Fusco S, Leone L, Barbati SA, et al. Anodal transcranial direct current stimulation boosts synaptic plasticity and memory in mice via epigenetic regulation of BDNF expression. *Sci Rep.* (2016) 6:1–19. doi: 10.1038/srep22180
23. Wiegand A, Blickle A, Brückmann C, Weller S, Nieratschker V, Plewnia C. Dynamic DNA methylation changes in the comt gene promoter region in response to mental stress and its modulation by transcranial direct current stimulation. *Biomolecules.* (2021) 11:1726. doi: 10.3390/biom11111726
24. Fregni F, El-Hagrassy MM, Pacheco-Barrios K, Carvalho S, Leite J, Simis M, et al. Evidence-based guidelines and secondary meta-analysis for the use of transcranial direct current stimulation in neurological and psychiatric disorders. *Int J Neuropsychopharmacol.* (2021) 24:256–313. doi: 10.1093/ijnp/pyaa051
25. Liu X, Liu H, Liu Z, Rao J, Wang J, Wang P, et al. Transcranial direct current stimulation for Parkinson's disease: a systematic review and meta-analysis. *Front Aging Neurosci.* (2021) 13:746797. doi: 10.3389/fnagi.2021.746797
26. Mitsutake T, Imura T, Hori T, Sakamoto M, Tanaka R. Effects of combining online anodal transcranial direct current stimulation and gait training in stroke patients: a systematic review and meta-analysis. *Front Hum Neurosci.* (2021) 15:782305. doi: 10.3389/fnhum.2021.782305
27. Siegert A, Diedrich L, Antal A. New methods, old brains—a systematic review on the effects of tDCS on the cognition of elderly people. *Front Hum Neurosci.* (2021) 15:730134.
28. Guttesen LL, Albert N, Nordentoft M, Hjorthøj C. Repetitive transcranial magnetic stimulation and transcranial direct current stimulation for auditory

hallucinations in schizophrenia: systematic review and meta-analysis. *J Psychiatr Res.* (2021) 143:163–75. doi: 10.1016/j.jpsychires.2021.09.001
29. Narita Z, Stickley A, DeVylder J, Yokoi Y, Inagawa T, Yamada Y, et al. Effect of multi-session prefrontal transcranial direct current stimulation on cognition in schizophrenia: a systematic review and meta-analysis. *Schizophr Res.* (2020) 216:367–73. doi: 10.1016/j.schres.2019.11.011
30. Yu L, Fang X, Chen Y, Wang Y, Wang D, Zhang C. Efficacy of transcranial direct current stimulation in ameliorating negative symptoms and cognitive impairments in schizophrenia: a systematic review and meta-analysis. *Schizophr Res.* (2020) 224:2–10. doi: 10.1016/j.schres.2020.10.006
31. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* (2019) 366:l4898. doi: 10.1136/bmj.l4898
32. Fitzgerald PB, McQueen S, Daskalakis ZJ, Hoy KE. A negative pilot study of daily bimodal transcranial direct current stimulation in schizophrenia. *Brain Stimul.* (2014) 7:813–6. doi: 10.1016/j.brs.2014.08.002
33. Brunelin J, Mondino M, Gassab L, Haesebaert F, Gaha L, Suaud-Chagny MF, et al. Examining transcranial direct-current stimulation (tDCS) as a treatment for hallucinations in schizophrenia. *Am J Psychiatry.* (2012) 169:719–24. doi: 10.1176/appi.ajp.2012.11071091
34. Mondino M, Haesebaert F, Poulet E, Suaud-Chagny MF, Brunelin J. Fronto-temporal transcranial Direct Current Stimulation (tDCS) reduces source-monitoring deficits and auditory hallucinations in patients with schizophrenia. *Schizophr Res.* (2015) 161:515–6. doi: 10.1016/j.schres.2014.10.054
35. Mondino M, Jardri R, Suaud-Chagny MF, Saoud M, Poulet E, Brunelin J. Effects of fronto-temporal transcranial direct current stimulation on auditory verbal hallucinations and resting-state functional connectivity of the left temporo-parietal junction in patients with schizophrenia. *Schizophr Bull.* (2016) 42:318–26. doi: 10.1093/schbul/sbv114
36. Bose A, Shivakumar V, Agarwal SM, Kalmady SV, Shenoy S, Sreeraj VS, et al. Efficacy of fronto-temporal transcranial direct current stimulation for refractory auditory verbal hallucinations in schizophrenia: a randomized, double-blind, sham-controlled study. *Schizophr Res.* (2018) 195:475–80. doi: 10.1016/j.schres.2017.08.047
37. Chang CC, Tzeng NS, Chao CY, Yeh CB, Chang HA. The effects of add-on fronto-temporal transcranial direct current stimulation (tDCS) on auditory verbal hallucinations, other psychopathological symptoms, and insight in schizophrenia: a randomized, double-blind, sham-controlled trial. *Int J Neuropsychopharmacol.* (2018) 21:979–87. doi: 10.1093/ijnp/pyy074
38. Koops S, Blom JD, Bouachmir O, Slot MI, Neggers B, Sommer IE. Treating auditory hallucinations with transcranial direct current stimulation in a double-blind, randomized trial. *Schizophr Res.* (2018) 201:329–6. doi: 10.1016/j.schres.2018.06.010
39. Kantrowitz JT, Sehatpour P, Avissar M, Horga G, Gwak A, Hoptman MJ, et al. Significant improvement in treatment resistant auditory verbal hallucinations after 5 days of double-blind, randomized, sham controlled, fronto-temporal, transcranial direct current stimulation (tDCS): a replication/extension study. *Brain Stimul.* (2019) 12:981–91. doi: 10.1016/j.brs.2019.03.003
40. Fröhlich F, Burrello TN, Mellin JM, Cordle AL, Lustenberger CM, Gilmore JH, et al. Exploratory study of once-daily transcranial direct current stimulation (tDCS) as a treatment for auditory hallucinations in schizophrenia. *Eur Psychiatry.* (2016) 33:54–60. doi: 10.1016/j.eurpsy.2015.11.005
41. Lindenmayer JP, Kulsa MKC, Sultana T, Kaur A, Yang R, Ljuri I, et al. Transcranial direct-current stimulation in ultra-treatment-resistant schizophrenia. *Brain Stimul.* (2019) 12:54–61. doi: 10.1016/j.brs.2018.10.002
42. Chang CC, Kao YC, Chao CY, Chang HA. Enhancement of cognitive insight and higher-order neurocognitive function by fronto-temporal transcranial direct current stimulation (tDCS) in patients with schizophrenia. *Schizophr Res.* (2019) 208:430–8. doi: 10.1016/j.schres.2018.12.052
43. Kao YC, Tzeng NS, Chao CY, Chang CC, Chang HA. Modulation of self-appraisal of illness, medication adherence, life quality and autonomic functioning by transcranial direct current stimulation in schizophrenia patients. *Clin Neurophysiol.* (2020) 131:1997–2007. doi: 10.1016/j.clinph.2020.02.029
44. Jardri R, Pouchet A, Pins D, Thomas P. Cortical activations during auditory verbal hallucinations in schizophrenia: a coordinate-based meta-analysis. *Am J Psychiatry.* (2011) 168:73–81. doi: 10.1176/appi.ajp.2010.09101522
45. Mondino M, Fonteneau C, Simon L, Dondé C, Haesebaert F, Poulet E, et al. Advancing clinical response characterization to frontotemporal transcranial direct current stimulation with electric field distribution in patients with schizophrenia and auditory hallucinations: a pilot study. *Eur Arch Psychiatry Clin Neurosci.* (2021) 271:85–92. doi: 10.1007/s00406-020-01149-4
46. Waters F, Woodward T, Allen P, Aleman A, Sommer I. Self-recognition deficits in schizophrenia patients with auditory hallucinations: a meta-analysis of the literature. *Schizophr Bull.* (2012) 38:741–50. doi: 10.1093/schbul/sbq144
47. Bose A, Nawani H, Agarwal SM, Shivakumar V, Kalmady SV, Shenoy S, et al. Effect of fronto-temporal transcranial direct current stimulation on corollary discharge in schizophrenia: a randomized, double-blind, sham-controlled mediation analysis study. *Schizophr Res.* (2019) 204:411–2. doi: 10.1016/j.schres.2018.07.040
48. Correll CU, Schooler NR. Negative symptoms in schizophrenia: a review and clinical guide for recognition, assessment, and treatment. *Neuropsychiatr Dis Treat.* (2020) 16:519–34. doi: 10.2147/NDT.S225643
49. An Der Heiden W, Häfner H. The epidemiology of onset and course of schizophrenia. *Eur Arch Psychiatry Clin Neurosci.* (2000) 250:292–303.
50. Aleman A, Lincoln TM, Bruggeman R, Melle I, Arends J, Arango C, et al. Treatment of negative symptoms: where do we stand, and where do we go? *Schizophr Res.* (2017) 186:55–62. doi: 10.1016/j.schres.2016.05.015
51. Sanfilipo M, Lafargue T, Rusinek H, Arena L, Loneragan C, Lautin A, et al. Volumetric measure of the frontal and temporal lobe regions in schizophrenia. *Arch Gen Psychiatry.* (2000) 57:471. doi: 10.1001/archpsyc.57.5.471
52. Valiengo LDCL, Goerigk S, Gordon PC, Padberg F, Serpa MH, Koebe S, et al. Efficacy and safety of transcranial direct current stimulation for treating negative symptoms in schizophrenia: a randomized clinical trial. *JAMA Psychiatry.* (2020) 77:121–9. doi: 10.1001/jamapsychiatry.2019.3199
53. Gomes JS, Shiozawa P, Dias ÁMH, Valverde Ducos D, Akiba H, Trevizol AP, et al. Left dorsolateral prefrontal cortex anodal tDCS effects on negative symptoms in schizophrenia. *Brain Stimul.* (2015) 8:989–1. doi: 10.1016/j.brs.2015.07.033
54. Palm U, Keeser D, Hasan A, Kupka MJ, Blautzik J, Sarubin N, et al. Prefrontal transcranial direct current stimulation for treatment of schizophrenia with predominant negative symptoms: a double-blind, sham-controlled proof-of-concept study. *Schizophr Bull.* (2016) 42:1253–61. doi: 10.1093/schbul/sbw041
55. Chang CC, Kao YC, Chao CY, Tzeng NS, Chang HA. Examining bi-anodal transcranial direct current stimulation (tDCS) over bilateral dorsolateral prefrontal cortex coupled with bilateral extracephalic references as a treatment for negative symptoms in non-acute schizophrenia patients: a randomized, double. *Prog Neuro Psychopharmacol Biol Psychiatry.* (2020) 96:109715. doi: 10.1016/j.pnpbp.2019.109715
56. Dharani R, Goyal N, Mukherjee A, Umesh S. Adjuvant high-definition transcranial direct current stimulation for negative symptoms in schizophrenia: a pilot study. *J ECT.* (2021) 37:195–201. doi: 10.1097/YCT.0000000000000756
57. Chang CC, Kao YC, Chao CY, Tzeng NS, Chang HA. The effects of bi-anodal tdcs over the prefrontal cortex regions with extracephalic reference placement on insight levels and cardio-respiratory and autonomic functions in schizophrenia patients and exploratory biomarker analyses for treatment response. *Int J Neuropsychopharmacol.* (2021) 24:40–53. doi: 10.1093/ijnp/pyaa063
58. Bulubas L, Goerigk S, Gomes JS, Brem A-K, Carvalho JB, Pinto BS, et al. Cognitive outcomes after tDCS in schizophrenia patients with prominent negative symptoms: results from the placebo-controlled STARTS trial. *Schizophr Res.* (2021) 235:44–51. doi: 10.1016/j.schres.2021.07.008
59. Bozikas VP, Giannakou M, Kosmidis MH, Kargopoulos P, Kioseoglou G, Liolios D, et al. Insights into theory of mind in schizophrenia: the impact of cognitive impairment. *Schizophr Res.* (2011) 130:130–6. doi: 10.1016/j.schres.2011.04.025
60. Keefe RSE, Harvey PD. Novel antischizophrenia treatments – cognitive impairment in schizophrenia. *Handb Exp Pharmacol.* (2012) 213:11–37. doi: 10.1007/978-3-642-25758-2
61. Fioravanti M, Bianchi V, Cinti ME. Cognitive deficits in schizophrenia: an updated metanalysis of the scientific evidence. *BMC Psychiatry.* (2012) 12:64. doi: 10.1186/1471-244X-12-64
62. Orlov ND, Tracy DK, Joyce D, Patel S, Rodzinka-Pasko J, Dolan H, et al. Stimulating cognition in schizophrenia: a controlled pilot study of the effects of

prefrontal transcranial direct current stimulation upon memory and learning. *Brain Stimul.* (2017) 10:560–6. doi: 10.1016/j.brs.2016.12.013
63. Schilling TM, Bossert M, König M, Wirtz G, Weisbrod M, Aschenbrenner S. Acute effects of a single dose of 2 mA of anodal transcranial direct current stimulation over the left dorsolateral prefrontal cortex on executive functions in patients with schizophrenia-a randomized controlled trial. *PLoS One.* (2021) 16:e0254695. doi: 10.1371/journal.pone.0254695
64. Nienow TM, MacDonald AW, Lim KO. TDCS produces incremental gain when combined with working memory training in patients with schizophrenia: a proof of concept pilot study. *Schizophr Res.* (2016) 172:218–9. doi: 10.1016/j.schres.2016.01.053
65. Smith RC, Md WL, Wang Y, Jiang J, Wang JJ, Szabo V, et al. Effects of transcranial direct current stimulation on cognition and symptoms in Chinese patients with schizophrenia*. *Psychiatry Res.* (2020) 284:112617. doi: 10.1016/j.psychres.2019.112617
66. Smith RC, Boules S, Mattiuz S, Youssef M, Tobe RH, Sershen H, et al. Effects of transcranial direct current stimulation (tDCS) on cognition, symptoms, and smoking in schizophrenia: a randomized controlled study. *Schizophr Res.* (2015) 168:260–6. doi: 10.1016/j.schres.2015.06.011
67. Gögler N, Papazova I, Oviedo-Salcedo T, Filipova N, Strube W, Funk J, et al. Parameter-based evaluation of attentional impairments in schizophrenia and their modulation by prefrontal transcranial direct current stimulation. *Front Psychiatry.* (2017) 8:259. doi: 10.3389/fpsyt.2017.00259
68. Jeon DW, Jung DU, Kim SJ, Shim JC, Moon JJ, Seo YS, et al. Adjunct transcranial direct current stimulation improves cognitive function in patients with schizophrenia: a double-blind 12-week study. *Schizophr Res.* (2018) 197:378–85. doi: 10.1016/j.schres.2017.12.009
69. Gomes JS, Trevizol AP, Ducos DV, Gadelha A, Ortiz BB, Fonseca AO, et al. Effects of transcranial direct current stimulation on working memory and negative symptoms in schizophrenia: a phase II randomized sham-controlled trial. *Schizophr Res Cogn.* (2018) 12:20–8. doi: 10.1016/j.scog.2018.02.003
70. Shiozawa P, Gomes JS, Ducos DV, Akiba HT, Dias ÁM, Trevizol AP, et al. Efeito da estimulação transcraniana por corrente contínua (ETCC) sobre o córtex pré-frontal combinada a treinamento cognitivo para o tratamento da esquizofrenia: ensaio clínico randomizado simulação controlado. *Trends Psychiatry Psychother.* (2016) 38:175–7.
71. Meiron O, David J, Yaniv A. Left prefrontal transcranial direct-current stimulation reduces symptom-severity and acutely enhances working memory in schizophrenia. *Neurosci Lett.* (2021) 755:135912. doi: 10.1016/j.neulet.2021.135912
72. Rassovsky Y, Dunn W, Wynn J, Wu AD, Iacoboni M, Hellemann G, et al. The effect of transcranial direct current stimulation on social cognition in schizophrenia: a preliminary study. *Schizophr Res.* (2015) 165:171–4. doi: 10.1016/j.schres.2015.04.016
73. Orlov ND, O'Daly O, Tracy DK, Daniju Y, Hodsoll J, Valdearenas L, et al. Stimulating thought: a functional MRI study of transcranial direct current stimulation in schizophrenia. *Brain.* (2017) 140:2490–7. doi: 10.1093/brain/awx170
74. Weickert TW, Salimuddin H, Lenroot RK, Bruggemann J, Loo C, Vercammen A, et al. Preliminary findings of four-week, task-based anodal prefrontal cortex transcranial direct current stimulation transferring to other cognitive improvements in schizophrenia. *Psychiatry Res.* (2019) 280:112487. doi: 10.1016/j.psychres.2019.112487
75. Bikson M, Grossman P, Thomas C, Louis A, Jiang J, Adnan T, et al. Brain stimulation safety of transcranial direct current stimulation: evidence based update 2016. *Brain Stimul.* (2016) 9:641–1. doi: 10.1016/j.brs.2016.06.004
76. Matsumoto H, Ugawa Y. Adverse events of tDCS and tACS: a review. *Clin Neurophysiol Pract.* (2017) 2:19–25. doi: 10.1016/j.cnp.2016.12.003
77. Anticevic A, Hu X, Xiao Y, Hu J, Li F, Bi F, et al. Early-course unmedicated schizophrenia patients exhibit elevated prefrontal connectivity associated with longitudinal change. *J Neurosci.* (2015) 35:267–86. doi: 10.1523/JNEUROSCI.2310-14.2015
78. De Witte S, Klooster D, Dedoncker J, Duprat R, Remue J, Baeken C. Left prefrontal neuronavigated electrode localization in tDCS: 10–20 EEG system versus MRI-guided neuronavigation. *Psychiatry Res Neuroimaging.* (2018) 274:1–6. doi: 10.1016/j.pscychresns.2018.02.001
79. Vignaud P, Mondino M, Poulet E, Palm U, Brunelin J. Duration but not intensity influences transcranial direct current stimulation (tDCS) after-effects on cortical excitability. *Neurophysiol Clin.* (2018) 48:89–92. doi: 10.1016/j.neucli.2018.02.001
80. Hassanzahraee M, Nitsche MA, Zoghi M, Jaberzadeh S. Determination of anodal tDCS duration threshold for reversal of corticospinal excitability: an investigation for induction of counter-regulatory mechanisms. *Brain Stimul.* (2020) 13:832–9. doi: 10.1016/j.brs.2020.02.027
81. Goldsworthy MR, Pitcher JB, Ridding MC. Spaced noninvasive brain stimulation. *Neurorehabil Neural Repair.* (2015) 29:714–21. doi: 10.1177/1545968314562649
82. Monte-Silva K, Kuo MF, Liebetanz D, Paulus W, Nitsche MA. Shaping the optimal repetition interval for cathodal transcranial direct current stimulation (tDCS). *J Neurophysiol.* (2010) 103:1735–40. doi: 10.1152/jn.00924.2009
83. Agboada D, Mosayebi-Samani M, Kuo MF, Nitsche MA. Induction of long-term potentiation-like plasticity in the primary motor cortex with repeated anodal transcranial direct current stimulation – Better effects with intensified protocols? *Brain Stimul.* (2020) 13:987–7. doi: 10.1016/j.brs.2020.04.009
84. Monte-Silva K, Kuo MF, Hessenthaler S, Fresnoza S, Liebetanz D, Paulus W, et al. Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. *Brain Stimul.* (2013) 6:424–32. doi: 10.1016/j.brs.2012.04.011
85. Bystad M, Storø B, Gundersen N, Wiik IL, Nordvang L, Grønli O, et al. Can accelerated transcranial direct current stimulation improve memory functions? An experimental, placebo-controlled study. *Heliyon.* (2020) 6:0–6. doi: 10.1016/j.heliyon.2020.e05132
86. Mondino M, Poulet E, Brunelin J. Moving to accelerated protocols of tDCS in schizophrenia: a case report. *Brain Stimul.* (2021) 14:822–4. doi: 10.1016/j.brs.2021.05.006
87. Cahill L. Why sex matters for neuroscience. *Nat Rev Neurosci.* (2006) 7:477–84. doi: 10.1038/nrn1909
88. Rudroff T, Workman CD, Fietsam AC, Kamholz J. Response variability in transcranial direct current stimulation: why sex matters. *Front Psychiatry.* (2020) 11:19–22. doi: 10.3389/fpsyt.2020.00585
89. Adenzato M, Brambilla M, Manent R, De Lucia L, Trojano L, Garofalo S, et al. Gender differences in cognitive theory of mind revealed by transcranial direct current stimulation on medial prefrontal cortex. *Sci Rep.* (2017) 7:41219. doi: 10.1038/srep41219
90. Fehring DJ, Samandra R, Haque ZZ, Jaberzadeh S, Rosa M, Mansouri FA. Investigating the sex – dependent effects of prefrontal cortex stimulation on response execution and inhibition. *Biol Sex Differ.* (2021) 12:47. doi: 10.1186/s13293-021-00390-3
91. Bhattacharjee S, Kashyap R, Goodwill AM, Brien BAO, Rapp B, Oishi K, et al. Brain stimulation sex difference in tDCS current mediated by changes in cortical anatomy: a study across young, middle and older adults. *Brain Stimul.* (2022) 15:125–40. doi: 10.1016/j.brs.2021.11.018

Conflict of Interest: ZS was employed by the company Hospital České Budějovice, a.s.

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

frontiers | Frontiers in Psychiatry

REVIEW
published: 18 May 2022
doi: 10.3389/fpsyt.2022.874137

The Development of GABAergic Network in Depression in Recent 17 Years: A Visual Analysis Based on CiteSpace and VOSviewer

Jieping Lin[1], *Fa Ling*[1], *Ping Huang*[2], *Min Chen*[3], *Min Song*[4], *Kangrong Lu*[5*] and *Wanshan Wang*[2,6*]

[1] Nanfang Hospital, Southern Medical University, Guangzhou, China, [2] Laboratory Animal Management Center, Southern Medical University, Guangzhou, China, [3] College of Medical Examination and Biotechnology, Southern Medical University, Guangzhou, China, [4] Southern Medical University Library, Guangzhou, China, [5] NMPA Key Laboratory for Safety Evaluation of Cosmetics, Southern Medical University, Guangzhou, China, [6] Guangzhou Southern Medical Laboratory Animal Sci. and Tech. Co., Ltd., Guangzhou, China

In this study, we analyzed the status and research trends of the GABAergic system in depression from 2004 to 2020 to provide a reference for further research. The Web of Science database was used as the data source and 1,658 publishments were included. Using two visualization analysis software, CiteSpace and VOSviewer, we analyzed the publishing years, countries, institutions, authors, journals, categories, keywords, and research frontiers in depression. The publishments revealed an upward trend from 2004 to 2020; the most prolific country and institutions were the United States and INSERM, respectively. The journal of Neuroscience was the most published and cited journal. The most relevant category was neurosciences. The hot topics in this field were GABAergic research in Gaba(a) receptor; the research frontier was depressive model. These analysis results provide a new perspective for researchers to conduct studies on related topics in the future and guidance for scientists to identify potential collaborators and research cooperation institutions.

Keywords: GABAergic, depression, CiteSpace, visualization analysis, VOSviewer

OPEN ACCESS

Edited by:
Mirko Manchia,
University of Cagliari, Italy

Reviewed by:
Andy Wai Kan Yeung,
University of Hong Kong, China
Qun Li,
University of Szeged, Hungary

***Correspondence:**
Kangrong Lu
261267443@qq.com
Wanshan Wang
wws@smu.edu.cn

Specialty section:
This article was submitted to Mood Disorders, a section of the journal Frontiers in Psychiatry

Received: *11 February 2022*
Accepted: *27 April 2022*
Published: *18 May 2022*

Citation:
Lin JP, Ling F, Huang P, Chen M, Song M, Lu KR and Wang WS (2022) The Development of GABAergic Network in Depression in Recent 17 Years: A Visual Analysis Based on CiteSpace and VOSviewer. Front. Psychiatry 13:874137. doi: 10.3389/fpsyt.2022.874137

INTRODUCTION

Depression is one of the most common mental disorders, characterized by persistent depression and lack of pleasure. It includes anxiety, sleep disorders, lack of interest, hopelessness and helplessness, decreased attention, and suicidal thoughts. Worldwide, more than 350 million people are affected by depression. From 2005 to 2015, the number of patients with depression increased by 18%, making it one of the most common diseases globally (1). In 2015, the World Health Organization ranked depression as the most significant single factor for global disability, with two-thirds of suicides occurring due to depression. However, due to stigma, lack of effective treatment and insufficient mental health resources, depression is generally not diagnosed and treated (2). Depression is also difficult to treat because of phenotypic diversity and etiological heterogeneity (3). Depression is caused by several factors, including genetic and environmental factors. The underlying neurobiological determinants of depression remain unclear despite the efforts in exploring its pathophysiological mechanisms. First- and second-generation antidepressants are mainly based on the monoamine hypothesis. First-generation antidepressants include monoamine oxidase inhibitor (MAOI) and tricyclic drug (TCA), which inhibit the oxidation of monoamine

and increase the extracellular concentration of 5-hydroxytryptamine (5-HT), dopamine (DA), and noradrenaline (NE) (4–6). Second-generation antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), can increase 5-HT concentrations in the whole brain. At present, monoaminergic drugs, especially SSRIs, are recommended as the first-line therapy at home and abroad. However, monoamine drugs take weeks and months to produce a treatment response, and one-third of patients develop treatment resistance (7).

Considering the relatively low efficacy of monoamine drugs, new drugs with higher efficacy must be developed to resolve the current treatment limitations. Studies have reported the role of the GABAergic system in the pathogenesis of depression, antidepressants, anxiety, and schizophrenia. In 2011, Luscher proposed the GABAergic deficit hypothesis (8), which indicated an association among depressive symptoms, the gamma-aminobutyric acid (GABA) system, and GABA receptor deficiency (9). Stress regulation is based on GABAergic transmission, and chronic stress is the most critical vulnerability factor of major depressive disorder (MDD) (10). Mental pressure can also result in the loss of GABA function, caused by the change of reversal potential due to a decrease in the transmembrane KCl anion cotransporter function (11). However, so far, different neuropsychiatric diseases could not be distinguished by mutations or functional polymorphisms of genes closely related to GABAergic transmission, which must be further explored.

GABA is a crucial inhibitory neurotransmitter of the central nervous system (CNS). GABAergic neurons are located in the hippocampus (HPC), thalamus, basal ganglia, hypothalamus, and brainstem. GABA is synthesized by glutamate decarboxylases (GAD65 and GAD67) in the cytoplasm of presynaptic neurons. After synthesis, GABA is loaded into synaptic vesicles through vesicular inhibitory amino acid transporters (VGAT1 and VGAT2). The SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) complex helps to couple the vesicles to the plasma membrane of the cell. When the action potential reaches the presynaptic cell, the voltage-gated calcium channel opens, and calcium binds to a synaptic binding protein, fusing vesicles and plasma membrane and releasing GABA into the synaptic gap bind with the GABA receptor. GABA can then be degraded or transported back to glial or presynaptic cells. GABA is degraded into succinic semialdehyde by GABA transaminase and enters the citric acid cycle (12, 13).

Early pioneering studies have revealed that patients with depression have lower plasma and cerebrospinal fluid GABA levels (14–16). The introduction of magnetic resonance spectroscopy (MRS) can directly and non-invasively measure GABA levels in the brain. Studies have indicated that GABA levels in the prefrontal cortex (PFC), anterior cingulate cortex, and occipital lobe are decreased in patients with MDD (17–20). This is the most substantial evidence that GABA deficiency may cause depression. Gabbay et al. concluded that the therapeutic effect of SSRIs may involve a GABAergic mechanism (21). Additionally, SSRIs increase GABA levels in the brain by stimulating the 5-HT2B receptor of astrocytes (22). Transcranial magnetic stimulation (TMS) can regulate cortical GABAergic and glutamatergic imbalance. TMS has been widely used in adult clinical treatment and is highly considered an experimental treatment for depression in adolescents who do not respond to conventional treatments, such as cognitive behavioral therapy and SSRIs. However, unknown factors related to neurodevelopment and TMS exposure in adolescents must be considered (23).

With the development of research, the GABAergic system plays an increasingly crucial role in depression. In this study, we discussed the research status, hot spots, and development trend of the GABAergic system in the field of depression through the visual analysis of literature data by CiteSpace to provide a reference for research in related areas in the future.

MATERIALS AND METHODS

Data Acquisition

Data for GABAergic and depression analysis were collected from the Web of Science Core Collection (WoSCC), including SCI-Expanded, one of the most influential scientific literature databases, on 1 August 2021. The retrieval strategy in WoSCC is [(TS = (gabaergic) OR TS = (GABAergic)] AND TS = (depression) AND DT = (Article OR Review) AND Timespan: 2004-01-01–2020-12-31. The search produced 1,658 records, and only the original articles and reviews were included (**Figure 1**). All the retrieved publishments were exported in plain text format.

Statistical Analysis

Origin is a scientific drawing and data analysis software developed by the OriginLab company. In the current study, we drew charts using Origing 2018 to display trends between publishments and year intuitively.

CiteSpace is a visualization software for creating scientific knowledge maps. CiteSpace draws the knowledge map of related fields, directly displays the information panorama of a certain knowledge field, identifies imperative literature, hot research, and Frontier direction of a certain scientific field through diversified and dynamic network analysis (24). Node centrality is an index to quantify the importance of nodes in the network; higher centrality indicates more contacts in the network that must pass through the node, indicating its vital role in communicating with other nodes and acting as a bridge. As the representative of core words with high frequency in papers, a keyword embodies crucial information. The module value (Q value) and average contour value (S value) are calculated according to the network structure and clustering clarity in the keyword clustering network. $Q > 0.3$ indicates significant clustering structure, $S > 0.5$ indicates reasonable clustering, and $S > 0.7$ indicates reliable clustering. In addition, the variant words of a topic in the future are a sign of the sudden growth of hot spots in the field and a valuable measure of the future development trend of the topic. The mutation value represents the mutation size; the larger the variation value, the more obvious the developmental trend of topics related to variation words. Using the bibliometric research method, we used the CiteSpace 5.8.R3 software to discuss the years, countries, institutions, journals, categories, keywords and hotspot from 2004 to 2020 (**Figure 1**). We set the threshold value as slice length = 1, selection criteria select Top50, respectively select "country,"

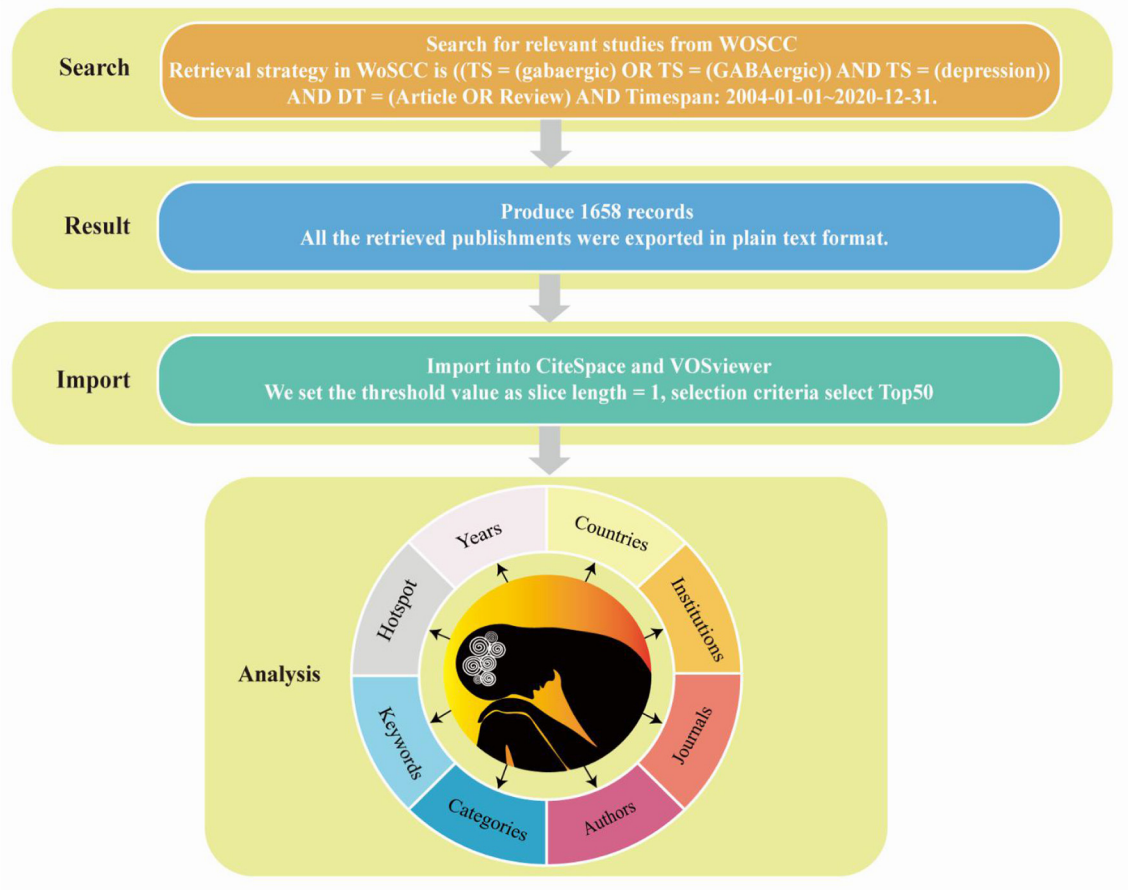


FIGURE 1 | Flow chart of retrieving publishments from Web of Science Core Collection, obtaining publishments and importing them into CiteSpace and VOSviewer for analysis.

"institution," "keyword," "category," four nodes to explore the author, country, institution and keywords of publishments, and selected "cited author," and "cited journal" three nodes to explore the co-citation of papers.

VOSviewer is a bibliometric analysis software, which is easy to operate and presents a more concise diagram than CiteSpace. The results were shown in two forms, namely, general view and thermal diagram. This paper used it to analyse countries, institutions and keywords.

RESULTS

Research Trends of the GABAergic System and Depression

The number and changes of published papers in a certain period are important indicators to measure the research status in related fields. **Figure 2A** showed the number of publishments related to GABAergic system and depression over the years. From 2004 to 2020, the overall number of publishments showed an upward trend, indicating that the research had attracted more attention. Before 2015, the number of publishments increased year by year. From 2016 to 2018, the number of publishments decreased and fluctuated slightly compared with 2015. In the past 3 years, the publishing volume had increased rapidly. By 2020, the number of publishments had doubled from 2004.

Visual Analysis of Countries and Institutions

Among the papers published in the research field of depression and GABAergic system, the United States had the largest number, with 680 (41%), which was much higher than that of other countries (**Figure 2B**). China, Germany, Japan and Italy ranked second to fifth. In the visual density map, the area and brightness of the United States were also much higher than those of other countries (**Figure 2C**). The visual density map was made by VOSviewer. In **Figure 2C**, if the density of countries and institutions was smaller, the color of nodes was closer to blue; if the density of countries or institutions was bigger, the color of nodes was closer to yellow, indicating the closer relationship between countries or institutions.

A total of 1,469 institutions participated in the issuance of papers, of which 6 institutions issued more than 2%. The

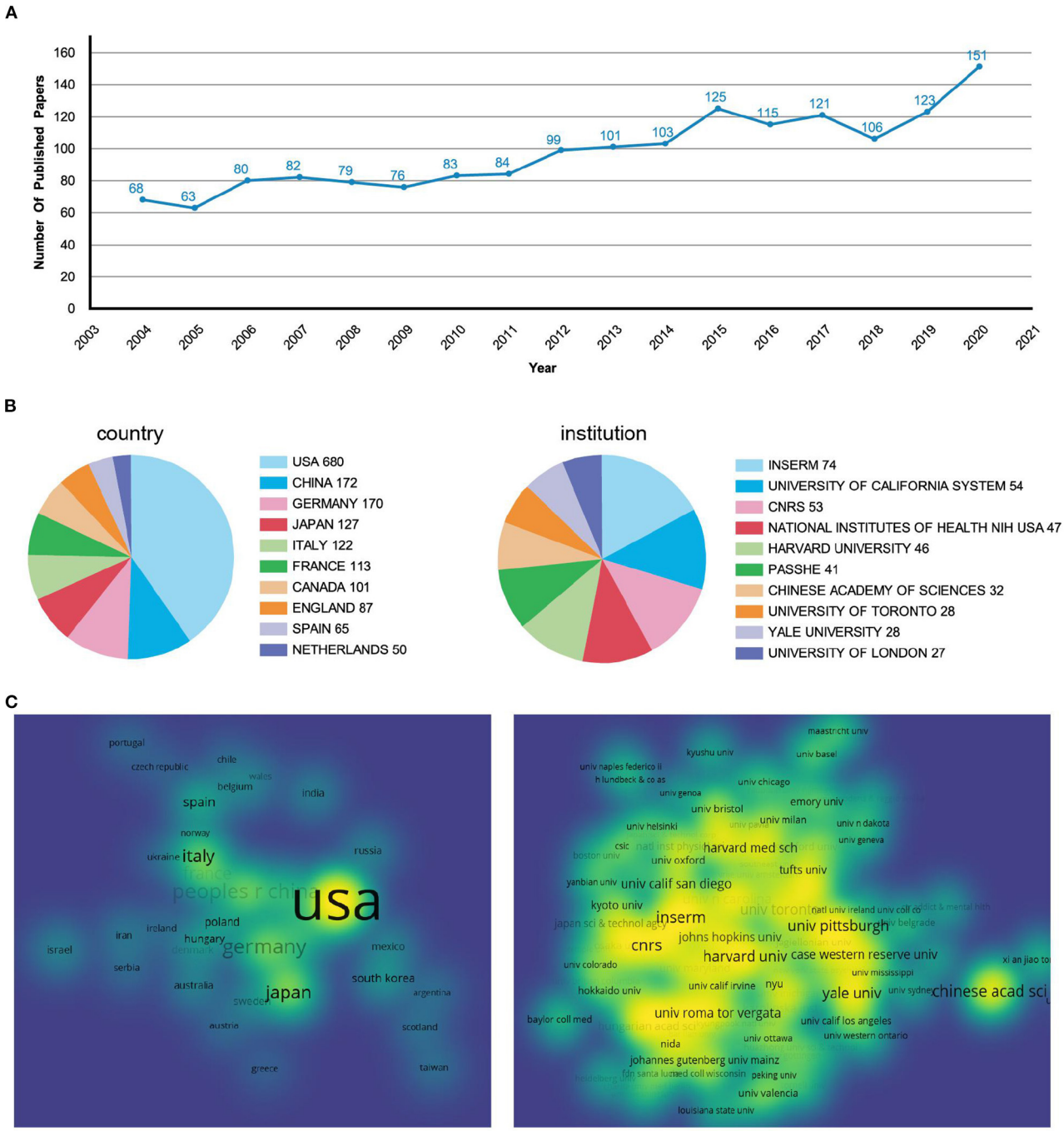
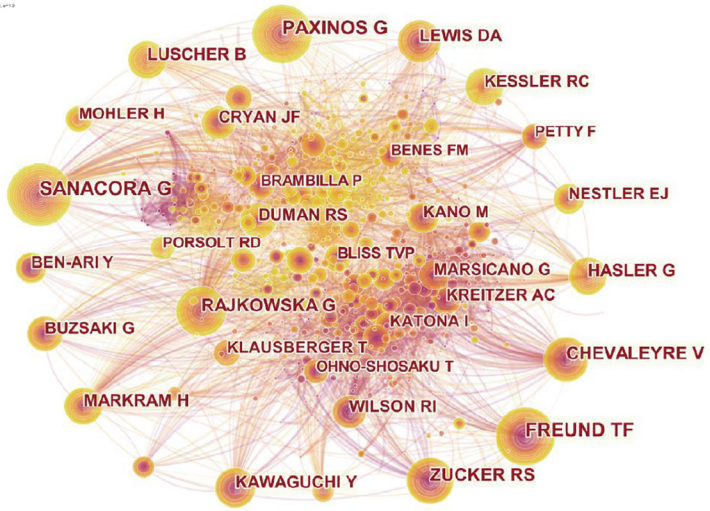


FIGURE 2 | Analysis of the annual publishments, countries, and institutions. **(A)** Line graphs of papers published every year from 2004 to 2020. **(B)** Pie chart of publishment issued by countries and institutions. **(C)** The density visualization of countries and institutions.

institution with the highest number of articles was Institut National de la Sant é et de la recherche médicale (INSERM), which had published 74 articles (4.5%) (**Figure 2B**). INSERM, founded in 1964, is the only public research organization fully committed to human health in France (https://www.inserm.fr/). Although France was not among the top five countries with the largest number of publishments, the institution with the largest number of publishments was in France. In the visual density map, its color was yellow and its area was large, indicating that it had carried out close cooperation with the world's top research institutions in the past 17 years (**Figure 2C**).

A



B

Top 25 Cited Authors with the Strongest Citation Bursts

Cited Authors	Year	Strength	Begin	End	2004 - 2020
GERDEMAN GL	2004	11.23	2004	2010	
CALABRESI P	2004	9.89	2004	2011	
KREITZER AC	2004	9.56	2004	2011	
JONES MV	2004	9.31	2004	2006	
ROBBE D	2004	8.69	2004	2011	
PIOMELLI D	2004	8.21	2004	2008	
SJOSTROM PJ	2004	7.28	2008	2012	
MARSICANO G	2004	8.04	2010	2015	
HEIFETS BD	2004	7.69	2010	2012	
KRISHNAN V	2004	8.39	2011	2014	
LUSCHER B	2004	8.55	2012	2020	
GONZALEZ-BURGOS G	2004	8.73	2015	2018	
LEVINSON AJ	2004	7.1	2015	2017	
LI B	2004	9.62	2016	2020	
PORSOLT RD	2004	8.22	2016	2020	
WILLNER P	2004	8.01	2016	2020	
CROARKIN PE	2004	7.03	2016	2017	
DUMAN RS	2004	9.7	2017	2020	
CZEH B	2004	7.94	2017	2020	
KESSLER RC	2004	7.73	2017	2020	
LECCA S	2004	7.41	2017	2020	
MA K	2004	7.41	2017	2020	
YANG Y	2004	11.17	2018	2020	
ZARATE CA	2004	7.83	2018	2020	
BERMAN RM	2004	7.55	2018	2020	

FIGURE 3 | The analysis of cited-authors. **(A)** Visualization of cited authors. **(B)** The top cited authors with the strongest citation bursts.

Analysis of Co-authors

Through the co-analysis of authors by CiteSpace, we can show the core authors in a discipline or research field and their cooperation intensity and mutual citation relationship. From 2004 to 2020, the map (**Figure 3A**) had 866 nodes and 5,249 connections, and the network density was 0.014. It can be seen from the map that Sanacora G, Paxinos G and Freund TF appeared the most frequently, indicating that their papers was cited more and played an important role in this field.

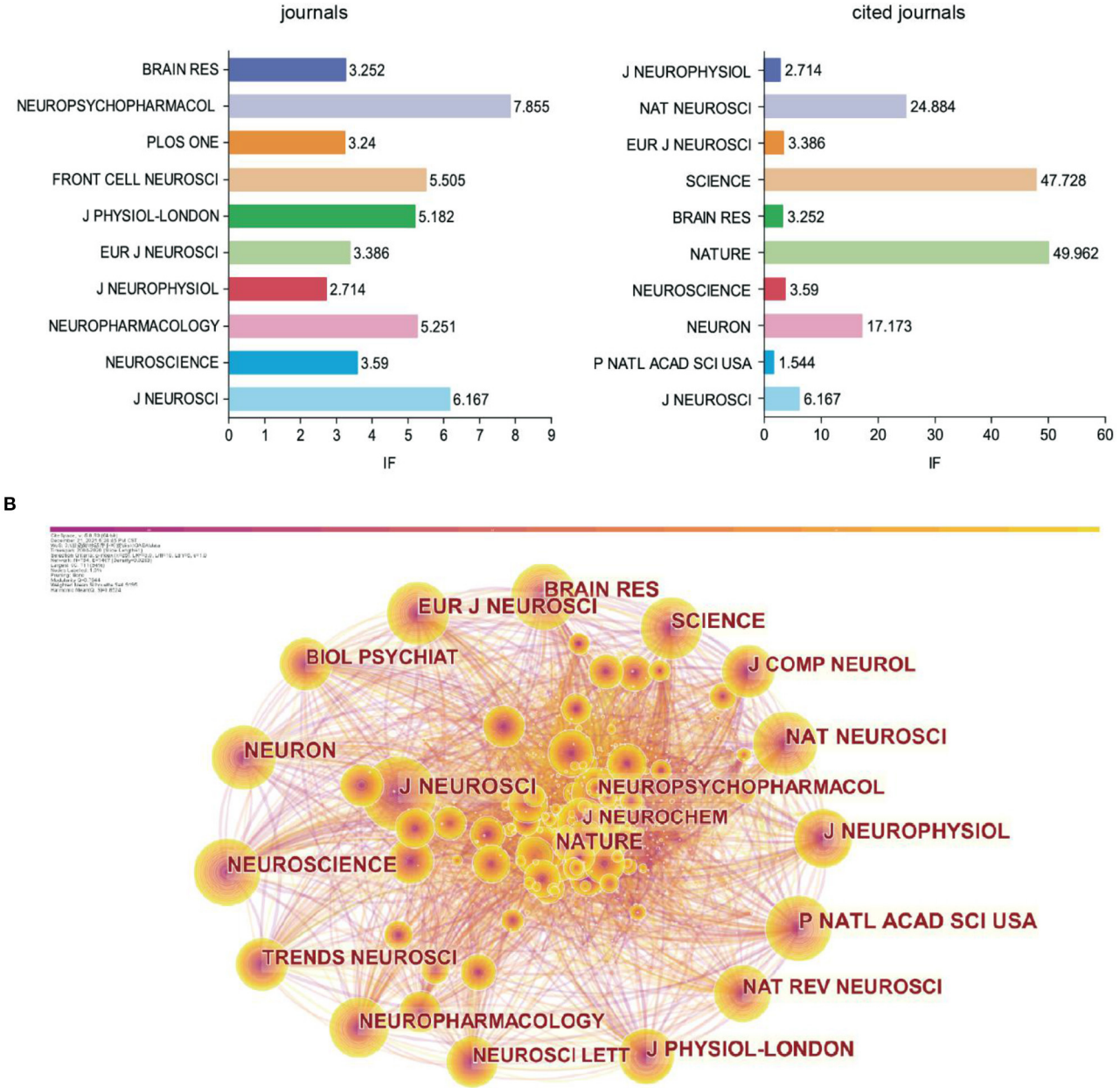


FIGURE 4 | The analysis of cited-journal. **(A)** Bar chart of journals and cited journals and its IF. **(B)** Visualization of cited journals.

Among the strongest citation bursts of the top 25 cited authors from 2004 to 2005, Luscher was the author with the longest duration, from 2012 to 2020, indicating that his articles had a great impact after publishment (**Figure 3B**). The red bars indicated keywords cited frequently; the green bars indicated keywords cited infrequently.

Analysis of Journals and Cited Journals

The 1,659 publishments involved 97 journals. The top 10 journals with published articles and the top 10 journals with cited times were shown in **Figure 4A**. The Journal of Neuroscience was ranked first, followed by Neuroscience, Neuropharmacology, Journal of Neurophysiology, and European Journal of Neuroscience. For all the top 10 journals with published articles, the impact factor (IF) was <10. The IF was acquired from Clarivate Analytics' Journal Citation Reports.

The IF of co-cited journals was generally higher than that of published journals. In addition, the Journal of Neuroscience ranked first among the co-cited journals. The Journal of Neuroscience had the largest node in the visual map (**Figure 4B**).

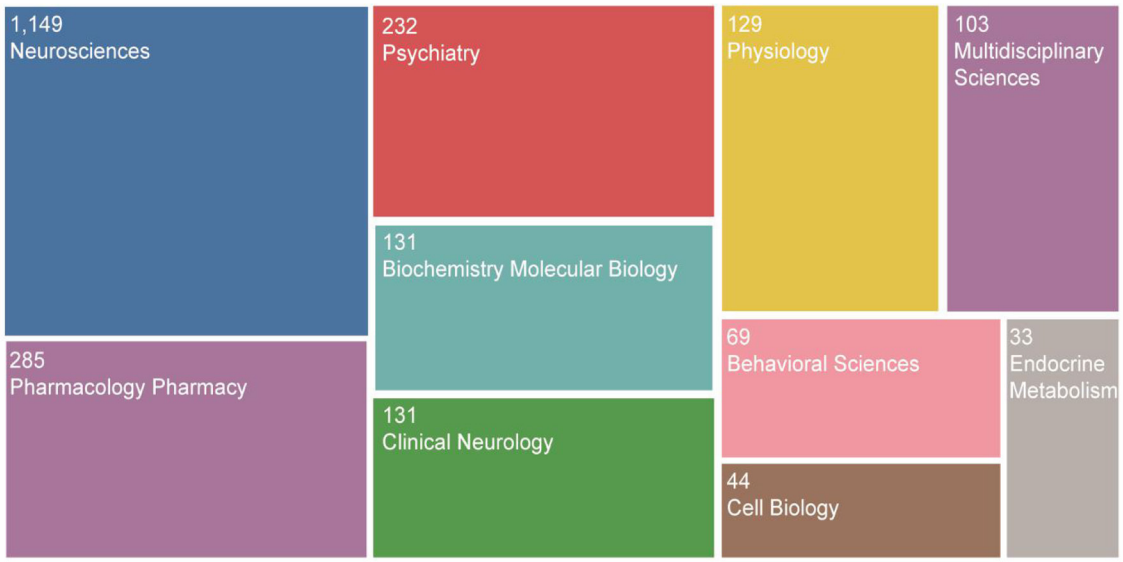


FIGURE 5 | The top 10 categories.

Combining the findings presented in **Figure 4A**, we confirmed that the Journal of Neuroscience was the core journal with the most relevant papers, indicating its comprehensive strength and influence over the other journals in GABAergic research of depression.

Analysis of Categories

GABAergic research in depression primarily involved the field of Neuroscience and Pharmacology, Psychiatry, Biochemistry Molecular Biology and Clinical Neurology. The top 10 categories were shown in **Figure 5**. In addition, it also involved the multidisciplinary science and endocrine metabolism of depression, indicating that its research and application in these two directions had further exploration value.

TABLE 1 | The top 10 centrality of keyword.

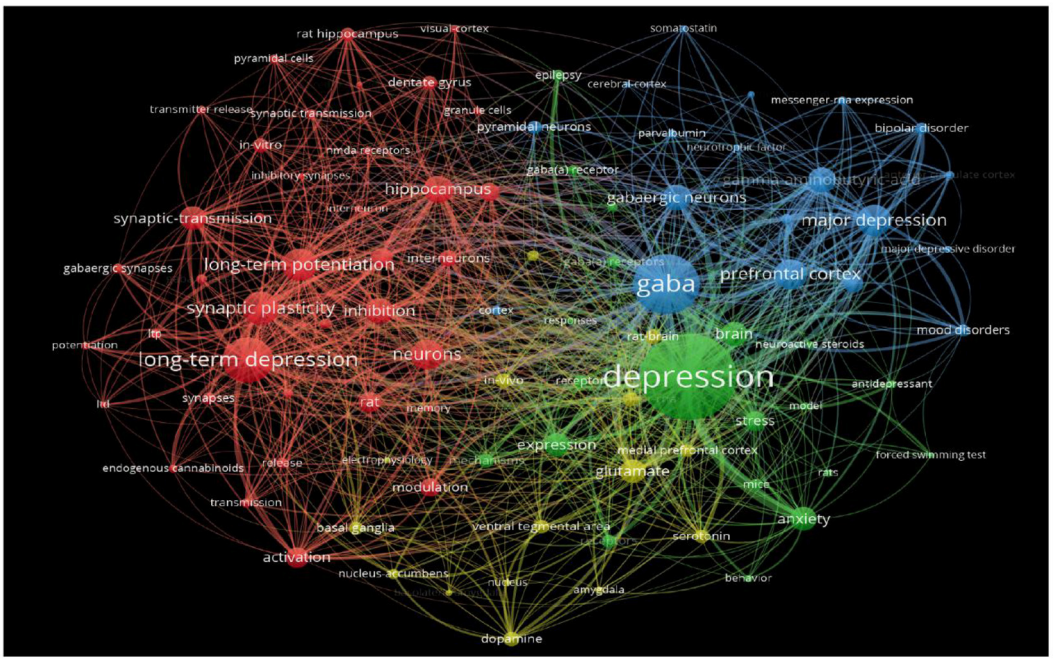
Rank	Keyword	Centrality	Number
1	Gaba(a) receptor	0.10	103
2	Hippocampus	0.07	135
3	Synapse	0.07	77
4	Central nervous system	0.07	57
5	Cerebral cortex	0.07	35
6	Rat	0.06	142
7	Receptor	0.06	127
8	GABAergic neuron	0.06	104
9	Serotonin	0.06	62
10	Dentate gyrus	0.06	59

Analysis of Keywords

Statistics revealed 491 keywords in the papers related to the GABAergic system of depression from 2004 to 2020. As shown in **Table 1**, the top 10 keywords with the highest centrality ranking were more than 0.05, but only one keyword had strong centrality (>0.1). The crucial central node was the "GABA(a) receptor," indicating that the research of GABAergic system in depression mainly focuses on GABA(a) receptor. The primary keywords in the literature related to the study of the GABAergic system of visual depression were shown in **Figure 6A**. The node size indicated the frequency of referencing keywords; the higher the frequency, the larger the corresponding node. The visualization map divided the keywords into three categories: red for related mechanisms, blue for drug research, and green for clinical research.

At present, the rodent model of depression is more mature, and relevant research is also more extensive. The application of the depression model in non-human primates, which are closely related to human beings, is still under exploration, and primates have a better simulation effect than rodents (25). Some chronic stress models model depressive behaviors in rodents, such as chronic restraint stress, chronic unpredictable stress (CUS), and chronic social frustration stress (CSDS) (26). Chronic unpredictable mild stress (CUMS) is a widely accepted model to induce depression-like behavior in rodents (27). In the brain, chronic stress changes the function of neurotransmitters and appropriate neuroplasticity, resulting in human depression (28). Therefore, this is widely used by researchers as a depression model in rodents. The CUMS model summarizes several core behavioral characteristics of human depression. In addition to depression, the cumulative effect of CUMS may result in transient overload *in vivo*, and it may lead to systemic diseases, such as atrophy of neurons in the HPC and PFC, myocardial ischaemia, abnormal liver metabolism, and poor renal prognosis (29).

A



B

Top 25 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	2004 - 2020
transmitter release	2004	9.07	**2004**	2010	
in vitro	2004	7.53	**2004**	2008	
endogenous cannabinoid	2004	5.59	**2004**	2006	
response	2004	4.84	**2004**	2006	
neurotransmitter release	2004	4.73	**2004**	2005	
calcium channel	2004	4.7	**2004**	2008	
synapse	2004	4.64	**2004**	2009	
long-term potentiation	2004	6.71	**2005**	2008	
presynaptic inhibition	2004	5.56	**2005**	2007	
gaba(a) receptor	2004	6.71	**2006**	2007	
ltp	2004	4.94	**2006**	2008	
spinal cord	2004	5.13	**2007**	2008	
in vivo	2004	6.52	**2009**	2011	
neurotrophic factor	2004	5.15	**2010**	2014	
nitric oxide	2004	4.89	**2010**	2012	
neuron	2004	5.18	**2011**	2012	
dorsolateral prefrontal cortex	2004	5.65	**2013**	2016	
magnetic resonance spectroscopy	2004	5.34	**2013**	2017	
neuroactive steroid	2004	4.69	**2013**	2014	
synapticplasticity	2004	5.89	**2015**	2020	
model	2004	9.63	**2017**	2020	
mice	2004	6.83	**2017**	2018	
system	2004	6.17	**2017**	2020	
mouse model	2004	5.82	**2017**	2020	
oxidative stress	2004	5.03	**2018**	2020	

FIGURE 6 | The analysis of keywords. **(A)** Visualization of keywords. **(B)** The top 25 keywords with the strongest citation bursts.

Astrocytes are a central target for identifying newer and more effective treatments for depression.

Hot Research Analysis

Figure 6B showed the top 10 keywords, of which the keyword with the most robust citation bursts was "transmitter release," and the duration was from 2004 to 2010. The current research Frontier trends were "synaptic plasticity," "MRS," "pyramidal neurons."

Synaptic plasticity was the research Frontier in this field. Decreased synaptic plasticity and altered excitatory or inhibitory balance were considered potential mechanisms of depression to study the effect of GABA on synaptic plasticity, especially in the PFC (30). The role of astrocytes in regulating neuronal activity and plasticity suggests that astrocytes are the central target of new and more effective treatments for depression. In addition, it also proves the importance of developing future treatment strategies using cell type specific drug delivery. In addition, NMDA receptor (NMDAR) was a unique ionic glutamate receptor that played a vital role in neural plasticity. The decline of plasticity caused by the deterioration of the NMDAR function results in learning and memory impairment. Learning and memory dysfunction in severe depression was related to the deterioration of the NMDAR function. Blocking NMDAR in a depression-like state can lead to improvement or remission of symptoms (31).

DISCUSSION

Summary of Findings

Using CiteSpace and VOSviewer, we analyzed the publishing years, countries, institutions, authors, journals, categories, keywords, and research frontiers in depression. The publishments revealed an upward trend from 2004 to 2020; the most prolific country and institutions were the United States and INSERM, respectively. The Journal of Neuroscience was the most published and cited journal. The most relevant category was neurosciences. The hot topics in this field were GABAergic research in Gaba(a) receptor; the research frontier was depressive model.

There were two reasons for the rapid growth in the publishments on GABA in depression in the past 3 years. First, it was inseparable from the policies of various countries. According to the survey statistics of the World Health Organization, from 2017 to 2020, the proportion of countries in which the treatment of patients with specific mental health conditions (psychosis, bipolar disorder and depression) was included in the national health insurance or reimbursement plan increased from 73% in 2017 to 80% in 2020 (32).

Another major reason affecting the publishment volume was that the outbreak of coronavirus at the end of 2019 and the epidemic by 2020 had affected individual mental health, including patients, individuals contacting patients and medical personnel, and worsened many determinants of mental health through direct psychological effects and long-term economic and social consequences (33–35). In the first year of the COVID-19 pandemic, global prevalence of anxiety and depression increased by a massive 25%, according to a scientific brief released by the World Health Organization (WHO) (36). A systematic review was published in the Lancet, collecting data on mental illness patients from various countries and regions in the world from January 2020 to January 2021 and compared the prevalence of depression and anxiety before and after COVID-19, which showed that the incidence rate of psychological diseases increased significantly during COVID-19 period (37).

Pathogenesis of GABAergic-Related Depression

There is increasing evidence that GABAergic system changes in depression. In 1980, clinical statistics showed that the GABA level in lumbar cerebrospinal fluid of patients with depression decreased, which was proved after the appearance of nuclear magnetic resonance spectroscopy (18, 38). GABA levels in plasma or cerebrospinal fluid are normal in other major mental diseases, such as schizophrenia and anxiety (39). The density of GAD65 or GAD67-immunoreactivity in hypothalamic paraventricular nucleus of patients with depression decreased, which was significant in major depression (40). Somatostatin (SST) is a γ-Neuropeptides expressed in GABA interneuron subtypes target the dendrites of pyramidal neurons. It was found that the density of SST-labeled neurons in lateral amygdala, lateral basolateral nucleus and medial basolateral nucleus decreased significantly in patients with MDD (41). The functional defect of α1βγ2-adrenoceptor may increase the GABA release of the ventral tegmental area interneurons and enhance the GABAergic inhibition of the adjacent dopaminergic neurons, inducing loss of pleasure, the core symptom of severe depressive disorder (8, 42).

Chronic stress is one of the inducing factors of depression. In rodents, stress-induced behavioral changes were related to decreased glutamate decarboxylase expression, vesicles and plasma membrane transporters during GABA release, injury of GABAergic interneurons, and reduced density and function GABAergic synapses in addition (43–45). Western blot analysis and quantitative real-time PCR have shown that CUS exposure for 5 weeks could significantly reduce the GAD67 protein levels in the PFC of rats (46). Chronic stress can also change chloride ion reversal potential to depolarisation membrane potential (47). Benzodiazepines can enhance GABA activity, thereby opening chloride channels and allowing chloride ions to enter neurons (27). However, the long-term use of benzodiazepine results in a decrease in GABA levels; the resulting depolarization of neurons blocks the action potential and induces anti-anxiety, muscle relaxing, sedative, and antiepileptic activities (48).

GABA Receptor

GABA receptors are divided into GABA-A receptor (GABAAR) and GABA-B receptor (GABABR) subtypes (49). GABA-C receptor is usually classified as a subtype of the GABAAR, named GABA-A-rho (50). The GABAAR is a ligand-gated chloride channel (ionic type). It is a tetramer or pentamer uniquely composed of multiple subunits. At present, at least 19 different GABAAR subunits (termed α1-6, β1-3, γ1-3, δ, ε, π, θ and ρ1-3) have been reported (51).

GABAAR mediates rapid synaptic transmission, which is located in the postsynaptic membrane. The level of GABAAR and its subnunites changes in some patients with depression. Fatemi et al. revealed that postnatal lipopolysaccharide exposure can damage adult hippocampal neurogenesis and trigger the down-regulation of GABAAR in the later stage through early astrocyte activation, leading to depression like behavior (52). The GABRα1 subunit is expressed in most GABAARs. Some studies has found that GABRα1 protein level was significantly increased in lateral cerebellum of subjects with major depression (53). Therefore, drugs targeting GABAAR sites have also been used to treat depression. In the 1940s, Selye proved that some pregnane steroids have the effect of rapid sedation and anesthesia (54). Furthermore, electrophysiological experiments of rat brains that general steroid anesthesia enhances the stimulation of exogenous GABAAR (55). GABA receptor subunits are assembled near the central chloride pore and have been widely described as the target of several psychotropic drugs, such as the GABA-A agonist/antagonist site. Benzodiazepines bind to the GABAAR and increase the permeability of chloride ions by changing the opening frequency of the chloride channel (56). α2/α3 GABAAR modulators, such as TPA023, are a new type of anti-anxiety drugs that are superior to traditional benzodiazepines because they lack sedative effect and drug dependency (57).

GABABR is a G protein-coupled receptor, a heterodimer composed of GABAB1 and GABAB2 subunits; they are mainly located in the presynaptic region act as their receptors to inhibit the release of GABA (40). GABA-B mediates slow synaptic transmission related to memory, emotion, and pain (58, 59). The activation of GABABR can inhibit the transmission of serotonergic, and the decrease of serotonergic neuron activity is related to the development of depression (60, 61).

GABAergic System in the Treatment of Depression

At present, the first-line treatment of depression includes antidepressants and cognitive behavioral therapy, but 30–50% of patients are ineffective (62). Studies have shown that after successful maintenance treatment of acute TMS can sometimes alleviate for 3 months or even 8 years (63–65). In refractory depression, TMS reduced the inhibitory neurophysiological markers of GABA receptor-mediated depression (N45 and N100) (66, 67). Scangos et al. (68) improved patients' depression rapidly and continuously through closed-loop therapy. Other treatments include electroconvulsive therapy, transcranial direct current stimulation and vagus nerve stimulation (69–73). Traditional antidepressants mainly inhibit monoamine transporters. Monoamine antidepressants have excellent limitations, such as low efficacy, delayed treatment, and most importantly, treatment unresponsiveness in some patients (estimated to be one-third of patients with depression) (74–76). Practicing yoga at least once a week helps maintain the improvement of GABA levels (77).

The drug treatment of depression needs to improve and go beyond the limitations of monoamine system, and may even put forward new ideas to improve the treatment effect of patients. A diminished GABAergic input to the hypothalamic paraventricular nucleus may contribute to the activation of corticotropin releasing hormone-immunoreactivity neurons in depression, most prominently in major depression, which provides a rationale for prescribing GABAergic agonists for these patients (40). The emergence of new rapid drugs for the GABA system has solved specific problems and provided better therapeutic intervention for this persistent disease (78). The emergence of ketamine, a new rapid drug for GABA system, solves specific problems and provides better therapeutic intervention for this persistent disease (78). The initial cellular trigger of ketamine's rapid antidepressant effect is Glun2b NMDAR on GABA interneurons (16). Ketamine has recently been approved for the treatment of refractory depression, and its dose and plasma concentration are positively correlated with antidepressant response (79, 80).

Enhancing the transmission of GABA is the core of some new antidepressant treatments. Several studies have supported that primary excitatory neuron play a role in the GABAergic neuroactive steroids (NASS) synthesis, an endogenous steroid synthesized by cholesterol in the brain and nervous system (81–83). NASS can regulate the surface expression of the GABAAR. However, unlike phenylene bisulfide, they only regulate the receptor containing gamma subunit; based on the multichannel characteristics of the GABAAR, positive allosteric modulators may improve the therapeutic effect (84, 85). This suggests that a novel technique to treat depression is to develop novel antidepressants that can enhance the function of GABA and act on GABA receptors. The deletion of the GABA receptor-γ2 subunit increases GABA inhibition and results in anti-anxiety and antidepressant behaviors (45). Cognitive impairment is now considered the core symptom of depression and other mental disorders (86–88). A decrease in the signal pathway of SST + neurons/α5-GABA receptor pathway will lead to cognitive dysfunction, representing a new treatment target for treating cognitive disorder symptoms of depression (45). However, more studies must be carried out on the association of GABAergic deficiency with other pathophysiological changes of depression, such as inflammation, apoptosis, and oligodendrocyte dysfunction (89–91).

CONCLUSION

Based on the CiteSpace, VOSviewer, and WoSCC, the current study performed a bibliometric analysis and in-depth interpretation on the research of the GABAergic system in depression in the last 10 years from the aspects of the number of studies published, co-occurrence of research authors, journals, countries, categories, institutions, keywords, and research hotspots. Our study's findings revealed that the research had developed rapidly over the past 17 years, especially in the last 5 years. Further developments in GABAergic research are promoting the exploration of the pathogenesis of depression to a certain degree. In this review, we systematically summarized the basic information and pathogenesis of GABAergic system. We discussed the potential value of the GABAergic system in treating depression, which may provide

strategic suggestions for future research and more ideas for clinicians and researchers.

AUTHOR CONTRIBUTIONS

JL and KL conceived and designed the study. PH and MC collected data based on WOS. JL, MS, and FL analyzed by using CiteSpace. KL and WW reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by Guangdong Basic and Applied Basic Research Foundation 2018A0303130259 (Regulation of GABAA-mediated tonic inhibition on cognitive impairment in Parkinson's disease and its mechanism) and by Guangdong Basic and Applied Basic Research Foundation 2021A1515012481 (Role of projection of cholinergic neurons from medial septal nucleus to hippocampus in re-consolidation of cocaine reward memory).

REFERENCES

1. Ledford H. Medical research: if depression were cancer. *Nature.* (2014) 515:182–4. doi: 10.1038/515182a
2. WHO. *Depression and Other Common Mental Disorders: Global Health Estimates*. Geneva, Switzerland: World Health Organization (2017).
3. Smith K. Mental health: a world of depression. *Nature.* (2014) 515:181. doi: 10.1038/515180a
4. Kendler KS. The phenomenology of major depression and the representativeness and nature of DSM criteria. *Am J Psychiatry.* (2016) 173:771–80. doi: 10.1176/appi.ajp.2016.15121509
5. Tatsumi M, Groshan K, Blakely RD, Richelson E. Pharmacological profile of antidepressants and related compounds at human monoamine transporters. *Eur J Pharmacol.* (1997) 340:249–58. doi: 10.1016/S0014-2999(97)01393-9
6. Glowinski J, Axelrod J. Inhibition of uptake of tritiated-noradrenaline in the intact rat brain by imipramine and structurally related compounds. *Nature.* (1964) 204:1318–9. doi: 10.1038/2041318a0
7. Ross SB, Renyi AL. Inhibition of the uptake of tritiated 5-hydroxytryptamine in brain tissue. *Eur J Pharmacol.* (1969) 7:270–7. doi: 10.1016/0014-2999(69)90091-0
8. Bauer M, Bschor T, Pfennig A, Whybrow PC, Angst J, Versiani M, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders in primary care. *World J Biol Psychiatry*. (2007) 8:67–104. doi: 10.1080/15622970701227829
9. Luscher B, Shen Q, Sahir N. The GABAergic deficit hypothesis of major depressive disorder. *Mol Psychiatry.* (2011) 16:383–406. doi: 10.1038/mp.2010.120
10. Vollenweider I, Smith KS, Keist R, Rudolph U. Antidepressant-like properties of α2-containing GABA(A) receptors. *Behav Brain Res.* (2011) 217:77–80. doi: 10.1016/j.bbr.2010.10.009
11. Gold PW, Chrousos GP. Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs. low CRH/NE states. *Mol Psychiatry.* (2002) 7:254–75. doi: 10.1038/sj.mp.4001032
12. MacKenzie G, Maguire J. Chronic stress shifts the GABA reversal potential in the hippocampus and increases seizure susceptibility. *Epilepsy Res.* (2015) 109:13–27. doi: 10.1016/j.eplepsyres.2014.10.003
13. Allen MJ, Sabir S, Sharma S. GABA receptor. In: *StatPearls*. Treasure Island, FL: StatPearls Publishing (2021).
14. Jewett BE, Sharma S. Physiology, GABA. In: *StatPearls*. Treasure Island, FL: StatPearls Publishing (2021).
15. Fogaça MV, Duman RS. Cortical GABAergic dysfunction in stress and depression: new insights for therapeutic interventions. *Front Cell Neurosci.* (2019) 13:87. doi: 10.3389/fncel.2019.00087
16. Sarasa SB, Mahendran R, Muthusamy G, Thankappan B, Selta DRF, Angayarkanni J, et al. Brief review on the non-protein amino acid, gamma-amino butyric acid (GABA): its production and role in microbes. *Curr Microbiol.* (2020) 77:534–44. doi: 10.1007/s00284-019-01839-w
17. Petty F, Sherman AD. Plasma GABA levels in psychiatric illness. *J Affect Disord.* (1984) 6:131–8. doi: 10.1016/0165-0327(84)90018-1
18. Gold BI, Bowers MB Jr, Roth RH, Sweeney DW, GABA. levels in CSF of patients with psychiatric disorders. *Am J Psychiatry.* (1980) 137:362–4. doi: 10.1176/ajp.137.3.362
19. Gerner RH, Hare TA, CSF GABA. In normal subjects and patients with depression, schizophrenia, mania, and anorexia nervosa. *Am J Psychiatry.* (1981) 138:1098–101. doi: 10.1176/ajp.138.8.1098
20. Hasler G, van der Veen JW, Tumonis T, Meyers N, Shen J, Drevets WC. Reduced prefrontal glutamate/glutamine and gamma-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy. *Arch Gen Psychiatry.* (2007) 64:193–200. doi: 10.1001/archpsyc.64.2.193
21. Gabbay V, Mao X, Klein RG, Ely BA, Babb JS, Panzer AM, et al. Anterior cingulate cortex γ-aminobutyric acid in depressed adolescents: relationship to anhedonia. *Arch Gen Psychiatry.* (2012) 69:139–49. doi: 10.1001/archgenpsychiatry.2011.131
22. Song Z, Huang P, Qiu L, Wu Q, Gong Q, Zhang B, et al. Decreased occipital GABA concentrations in patients with first-episode major depressive disorder: a magnetic resonance spectroscopy study. *Sheng Wu Yi Xue Gong Cheng Xue Za Zhi.* (2012) 29:233–6. (in Chinese).
23. Schür RR, Draisma LW, Wijnen JP, Boks MP, Koevoets MG, Joëls M, et al. Brain GABA levels across psychiatric disorders: a systematic literature review and meta-analysis of (1) H-MRS studies. *Hum Brain Mapp.* (2016) 37:3337–52. doi: 10.1002/hbm.23244
24. Godfrey KEM, Gardner AC, Kwon S, Chea W, Muthukumaraswamy SD. Differences in excitatory and inhibitory neurotransmitter levels between depressed patients and healthy controls: a systematic review and meta-analysis. *J Psychiatr Res.* (2018) 105:33–44. doi: 10.1016/j.jpsychires.2018.08.015
25. Khisti RT, Chopde CT, Jain SP. Antidepressant-like effect of the neurosteroid 3alpha-hydroxy-5alpha-pregnan-20-one in mice forced swim test. *Pharmacol Biochem Behav.* (2000) 67:137–43. doi: 10.1016/S0091-3057(00)00300-2
26. Pehrson AL, Sanchez C. Altered γ-aminobutyric acid neurotransmission in major depressive disorder: a critical review of the supporting evidence and the influence of serotonergic antidepressants. *Drug Des Devel Ther.* (2015) 9:603–24. doi: 10.2147/DDDT.S62912
27. Croarkin PE, MacMaster FP. Transcranial magnetic stimulation for adolescent depression. *Child Adolesc Psychiatr Clin N Am.* (2019) 28:33–43. doi: 10.1016/j.chc.2018.07.003
28. Chen C. Searching for intellectual turning points: progressive knowledge domain visualization. *Proc Natl Acad Sci USA.* (2004) 101(suppl):5303–10. doi: 10.1073/pnas.0307513100
29. Chen C. CiteSpace II: detecting and visualizing emerging trends and transient patterns in scientific literature. New York, NY: Wiley (2006).
30. Yang J, Cheng C, Shen S, Yang S. Comparison of complex network analysis software: Citespace, SCI2 and Gephi. In*: IEEE International Conference on Big Data Analysis.* (2017) 2017:169–72. doi: 10.1109/ICBDA.2017.8078800
31. Tremblay R, Lee S, Rudy B. GABAergic interneurons in the neocortex: from cellular properties to circuits. *Neuron.* (2016) 91:260–92. doi: 10.1016/j.neuron.2016.06.033
32. WHO. *World Misses Most 2020 Mental Health Targets; Extension of WHO Mental Health Action Plan to 2030 Provides New Opportunity for Progress.* Geneva: World Health Organization (2021).
33. Mazza MG, De Lorenzo R, Conte C, Poletti S, Vai B, Bollettini I, et al. Anxiety and depression in COVID-19 survivors: role of inflammatory and clinical predictors. *Brain Behav Immun.* (2020) 89:594–600. doi: 10.1016/j.bbi.2020.07.037

34. Abdel-Bakky MS, Amin E, Faris TM, Abdellatif AAH. Mental depression: relation to different disease status, newer treatments and its association with COVID-19 pandemic (Review). *Mol Med Rep.* (2021) 24:839. doi: 10.3892/mmr.2021.12479
35. Santomauro DF, Herrera AM, Shadid J, Zheng P, Ashbaugh C, et al. COVID-19 Mental Disorders Collaborators. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *Lancet.* (2021) 398:1700–12. doi: 10.1016/S0140-6736(21)02143-7
36. WHO. *Wake-Up Call to All Countries to Step Up Mental Health Services and Support*. Geneva: World Health Organization (2022).
37. Magnúsdóttir I, Lovik A, Unnarsdóttir AB, McCartney D, Ask H, Kõiv K, et al. Acute COVID-19 severity and mental health morbidity trajectories in patient populations of six nations: an observational study. Lancet Public Health. (2022) 2022:S2468-2667(22)00042-1. doi: 10.1016/S2468-2667(22)00042-1
38. Price RB, Shungu DC, Mao X, Nestadt P, Kelly C, Collins KA, et al. Amino acid neurotransmitters assessed by proton magnetic resonance spectroscopy: relationship to treatment resistance in major depressive disorder. *Biol Psychiatry.* (2009) 65:792–800. doi: 10.1016/j.biopsych.2008.10.025
39. Gao SF, Bao AM. Corticotropin-releasing hormone, glutamate, and γ-aminobutyric acid in depression. *Neuroscientist.* (2011) 17:124–44. doi: 10.1177/1073858410361780
40. Gao SF, Klomp A, Wu JL, Swaab DF, Bao AM. Reduced GAD(65/67) immunoreactivity in the hypothalamic paraventricular nucleus in depression: a postmortem study. *J Affect Disord.* (2013) 149:422–5. doi: 10.1016/j.jad.2012.12.003
41. Douillard-Guilloux G, Lewis D, Seney ML, Sibille E. Decrease in somatostatin-positive cell density in the amygdala of females with major depression. *Depress Anxiety.* (2017) 34:68–78. doi: 10.1002/da.22549
42. Lim B, Sproule BA, Zahra Z, Sunderji N, Kennedy SH, Rizvi SJ. Understanding the effects of chronic benzodiazepine use in depression: a focus on neuropharmacology. *Int Clin Psychopharmacol.* (2020) 35:243–53. doi: 10.1097/YIC.0000000000000316
43. Geng C, Guo Y, Wang C, Liao D, Han W, Zhang J, et al. Systematic impacts of chronic unpredictable mild stress on metabolomics in rats. *Sci Rep.* (2020) 10:700. doi: 10.1038/s41598-020-57566-x
44. Srivastava I, Vazquez-Juarez E, Henning L, Gómez-Galán M, Lindskog M. Blocking astrocytic GABA restores synaptic plasticity in prefrontal cortex of rat model of depression. *Cells.* (2020) 9:1705. doi: 10.3390/cells9071705
45. Adell A. Brain NMDA Receptors in schizophrenia and depression. *Biomolecules.* (2020) 10:947. doi: 10.3390/biom10060947
46. Gerhard DM, Pothula S, Liu RJ, Wu M, Li XY, Girgenti MJ, et al. GABA interneurons are the cellular trigger for ketamine's rapid antidepressant actions. *J Clin Invest.* (2020) 130:1336–49. doi: 10.1172/JCI130808
47. Fava M. Diagnosis and definition of treatment-resistant depression. *Biol Psychiatry.* (2003) 53:649–59. doi: 10.1016/S0006-3223(03)00231-2
48. Gaynes BN, Lux L, Gartlehner G, Asher G, Forman-Hoffman V, Green J, et al. Defining treatment-resistant depression. *Depress Anxiety*. (2020) 37:134–145. doi: 10.1002/da.22968
49. Ma K, Xu A, Cui S, Sun MR, Xue YC, Wang J. Impaired GABA synthesis, uptake and release are associated with depression-like behaviors induced by chronic mild stress. *Transl Psychiatry.* (2016) 6:e910. doi: 10.1038/tp.2016.181
50. Czéh B, Varga ZK, Henningsen K, Kovács GL, Miseta A, Wiborg O. Chronic stress reduces the number of GABAergic interneurons in the adult rat hippocampus, dorsal-ventral and region-specific differences. *Hippocampus.* (2015) 25:393–405. doi: 10.1002/hipo.22382
51. Banasr M, Lepack A, Fee C, Duric V, Maldonado-Aviles J, DiLeone R, et al. Characterization of GABAergic marker expression in the chronic unpredictable stress model of depression. *Chronic Stress.* (2017) 1:2470547017720459. doi: 10.1177/2470547017720459
52. Fatemi SH, Folsom TD, GABA. receptor subunit distribution and FMRP-mGluR5 signaling abnormalities in the cerebellum of subjects with schizophrenia, mood disorders, and autism. *Schizophr Res.* (2015) 167:42–56. doi: 10.1016/j.schres.2014.10.010
53. Liang M, Zhong H, Rong J, Li Y, Zhu C, Zhou L, et al. Postnatal lipopolysaccharide exposure impairs adult neurogenesis and causes depression-like behaviors through astrocytes activation triggering GABAA receptor downregulation. *Neuroscience.* (2019) 422:21–31. doi: 10.1016/j.neuroscience.2019.10.025
54. Olsen RW, Sieghart W. GABAA receptors: subtypes provide diversity of function and pharmacology. *Neuropharmacology.* (2009) 56:141–8. doi: 10.1016/j.neuropharm.2008.07.045
55. Klein RL, Harris RA. Regulation of GABAA receptor structure and function by chronic drug treatments *in vivo* and with stably transfected cells. *Jpn J Pharmacol.* (1996) 70:1–15. doi: 10.1254/jjp.70.1
56. Hewitt SA, Wamsteeker JI, Kurz EU, Bains JS. Altered chloride homeostasis removes synaptic inhibitory constraint of the stress axis. *Nat Neurosci.* (2009) 12:438–43. doi: 10.1038/nn.2274
57. Duman RS, Sanacora G, Krystal JH. Altered connectivity in depression: GABA and glutamate neurotransmitter deficits and reversal by novel treatments. *Neuron.* (2019) 102:75–90. doi: 10.1016/j.neuron.2019.03.013
58. Hill DR, Bowery NG. 3H-baclofen and 3H-GABA bind to bicuculline-insensitive GABA B sites in rat brain. *Nature.* (1981) 290:149–52. doi: 10.1038/290149a0
59. Olsen RW, Sieghart W. International Union of Pharmacology. LXX subtypes of gamma-aminobutyric acid(A) receptors: classification on the basis of subunit composition, pharmacology, and function update. *Pharmacol Rev.* (2008) 60:243–60. doi: 10.1124/pr.108.00505
60. Mannoury la Cour C, Hanoun N, Melfort M, Hen R, Lesch KP, Hamon M, Lanfumey L. GABA(B) receptors in 5-HT transporter- and 5-HT1A receptor-knock-out mice: further evidence of a transduction pathway shared with 5-HT1A receptors. *J Neurochem.* (2004) 89:886–96. doi: 10.1111/j.1471-4159.2004.02367.x
61. Cryan JF, Leonard BE. 5-HT1A and beyond: the role of serotonin and its receptors in depression and the antidepressant response. *Hum Psychopharmacol.* (2000) 15:113–35.doi: 10.1002/(SICI)1099-1077(200003)15:2<113::AID-HUP150>3.0.CO;2-W
62. Shen Q, Lal R, Luellen BA, Earnheart JC, Andrews AM, Luscher B. gamma-Aminobutyric acid-type A receptor deficits cause hypothalamic-pituitary-adrenal axis hyperactivity and antidepressant drug sensitivity reminiscent of melancholic forms of depression. *Biol Psychiatry.* (2010) 68:512–20. doi: 10.1016/j.biopsych.2010.04.024
63. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry.* (2006) 163:1905–17. doi: 10.1176/ajp.2006.163.11.1905
64. Klomjai W, Katz R, Lackmy-Vallée A. Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). *Ann Phys Rehabil Med.* (2015) 58:208–13. doi: 10.1016/j.rehab.2015.05.005
65. Rachid F. Maintenance repetitive transcranial magnetic stimulation (rTMS) for relapse prevention in with depression: a review. *Psychiatry Res.* (2018) 262:363–72. doi: 10.1016/j.psychres.2017.09.009
66. Voineskos D, Blumberger DM, Rogasch NC, Zomorrodi R, Farzan F, Foussias G, et al. Neurophysiological effects of repetitive transcranial magnetic stimulation (rTMS) in treatment resistant depression. *Clin Neurophysiol.* (2021) 132:2306–16. doi: 10.1016/j.clinph.2021.05.008
67. Godfrey KEM, Muthukumaraswamy SD, Stinear CM, Hoeh N. Effect of rTMS on GABA and glutamate levels in treatment-resistant depression: An MR spectroscopy study. *Psychiatry Res Neuroimaging.* (2021) 317:111377. doi: 10.1016/j.pscychresns.2021.111377
68. Scangos KW, Khambhati AN, Daly PM, Makhoul GS, Sugrue LP, Zamanian H, et al. Closed-loop neuromodulation in an individual with treatment-resistant depression. *Nat Med.* (2021) 27:1696–700. doi: 10.1038/s41591-021-01480-w
69. Kaster TS, Fitzgerald PB, Downar J, Vila-Rodriguez F, Daskalakis ZJ, Blumberger DM. Considerable evidence supports rTMS for treatment-resistant depression. *J Affect Disord.* (2020) 263:549–51. doi: 10.1016/j.jad.2019.11.017
70. Folkerts HW, Michael N, Tölle R, Schonauer K, Mücke S, Schulze-Mönking H. Electroconvulsive therapy vs. paroxetine in treatment-resistant depression—a randomized study. *Acta Psychiatr Scand.* (1997) 96:334–42. doi: 10.1111/j.1600-0447.1997.tb09926.x
71. Chase HW, Boudewyn MA, Carter CS, Phillips ML. Transcranial direct current stimulation: a roadmap for research, from mechanism

of action to clinical implementation. *Mol Psychiatry.* (2020) 25:397–407. doi: 10.1038/s41380-019-0499-9
72. Milev RV, Giacobbe P, Kennedy SH, Blumberger DM, Daskalakis ZJ, Downar J, et al. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 4. Neurostimulation treatments. *Can J Psychiatry.* (2016) 61:561–75. doi: 10.1177/0706743716660033
73. Johnson RL, Wilson CG, A. review of vagus nerve stimulation as a therapeutic intervention. *J Inflamm Res.* (2018) 11:203–13. doi: 10.2147/JIR.S163248
74. Qiao H, Li MX, Xu C, Chen HB, An SC, Ma XM. Dendritic spines in depression: what we learned from animal models. *Neural Plast.* (2016) 2016:8056370. doi: 10.1155/2016/8056370
75. Cryan JF, Holmes A. The ascent of mouse: advances in modelling human depression and anxiety. *Nat Rev Drug Discov.* (2005) 4:775–90. doi: 10.1038/nrd1825
76. Duman RS, Aghajanian GK, Sanacora G, Krystal JH. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. *Nat Med.* (2016) 22:238–49. doi: 10.1038/nm.4050
77. Möhler H. The GABA system in anxiety and depression and its therapeutic potential. *Neuropharmacology.* (2012) 62:42–53. doi: 10.1016/j.neuropharm.2011.08.040
78. Ionescu DF, Rosenbaum JF, Alpert JE. Pharmacological approaches to the challenge of treatment-resistant depression. *Dialogues Clin Neurosci.* (2015) 17:111–26. doi: 10.31887/DCNS.2015.17.2/dionescu
79. Ngo DH, Vo TS. An updated review on pharmaceutical properties of gamma-aminobutyric acid. *Molecules.* (2019) 24:2678. doi: 10.3390/molecules24152678
80. Selye H. Anesthetic effect of steroid hormones. *Proc Soc Exp Biol Med.* (1941) 46:116–21. doi: 10.3181/00379727-46-11907
81. Selye H. The antagonism between anesthetic steroid hormones and pentamethylenetetrazol (metrazol). *J Lab Clin Med.* (1942).
82. Harrison NL, Simmonds MA. Modulation of the GABA receptor complex by a steroid anaesthetic. *Brain Res.* (1984) 323:287–92. doi: 10.1016/0006-8993(84)90299-3
83. Melcangi RC, Panzica G, Garcia-Segura LM. Neuroactive steroids: focus on human brain. *Neuroscience.* (2011) 191:1–5. doi: 10.1016/j.neuroscience.2011.06.024
84. Streeter CC, Gerbarg PL, Brown RP, Scott TM, Nielsen GH, Owen L, et al. Thalamic gamma aminobutyric acid level changes in major depressive disorder after a 12-week Iyengar yoga and coherent breathing intervention. *J Altern Complement Med.* (2020) 26:190–7. doi: 10.1089/acm.2019.0234
85. Erchinger VJ, Miller J, Jones T, Kessler U, Bustillo J, Haavik J, et al. Anterior cingulate gamma-aminobutyric acid concentrations and electroconvulsive therapy. *Brain Behav.* (2020) 10:e01833. doi: 10.1002/brb3.1833
86. Milak MS, Rashid R, Dong Z, Kegeles LS, Grunebaum MF, Ogden RT, et al. Assessment of relationship of ketamine dose with magnetic resonance spectroscopy of Glx and GABA responses in adults with major depression: a randomized clinical trial. *JAMA Netw Open.* (2020) 3:e2013211. doi: 10.1001/jamanetworkopen.2020.13211
87. Semkovska M, Quinlivan L, O'Grady T, Johnson R, Collins A, O'Connor J, et al. Cognitive function following a major depressive episode: a systematic review and meta-analysis. *Lancet Psychiatry.* (2019) 6:851–61. doi: 10.1016/S2215-0366(19)30291-3
88. Prévot T, Sibille E. Altered GABA-mediated information processing and cognitive dysfunctions in depression and other brain disorders. *Mol Psychiatry.* (2021) 26:151–67. doi: 10.1038/s41380-020-0727-3
89. Chisari M, Eisenman LN, Covey DF, Mennerick S, Zorumski CF. The sticky issue of neurosteroids and GABAA receptors. *Trends Neurosci.* (2010) 33:299–306. doi: 10.1016/j.tins.2010.03.005
90. Frieder A, Fersh M, Hainline R, Deligiannidis KM. Pharmacotherapy of postpartum depression: current approaches and novel drug development. *CNS Drugs.* (2019) 33:265–82. doi: 10.1007/s40263-019-00605-7
91. Althaus AL, Ackley MA, Belfort GM, Gee SM Dai J, Nguyen DP, et al. Preclinical characterization of zuranolone (SAGE-217), a selective neuroactive steroid GABAA receptor positive allosteric modulator. *Neuropharmacology.* (2020) 181:108333. doi: 10.1016/j.neuropharm.2020.108333

Conflict of Interest: WW was employed by Guangzhou Southern Medical Laboratory Animal Sci. and Tech. Co., Ltd.

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.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Psychiatry

TYPE Systematic Review
PUBLISHED 19 October 2022
DOI 10.3389/fpsyt.2022.939856

OPEN ACCESS

EDITED BY
Mirko Manchia,
University of Cagliari, Italy

REVIEWED BY
Maria Fernandez-del-Valle,
University of Oviedo, Spain
Joe Jacques Simon,
Heidelberg University, Germany

*CORRESPONDENCE
Marc Toutain
marctoutain@hotmail.com

SPECIALTY SECTION
This article was submitted to Psychological Therapy and Psychosomatics, a section of the journal Frontiers in Psychiatry

RECEIVED 09 May 2022
ACCEPTED 12 September 2022
PUBLISHED 19 October 2022

CITATION
Toutain M, Gauthier A and Leconte P (2022) Exercise therapy in the treatment of anorexia nervosa: Its effects depending on the type of physical exercise—A systematic review.
Front. Psychiatry 13:939856.
doi: 10.3389/fpsyt.2022.939856

Exercise therapy in the treatment of anorexia nervosa: Its effects depending on the type of physical exercise—A systematic review

Marc Toutain*, Antoine Gauthier and Pascale Leconte

UNICAEN, INSERM, COMETE, GIP CYCERON, Normandie University, Caen, France

Background and purpose: Clinical research focusing on the effectiveness of exercise therapy (ET) in patients with anorexia nervosa (AN) shows increasing interest in the last decade. The aim of this systematic review was to provide an overview of quantitative studies that have examined the impact of ET in AN patients and to examine its specific effects on physical and mental health according to the type of physical exercise (PE) practiced.

Methods: The review was carried out based on the PRISMA 2020. Electronic databases PubMed, Web of Science, Embase, and Wiley were searched from inception to December 2021. Quantitative studies assessing the effects of ET interventions on AN patients were included and study quality was assessed using the PEDro scale.

Results: A total of 27 studies were selected, including 13 randomized controlled trials. Regarding outcomes measured, results showed that aerobic and resistance exercise improved muscle strength, that mind-body PE decreased main symptoms of AN and mental health, and that combined PE reduced dysfunctional exercise and improved weight gain.

Conclusion: The findings suggest that ET intervention can induce benefits and has no deleterious effects on patients. In addition, specific effects on anorexia symptoms and physical and mental health have been observed according to the type of PE. However, this review reported several methodological weaknesses, including a lack of control group or randomization and statistical misconduct. Finally, ET intervention parameters were heterogeneous, and ET intervention generally lacked details, making reproducibility and comparability difficult. All these limitations underscore the need for a more rigorous methodology for further research.

KEYWORDS

anorexia nervosa, eating disorders, exercise therapy, psychiatry, mental Health, physical exercise

Introduction

Anorexia nervosa (AN) is an eating disorder (ED) that mainly affects women, particularly teenagers aged 15 to 19 years, with a peak in frequency at age 16 (1, 2). According to a recent review, the lifetime prevalence of AN is 4% in females and 0.3% in males (3). This disease has a low recovery rate of 50% six years after initial hospitalization (4) and a high relapse rate of over 50% (5). Moreover, a review of nearly fifty years of research has confirmed that AN has the highest mortality rate of any mental disorder (6). The main symptoms of AN are strict and voluntary food deprivation over a long period of time, ranging from several months to several years and resulting in significant weight loss, increased fear of gaining weight, and a distorted perception of the body (7). AN is associated with other mental health complications, such as body image disturbances (8), mood disorders, low self-esteem, exercise dependence, cognitive impairments (2, 9, 10), or sleep disturbances (11). AN also induces serious physical consequences, largely related to undernutrition, such as stunted growth, bone fragility (2), decrease in muscular strength and muscular endurance, hormonal and metabolic disorders (10), as well as hair loss, and kidney and bowel problems (12).

To prevent the aforementioned complications and to heal patients most efficiently and sustainably, a multidisciplinary approach to the treatment of AN is recommended by public health authorities, such as the "Haute Autorité de Santé" in France (13). Thereby, the standard care is composed of somatic and refeeding monitoring, nutritional rehabilitation, psychosocial interventions (family group psychotherapy, cognitive behavioral therapy, etc.) and medication (anxiolytics, antidepressants) (12, 14–16). Nevertheless, recovery remains long and difficult due not only to the diversity and severity of the symptoms and the associated comorbidities but also because of the patients' denial of the disease and their lack of adherence to the care program (2, 13, 17). To improve treatment efficacy and patient compliance, other therapies are usually included in the standard care, such as arts therapy, exercise therapy (ET), relaxation, massages, acupuncture, etc. (17, 18). Of these, ET is receiving increasing interest from dedicated units for ED. ET can be defined as physical exercises (PE) formally supervised by an exercise professional, in order to restore optimal mental and physical functioning for specific therapeutic goals (19). ET has already been integrated into the treatment of mental illnesses and is now considered a compelling therapy for ED in some hospital departments (20, 21).

However, in many countries, PE remains restricted in specialized units for ED because of the high occurrence of dysfunctional exercise in AN which is considered a common comorbidity among these patients (22–24). According to Rizk et al. (25), the prevalence of dysfunctional exercise varied considerably from 5% to 54% in patients with AN, depending on the number of criteria used for its definition (26). Since 1995, various studies have attempted to define dysfunctional exercise and have shown that it comprises two primary dimensions: a quantitative dimension and a qualitative dimension (23, 26–28). The quantitative dimension refers to the duration and intensity of the exercise. Several authors have suggested that exercise is dysfunctional when the weekly exercise duration is 6 hours or more (25, 28–30). However, there is no formal consensus on this criterion which is based on subjective assessments and observations (25, 27). The qualitative dimension refers to the compulsive and obsessive components of physical exercise, which are reflected in rigid exercise schedules, prioritization of exercise over other activities, episodes of exercise compulsion, and guilt and anxiety when sessions are incomplete or missed (25, 27). Thus, patients with AN regularly engage in dysfunctional exercise, especially in their room or out of sight, to increase weight loss (2, 9, 31). Even if physical activity is restricted or prohibited by the medical team, patients may continue to over exercise. The primary problem is that this dysfunctional exercise interferes with weight gain and the recovery process by increasing the body's energy expenditure (32). It is often associated with poorer treatment outcomes, longer inpatient stays, and a higher risk of relapse and disease chronicity (27). In light of this, it has become clear that PE should not be prohibited in the care of patients with AN, but rather be supervised by a professional to manage and encourage healthy behavior during exercise, and thus contribute to reduced dysfunctional exercise (32, 33).

Over the last two decades, some ET programs have been developed within specialized units for ED to promote better adherence to treatment and achieve more effective and sustainable reductions in the main symptoms of AN and associated disorders (17, 32, 34). Even if this remains a minority and no official recommendations exist, the development of ET in standard care is a growing phenomenon (32, 35). Achamrah et al.'s (32) review and Bratland-Sanda's et al. (34) publication both reported that different types of ET, including aerobic exercise, resistance exercise, and mind–body PE (MBPE), have been implemented for patients with AN and other ED. Aerobic exercise of low to moderate intensity involves sustained, continuous, or intermittent effort over time (e.g. walking, running, cycling, swimming or shadow boxing) (32, 34). Regarding the symptomatology and comorbidities of AN, this type of PE has been shown to have positive effects on physical and socio-psychological health (e.g., mood, depression, well-being, anxiety, and group relations) (32, 34–36). Resistance exercise involves exerting effort against resistance that is induced either with equipment (e.g., dumbbells, elastic bands, or machines) or without equipment (i.e., body weight) to increase muscular strength or endurance. Particularly for patients with AN, this type of PE has been revealed to elicit positive effects on muscle mass and body weight, as well as on other parameters such as metabolic adaptations, neuroplasticity, mental health (e.g., anxiety, depression, and behavioral changes), and bone

density (32, 36–38). MBPE, such as yoga, Pilates, stretching, tai chi, and qigong, has also been implemented in the care of AN (17, 32, 33, 36). This type of PE combines body movement, mental focus and controlled breathing which can improve strength, flexibility and balance, as well as relax the body and release psychological tension to achieve a state of well-being (32, 39).

Some studies have investigated the impact of ET interventions on AN patients and shown positive effects on the main symptoms of the disease, and physical and mental health, as well as better behavior toward the health care team (32, 35). However, to our knowledge, there are still few studies assessing the effects of ET interventions in patients with AN. This is partly due to the difficulty of conducting interventional studies in public health, but also to the fact that, as seen previously, ET has long been prohibited in the treatment of AN (34, 40, 41). This lack of studies was reported by reviews published in the last decade, which emphasized that more experimental studies were needed to explore the effects of ET interventions on AN (32, 33, 35, 42–44). This lack of proof was particularly highlighted in the most recent review conducted by Quiles Marcos et al. (35), which identified only twelve studies from 1970 to December 2019 (35). In addition, to our knowledge, none of these reviews sought to examine the effects of ET in patients with AN according to the type of PE implemented. Similarly, ET intervention parameters, such as session duration, exercise intensity, frequency, and period duration, were not generally highlighted or discussed. To date, the public health challenge is not only to demonstrate the health benefits of ET in patients with AN but also to determine which types of PE and which parameters might be recommended in a clinical or a research setting. This is one of the major interests of this literature review.

Therefore, the objectives of this systematic review are (i) to systematically review interventional studies that have assessed the effects of ET interventions in patients with AN, (ii) to examine effects according to the type of PE practiced on AN symptomatology and physical and mental health of patients, (iii) to examine the parameters of ET intervention and (iv) to discuss the relevance and limitations of these studies.

Materials and methods

Protocol and registration

This systematic review was carried out based on the 27 items of the PRISMA 2020 statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (45). The review was registered in the International Prospective Register of Systematic Reviews (PROSPERO): registration number CRD42022304532, available at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022304532.

Eligibility criteria

The eligibility criteria were formulated using the Population, Intervention, Comparison, Outcome, Study design (PICOS) framework, and two additional criteria were added: publication and date. We also added filters according to these criteria when applicable in databases (**Table 1**).

Population: Studies conducted with patients (i.e., in- and outpatients) diagnosed with AN were included. Studies carried out in other ED were also selected if they included patients with AN. Other studies, such as community sample prevention with participants at risk of ED were not included.

Intervention: Studies that have examined the effects of ET interventions on the main symptoms of AN and/or associated disorders were included, even if ET was combined with other therapy. ET with only an educational component and no PE program was not eligible.

Comparison: Pre- versus post-intervention studies with or without a comparison group were eligible for review.

Outcomes: Only quantitative studies were included in this review, as it should be difficult to assume a level of generalizability between quantitative and qualitative outcomes. Outcomes were grouped into three categories and are presented below:

- Symptomatology of ED: questionnaires of ED symptoms.
- Physical health: height, weight, body mass index (BMI), percentage of body fat, fat body mass, lean body mass, skin fold, skeletal muscle mass, heart rate, muscle strength (peak torque and 6-repetition maximum), muscle size (circumference and area), endurance measures (endurance time, oxygen volume uptake at anaerobic threshold and peak oxygen volume uptake), motor tests (timed up and go test, timed up and down stairs test, visual task, tactile estimation task), time to vital sign stabilization, bio-markers from blood analysis (nutritional status, bone health status and endocrinal status), and psychological variables.
- Mental health: depression, anxiety, quality of life, self-esteem, body image, body attitudes, alexithymia, state of mind, emotional regulation, body awareness, positive and negative affect, self-objectification, health profile, physical activity level, behavior toward exercise, interoception accuracy, and expectations and experience of treatment.

Study design: Randomized controlled trials (RCT), as well as non-randomized (NRCT) and uncontrolled trials (UT), were included. Although the cornerstone of clinical intervention research is generally considered to be the RCT, in areas where patient numbers are limited or the evidence is conflicting, systematic reviews drawing on a variety of sources can bring together all available

TABLE 1 PICOS (population, intervention, comparison and outcome), study design, publication and date criteria.

Items	Inclusion criteria	Exclusion criteria
Population	• Patient with a formal diagnosis of anorexia nervosa (DSM, CIM, clinical diagnosis).	• Prevention community sample. • Subject with only an history of AN
Intervention	• Exercise therapy including physical exercise.	• Exercise educational component only.
Comparison	• Pre versus post intervention with or without another group.	/
Outcomes	• Main symptoms of eating disorders with dedicated tools. • Physical and mental health parameters	• Qualitative outcomes only.
Study design	• Clinical trials. • Randomized controlled trials. • Non-randomized controlled trials. • Non-controlled trials. • Non-randomized trials.	• Case report. • Review articles. • Posters. • Conference paper. • Study protocols.
Publication	• Published in English or in French. • Published in a peer-reviewed journal. • Access to full text.	• Unpublished studies. Gray literature.
Date	• From inception to December 31 2021	/

TABLE 2 Databases search queries from inception to December 31 2021.

Database	Search query	Filter	Results
Web of Science	(TITLE = ('anorexia' OR "eating disorder*" OR 'anorexic*') AND ('yoga' OR 'qigong' OR 'Pilates' OR "physical activity" OR "physical therapy" OR "physical intervention" OR 'dance' OR 'exercise' OR 'training' OR "tai chi" OR 'stretching'))	Articles	372
Embase	('anorexia':ti OR 'eating disorder*':ti OR 'anorexic*':ti) AND ('yoga':ti OR 'qigong':ti OR 'Pilates':ti OR 'physical activity':ti OR 'physical therapy':ti OR 'physical intervention':ti OR 'dance':ti OR 'exercise':ti OR 'training':ti OR 'tai chi':ti OR 'stretching':ti)	Article + Article in press	346
PubMed	("exercise therapy"[MeSH Terms] OR "exercise movement techniques"[MeSH Terms]) AND ("anorexia nervosa"[MeSH Terms]) OR ((anorexia[Title] OR anorexic*[Title] OR "eating disorder*"[Title]) AND (yoga[Title] OR qigong[Title] OR Pilates[Title] OR "physical activity"[Title] OR "physical therapy"[Title] OR "physical intervention"[Title] OR dance[Title] OR exercise[Title] OR training[Title] OR "tai chi"[Title] OR stretching[Title]))	Clinical trial Randomized controlled trial	51
Wiley	('anorexia' OR "eating disorder*" OR 'anorexic' OR "eating disorders" OR 'anorexics') AND ('yoga' OR 'qigong' OR 'Pilates' OR "physical activity" OR 'physical therapy' OR 'physical intervention' OR 'dance' OR 'exercise' OR 'training' OR "tai chi" OR 'stretching')" in Title	Journals	132

evidence on a specific topic (46). Reviews, case reports, conference papers, posters, study protocols and letters to the editor were excluded.

Publication: Papers in English or French were included. Only available full-text articles published in peer-reviewed journals referenced in official databases were included. Unpublished or not yet published studies and gray literature were excluded.

Date: No limit in the past was applied and studies published until December 31, 2021, were included.

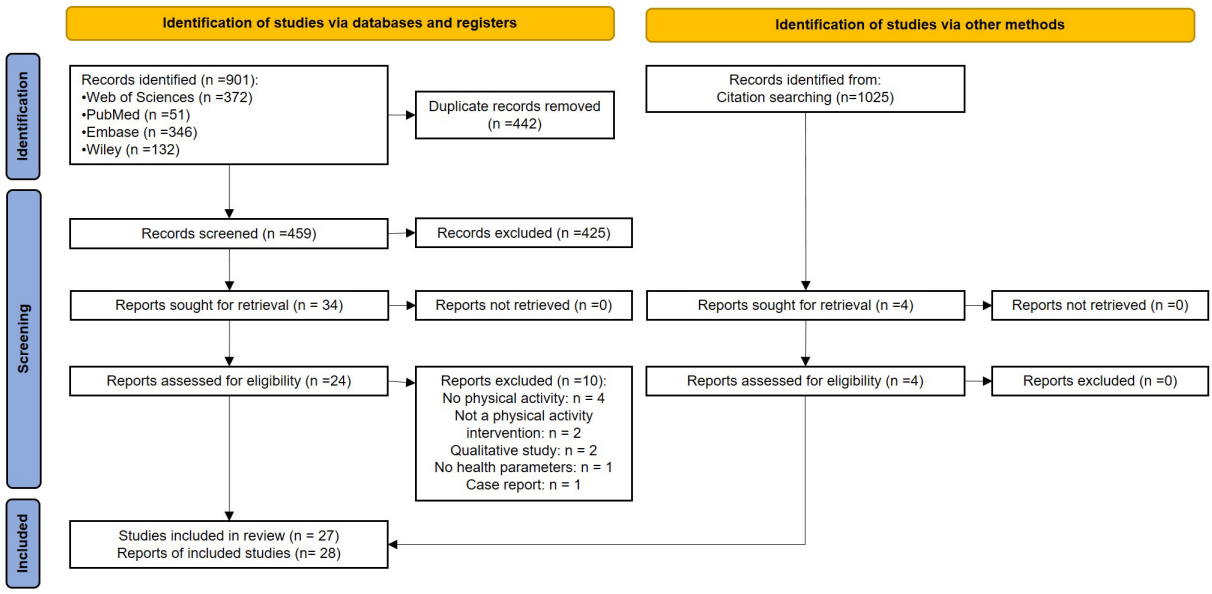


FIGURE 1
PRISMA flow diagram.

Information sources and search strategy

A systematic search of records was conducted by two authors (MT and PL) covering the period ranging from inception to December 31, 2021, in the following databases: PubMed, Web of Science, Embase (Elsevier) and Wiley Online Library. The search queries were designed according to Medical Subject Headings (MeSH) terms and usual key word terms according to the literature, combined with the Boolean operators "AND" and "OR" (Table 2).

The selection diagram is reported in Figure 1. The author MT used the desktop Zotero software (version 5.0.96.3, Corporation for Digital Scholarship, Vienna, Virginia) to extract reports from databases, remove duplicates, and select reports for full-text eligibility inspection. The author PL extracted reports from databases in a word processing document, then removed duplicates, and selected reports for full-text eligibility inspection. After having removed duplicates, the two authors independently screened the titles and abstracts of the articles, and when necessary, the full text, to determine whether the inclusion or exclusion criteria were met. They then shared their results for the full-text articles included. After the full-text inclusion, the two authors independently reviewed the reference lists of each full-text article included to identify new eligible articles. In case of disagreement, a third author (AG) was consulted in the decision-making process.

Data extraction

The following data were extracted from the selected articles: authors; year of publication; type of study; type of therapy; participant characteristics such as sample size, sex, age, BMI, ED type; attrition (post-intervention dropout, follow-up dropout); treatment settings (inpatient or outpatient); intervention parameters (type of PE, individualization status, instructor to patient ratio, session duration, exercise intensity, frequency and period); outcome measures; and significant results. This extraction included mean, standard deviation, and effect size when applicable. These data were first extracted in an Excel file and then transposed into four tables according to the type of PE provided within the ET (i.e., Table 3: aerobic exercise; Table 4: resistance exercise; Table 5: MBPEs; Table 6: combined PE).

Quality assessment

The methodological quality of the reports selected was assessed using the Physiotherapy Evidence Database (PEDro) scale (47, 48), which is an 11-item scale designed to measure the internal validity and statistical quality of a clinical trial. Two reviewers (MT and PL) independently read and assessed the reports. In case of discrepancies, the two reviewers had to agree on a common score. Studies were rated on a scale of 0 to 10, with excellent quality scores of 9 or higher, good quality scores between 6 and 8, fair

quality scores between 4 and 5, and poor quality scores between 0 and 3.

Results

A total of 901 records were extracted from the 4 databases, from 1950 to December 31, 2021, and 442 duplicates were excluded. Then, 459 records were screened for eligibility based on title and abstract information, excluding 425 records that did not meet inclusion criteria. Of these, 34 reports were selected for full-text assessment; 24 reports met the eligibility criteria and 10 reports were excluded for the following reasons: 4 reports focused on other therapies (e.g., cognitive behavioral therapy or educational program); 2 reports focused on patients who exercised by themselves, 2 reports were qualitative studies, 1 report did not assess effects of ET intervention on health parameters and 1 report was a case report. The references of each article included were screened by two authors (MT and PL) in an Excel spreadsheet to identify other eligible articles allowing the inclusion of 4 additional reports. The references of these 4 added reports were also screened and no other article was included. In the end, 1,025 references were screened.

Among the 28 selected reports, we found seven reports corresponding to three studies (i.e., same sample, same trial number, same authors, same hospital): the two reports of Szabo & Green (49) and Chantler et al. (50) were from the same study; the three reports of Fernandez-del-Valle et al. (51), Fernandez-del-Valle et al. (52) and Fernandez-del-Valle et al. (53) were from the same study; and the two reports of Martinez-Sanchez et al. (54) & Martinez-Sanchez et al. (55) were from the same study.

According to the PRISMA 2020 guidelines, we pooled results together only for the two reports of Martinez and collaborators, since the experimental design and the participants were identical. In the end, 27 studies were included (**Figure 1**).

The 28 reports from the 27 studies included and examined in this review aimed to assess the effects of ET on ED symptoms and/or on the physical and/or mental health of patients with AN. Thirteen studies were RCTs (49–53, 56–63), 8 studies were NRCTs (8, 64–70), and 6 studies were UTs (54, 55, 71–75). All studies included patients with a diagnosis of AN; 11 studies also included patients with other ED as well (58–60, 62, 63, 66, 69, 70, 72–74); while 16 of the 27 studies included only patients with AN (8, 49–57, 61, 64, 65, 67, 68, 71, 75). Ten studies were conducted with inpatients (49, 50, 60, 62, 64, 66, 68, 69, 74, 75), 15 were conducted with outpatients (51–53, 56–59, 61, 63, 65, 67, 70–73) and 2 did not report the treatment setting (8, 54, 55). A total of 1,316 participants were included, consisting of 1,246 patients diagnosed with an ED, 715 of which had AN, and 70 healthy controls. Among all participants, 16 were males diagnosed with an ED, of which 5 were diagnosed with AN. Eight studies included only adolescents (51–56, 64, 72, 75), 8 studies included only adults (8, 59, 61, 63, 65, 67, 70, 71), 10 studies included both adolescents and adults (49, 50, 57, 58, 60, 62, 66, 68, 69, 74), and one study did not report the participants' age (73). The mean age of all participants was 20.92 years, the lowest mean age was 12.61 years (51, 72), and the highest mean age was 36.1 years (61). Post-intervention, when reported, the overall mean dropout rate was 14.17% (± 15.10%), while the lowest dropout rate was 0% (56, 67), and the highest dropout rate was 45% (72). After the post-intervention follow-up period, when reported, the overall mean dropout rate was 10.34% (± 8.40%), the lowest dropout rate was 0% (63), and the highest dropout rate was 20% (62). In all studies, the PE sessions were supervised.

Regarding the aim of this systematic review, the 27 studies selected were divided into four categories according to the type of PE in the ET: (1) aerobic exercise (1 study) (64), (2) resistance exercise (7 studies) (49–53, 56, 57), (3) MBPE (11 studies) (8, 54, 55, 58–60, 65–67, 71–73), and (4) combined PE (8 studies) (61–63, 68–70, 74, 75).

Effects of aerobic exercise on cardiorespiratory measures and body mass index

To our knowledge, the study of Tokumura et al. (64) is the only one to have assessed the effects of ET intervention based on aerobic exercise alone in patients with AN (64). The study protocol included 17 young inpatients with AN divided non-randomly into two groups, a control group following standard care and an ET group following standard care combined with a training program consisting of 30 minutes of stationary bicycling at participants' individual anaerobic threshold level (approximately 50% of peak VO_2) five times per week for 6 to 12 months (mean duration of 40 weeks). Compared to the control group, the intervention group demonstrated a significant increase in maximal oxygen uptake value and peak heart rate from pre- to post-program, as well as a significant increase in BMI (**Table 3**).

Effects of resistance exercise on muscular strength, body composition, bone remodeling and symptoms of AN

Seven RCTs investigated the beneficial effects of ET including only resistance exercises in patients with AN. These studies were conducted between 2002 and 2017. The resistance exercise programs were carried out two (Szabo and Green, (49); Chantler et al., (50); Fernandez-del-Valle et al., (56)), three (Fernandez-del-Valle et al., (51); (52); (53)) or fourteen times per week (Martin et al., (57)), with a session duration of 60 minutes, except for Martin et al.'s program (57) which included 5-minute sessions. Only one report did not mention the duration of

10.3389/fpsyt.2022.939856

TABLE 3 Characteristics and main results of the study conducted on effects of aerobic exercise in patients with AN.

References	Study type	Type of therapy	Participants' characteristics Sample size (% female), mean age (SD) Mean BMI (SD) and ED type (%)	Post-intervention dropout n (%)	Follow-up dropout, n (%)	Treatment settings	Intervention parameters		Outcome measures
Tokumura et al. (64)	NRCT	ET + SC	n = 9 (100%), 12 to 17 (NR) 18.8 (± 0.5), AN (100%).	NR	/	Inpatient	Stationary bicycle Individualized: NR I/P ratio: NR NA = no	D = 30 min I = AT level F = 5x/week P = 6-12 months NA = no	**Physical health:** BMI*; %BF; HR rest; HR peak*; Endurance time; VO2 at AT; Peak VO2*.
		SC	n = 8 (100%), 12 to 16 (NR) 19.6 (± 0.7), AN (100%)	NR	/				

SD, standard deviation; ED, eating disorders; ET, exercise therapy; BMI, body mass index; NRCT, non-randomized controlled trial; SC, standard care; AN, anorexia nervosa; NR, not reported; I/P ratio, Instructor/Patient ratio; D, session duration; I, intensity; F, frequency; P, period; NA, nutritional adjustment;%BF;% body fat, HR, heart rate; VO2 at AT, oxygen volume uptake at anaerobic threshold; peak-VO2, peak oxygen volume uptake; *, improvement for the intervention group.

sessions (Szabo and Green, (49)). ET intervention period lasted 8 weeks, except for a 3-month program by Fernandez-del-Valle et al. (56) and 9 days by Martin et al. (57). Exercise intensity, when documented, ranged from low to high (50–53, 56), and the studies by Fernandez-del-Valle et al. (51–53, 56) reported a progression in intensity. For example, in their 2010 study, the exercise intensity was 20–30% of 6-repetition maximum (6RM) at the beginning of the program and was progressed to 50–60% of 6RM by the end of the program (56). In their 2014 study, the exercise load was gradually increased from 70% of 6RM at the beginning of the program to 100% of 6RM at the end of the program (51). The summary of ET parameters from these reports highlighted a mean frequency of 4.14 (± 4.37) sessions per week, a mean session length of 50 minutes (± 22.13), and a mean ET period of 7.61 weeks (± 3.16).

Szabo and Green (49) and Chantler et al. (50), conducted an RCT with three comparative groups of seven participants (i.e., AN exercisers and AN non-exercisers from inpatient treatment settings and healthy community sample exercisers). In a first report, Szabo and Green (49) showed no intervention effect on body composition and psychological well-being and muscle strength after 8 weeks of resistance exercise with 2 sessions of 60 minutes per week (49). This ET intervention consisted of a series of exercises targeting a wide range of muscle groups (i.e., back, chest, thighs, hips, calves, shoulders, arms, abdominal) with 2.5kg dumbbells, elastic band and body weight. In a second report, Chantler et al. (50) conducted the same ET intervention (i.e., 60 min of light resistance training exercises twice a week for 8 weeks) and showed an increase in peak torque of knee flexors, knee extensors and elbow extensors for the AN exercisers group (**Table 4**) (50).

Two RCTs published by the same team in 4 reports (2010, 2014, 2015, and 2016) revealed congruent results in patients with AN. In their first study, Fernandez-del-Valle et al. (56) assessed the effect of a 3-month ET intervention including two weekly 60-min sessions of resistance exercises that varied from low-to-moderate intensity (56). The results showed a significant increase in upper body strength (51). In the other three reports from the same study, the authors examined the effect of 8 weeks of ET intervention including three weekly 60-minute sessions of resistance exercises, ranging from moderate to high intensity. The results surpassed those of the previous study and revealed significant increases in lower and upper body strength (51, 53), as well as in lower and upper body muscle mass, mid-thigh circumference and arm muscle area (52) (**Table 4**).

More recently, the study by Martin et al. (57) examined the effect of two daily sessions of twenty low jumps, performed over nine days, on weight gain, length of stay, stabilization of vital signs (rest heart rate and blood pressure) and, with an emphasis, on biological markers for bone remodeling in female patients with AN hospitalized for medical stabilization (57). Their results showed no significant difference, especially in bone remodeling biomarker concentrations. However, they revealed a

TABLE 4 Characteristics and main results of studies (RCT, NRCT, UT) conducted on effects of resistance exercise in patients with AN.

Reference	Study type	Type of therapy	Participants' characteristics Sample size (% female), mean age (SD) Mean BMI (SD) and ED type (%)	Post-intervention dropout, n (%)	Follow-up dropout, n (%)	Treatment settings	Intervention parameters		Outcomes
Szabo and Green (49)	RC T	ET + SC	*n* = 7 (100%), 20.1 (NR) 15.1 (± 1.1), AN (100%)	NR	/	Inpatient	Resistance exercise Individualized: NR I/P ratio: NR	D = NR I = N R F = 2x/week P = 8 weeks NA = yes	**Physical health:** BMI;%BF; FM; LM; EDI; BDI; Muscle strength (tool NR).
		ET (H)	*n* = 7 (100%), 21 (NR) 21.4 (± 2.7)	NR	/				
		SC	*n* = 7 (100%), 20.1 (NR) 16.5 (± 1.3), AN (100%)	NR	/				
Chantler et al. (50)	RC T	ET + SC	*n* = 7 (100%), 20 (± 5) 15.1 (± 1.1), AN (100%)	NR	/	Inpatient	Resistance exercise In dividualized: NR I/P ratio: NR	D = 60 min I = low F = 2x/week P = 8 weeks NA = yes	**Physical health:** B MI,%BF; FM; LM; Peak torque of knee extensors* and flexors*, elbow extensors* and flexors.
		ET (H)	*n* = 7 (100%), 23 (± 3) 21.4 (± 2.7)	NR	/				
		SC	*n* = 7 (100%), 22 (± 6) 16.5 (± 1.3), AN (100%)	NR	/				
Fernandez-del-Valle et al. (56)	RC T	ET + SC	*n* = 11 (91%), 14.7 (± 0.6) 18.7 (± 1.7), AN (100%)	0 (0%)	/	Outpatient	Resistance exercise In dividualized: NR I/P ratio: 1/3	D = 60 min I = lo w to moderate F = 2x/week P = 3 months NA = no	**Physical health:** BF; LM; BMI; 6-RM SBP; 6-RM SLR*; 6-RM SLP; TUG-3m; TUG-10m; TUDS; SF-36.
		SC	*n* = 11 (91%), 14.2 (± 1.2) 18.2 (± 1.5), AN (100%)	0 (0%)	/				
Fernandez-del-Valle et al. (51)	RC T	ET + SC	*n* = 22 (100%), 12.61 (± 0.59) 17.28 (± 2.55), AN (100%)	0 (0%)	4 (18%)	Outpatient	Resistance exercise Individualized: NR I/P ratio: 1/2	D = 60 min I = hi gh F = 3x/week P = 8 weeks NA = yes	**Physical health:** BMI; 6-RM SBP*; 6-RM SLR*; 6-RM SLP*; TUG-3m; TUG-10m; TUDS.
		SC	*n* = 22 (100%), 13 (± 0.6) 18.12 (± 2.11), AN (100%)	2 (9%)	2 (9%)				
Fernandez-del-Valle et al. (52)	RC T	ET + SC	*n* = 22 (100%), 12.7 (± 0.7) 17.2 (± 2.4), AN (100%)	0 (0%)	/	Outpatient	Resistance ex ercise Individualized: NR I/P ratio: 1/2	D = 60 min I = moderate F = 3x/week P = 8 weeks NA = yes	**Physical he alth:** BMI; Triceps skinfold; mid-thigh skinfold; arm circumference; mid-thigh circumference*; arm muscle area* and thigh muscle area.
		SC	*n* = 22 (100%), 13 (± 0.6) 18.3 (± 2.1), AN (100%)	2 (9%)	/				

(Continued)

10.3389/fpsyt.2022.939856

TABLE 4 (Continued)

Reference	Study type	Type of therapy	Participants' characteristics Sample size (% female), mean age (SD) Mean BMI (SD) and ED type (%)	Post-intervention dropout, n (%)	Follow-up dropout, n (%)	Treatment settings	Intervention parameters	Outcomes
Fernandez-del-Valle et al. (53)	RC T	ET + SC	*n* = 22 (100%), 12.7 (± 0.7) 17.3 (NR), AN (100%)	4 (18%)		Outpatient	Resistance exercise Individualized: yes I/P ratio: NR	D = 50-60 m in I = moderate to high F = 3x/week P = 8 weeks NA = yes	**Physical heal th:** BMI;%BF; FM; SMM; Relative strength to body weight on 6-RM SBP*, 6-RM SLR* and 6-RM SLP*; Relative strength to LM on 6-RM SBP*, 6-RM SLR* and 6-RM SLP*; Skinfolds of biceps, triceps, subscapular and suprailiac; Circumference of thigh, arm and calf.
		SC	*n* = 22 (100%), 13 (± 0.6) 18.1 (NR), AN (100%)	4 (18%)					
Martin et al. (57)	RC T	ET + SC	*n* = 20 (95%), 16.8 (± 2.4) BMI = NR, AN (100%)	Global dropout n = 4/45 (9%)		Outpatient	20 vertical jumps Individualized: NR I/P ratio: NR	D = 5 min I = NR F = 2x/day P = 9 days NA = no	**Physical he alth:** BMI; BSAP, NTX, OC and VSS*.
		SC	*n* = 21 (95%), 16.8 (± 2.3) BMI = NR, AN (100%)						

SD, standard deviation; ED, eating disorders; ET, exercise therapy; BMI, body mass index; RCT, randomized controlled trial; SC, standard care; H, healthy community sample; NR, not reported; AN, anorexia nervosa; I/P ratio, Instructor/Patient ratio; D, session duration; I, intensity; F, frequency; P, period; NA, nutritional adjustment; 6-RM, 6-repetition maximum; SBP, seated bench press; SLR, seated lateral row; SLP, seated leg-press; TUG-3m, timed up and go 3 minutes; TUG-10m, timed up and go 10 minutes; TUDS, timed up and down stairs;%BF,% body fat, FM, fat body mass; LM, lean body mass; SMM, skeletal muscle mass; EDI, eating disorder inventory; BDI, Beck depression inventory; SF-36,medical outcomes study 36-item short-form health survey; BSAP, bone-specific alkaline phosphatase; NTX, N-telopeptide; OC, osteocalcin; VSS, time to vital sign stabilization; *, significant improvement for the intervention group.

shorter time to vital sign stabilization in the intervention group, as compared to the control group (**Table 4**).

Effects of mind-body physical exercise interventions

Eleven studies published in twelve reports investigated the benefits of MBPE interventions in patients with AN between 2008 and 2021, including three RCTs (58–60), four NRCTs (8, 65–67) and 4 UTs (54, 55, 71–73). Seven studies used yoga as ET intervention, one used basic body awareness therapy (i.e., based on massage and postural exercises), one used hoop training, one used Pilates, and one used dance movement therapy (**Table 5**). The MBPE interventions were carried out one (59, 66, 67, 71–73), two (39, 58), three (54, 55) or five times per week (60) depending on the study, with a session duration of 10 min (65), 60 min (8, 54, 58, 60), 75 min (67), 90 min (59, 66, 72) or 120 min (71). Only one study did not report the frequency of sessions (65). The duration of ET was 5 days (60), 8 weeks (58, 65, 66, 71, 73), 10 weeks (54, 55) or 12 weeks (8, 39, 72) depending on the study. Only one study carried out a single yoga session with patients with AN (67). The intensity of PE was not specified in all these studies. The summary of ET intervention parameters from these eleven studies highlighted a mean session length of 74.54 min (± 27.96), a mean frequency of 1.35 (± 0.74) sessions per week, and a mean ET duration of 8.5 weeks (± 4.56).

Of these studies, seven assessed the effects of ET on ED symptoms with validated questionnaires (55, 58–60, 67, 71, 72), such as the eating attitude test (EAT-26 and EAT-40) (76, 77), the eating disorder inventory (EDI versions 1, 2, and 3) (78–80), and the eating disorder examination questionnaire (EDE-Q) (81). Three studies showed a significant improvement in the ED symptoms for the intervention group post-program, and more specifically on the subscales assessing drive for thinness/body dissatisfaction and weight and shape concerns (59, 71, 72). Five studies assessed the effects on ED symptoms with other scales and four of them showed significant improvements in body image, body dissatisfaction and body attitude.

Seven studies evaluated the effect of ET interventions on psychological disorders associated with AN, such as anxiety, depression, positive and negative affect, self-esteem and quality of life. Of them, four studies revealed significant effects (**Table 5**). The results found by Hall et al. (72) showed that regular yoga training (i.e., one or two sessions per week for eight to twelve weeks) significantly decreased depression and anxiety scores, and improved state of mind in young women with AN or other ED (72). In their study, Pacanowski et al. (60) showed that one daily yoga session practiced for five days before dinner significantly reduced the negative affect of patients with AN or other ED, compared to the control group (60).

TABLE 5 Characteristics and main results of studies (RCT, NRCT, UT) conducted on effects of mind-body physical exercise in patients with AN.

References	Study type	Type of therapy	Participants' characteristics Sample size (% female), mean age (SD) Mean BMI (SD) and ED type (%)	Post-intervention dropout, n (%)	Follow-up dropout, n (%)	Treatment settings	Intervention parameters		Outcomes
Carei et al. (58)	RCT	ET + SC	*n* = 26 (92%), 10 to 21 (NR) 19.51 (± 3.01), AN (55%), BN (17%), EDNOS (28%)	2 (8%)	1 (4%)	Outpatient	Yoga Individualized: yes I/P ratio = 1/1	D = 60 min I = NR F = 2x/week P = 8 weeks NA = no	**ED symptoms:** EDE-Q; **Physical health:** BMI; **Mental health:** BDI-II; STAI.
		SC	*n* = 27 (92%), 10 to 21 (NR) 18.88 (± 2.32), AN (55%), BN (17%), EDNOS (28%)	1 (4%)	1 (4%)				
Catalan-Matamoros et al. (59)	RCT	ET + SC	*n* = 14 (93%), 29,5 (NR) 18.8 (± 0.5), AN (36%), BN (50%), EDNOS (14%)	0 (0%)	/	Outpatient	BBAT (based on massages and postures exercises) Individualized: no I/P ratio = NR (in group)	D = 90 min I = NR F = 1x/week P = 12 weeks NA = no	**ED sympto ms:** EDI*; EAT-40*; **Mental health:** SF-36*; BAT*.
		SC	*n* = 14 (93%), 25,2 (NR) 19.6 (± 0.7), AN (37.5%), BN (37,5%), EDNOS (25%)	6 (43%)	/				
Pacanowski et al. (60)	RCT	ET + SC	*n* = 20 (100%), 26.8 (± 10.3) 21.5 (± 7.5), AN (58%), BN (21%), EDNOS (21%)	1 (5%)	/	Inpatient	Yoga before dinner Individualized: NR I/P ratio = NR	D = 60 min I = NR F = 1x/day P = 5 days NA = no	**ED symp toms:** EDE-Q. **Physical health:** BMI; **Mental health:** EAQ; PANAS*.
		SC	*n* = 18 (100%), 26.8 (± 8.7) 18 (± 3.9), BN (21%), EDNOS (21%)	1 (6%)	/				
Moscone et al. (8)	NRCT	ET + SC	n = 19 (100%), 26 (± 6.5) 16.35 (± 2.49), AN (100%)	NR	/	Inpatient	Yoga/stretching Individualized: NR I/P ratio = NR	D = 60 min I = low F = 2x/week P = 3 months NA = no	**Mental health:** PSDQ; CDRS; RSES.
		NI (H)	*n* = 16 (100%), 24.6 (± 3) 21.7 (± 2.99)	NR	/				
Keizer et al. (65)	NRCT	ET + SC	*n* = 16 (100%), 22.87 (± 2.9) 19.53 (± 1.04), AN (100%)	2 (12%)	/	Outpatient	Hoop training (moving in hoops according to body size perception) Individualized: yes I/P ratio = 1/1	D = 5-10 min I = NR F = NR P = 8 weeks NA = no	**Mental heal th:** BAT; VET; TET; HT.
		SC	*n* = 14 (100%), 23.17 (± 5.67) 20.11 (± 1.17), AN (100%)	2 (14%)	/				
		NI (H)	*n* = 20 (100%), 21.21 (± 1.44) 20.8 (± 1.61)	1 (5%)	/				

(Continued)

10.3389/fpsyt.2022.939856

TABLE 5 (Continued)

References	Study type	Type of therapy	Participants' characteristics Sample size (% female), mean age (SD) Mean BMI (SD) and ED type (%)	Post-intervention dropout, n (%)	Follow-up dropout, n (%)	Treatment settings	Intervention parameters		Outcomes
Savidaki et al. (66)	NRCT	ET + SC	*n* = 7 (100%), 20.1 (± 5.9) 19.82 (± 4.37), AN (43%), EDNOS (57%)	0 (0%)	/	Inpatient	Dance movement therapy Individualized: yes I/P ratio = 1/4-5	D = 90 min I = NR F = 1x/week P =4 to 11 sessions (mean = 7.71) over 14 weeks NA = no	**Physical health:** BMI; **Mental health:** TAS-20; MBSRQ*.
		SC	*n* = 7 (100%), 20.3 (± 2.5) 19.07 (± 2.28), AN (40%), BN (20%), EDNOS (40%)	2 (29%)	/				
Demartini et al. (67)	NRCT	ET + SC	*n* = 15 (100%), 28 (± 11.22) 16.11 (± 4.33), AN (100%)	0 (0%)	/	Outpatient	One yoga class Individualized: yes I/P ratio = NR (in group)	D = 75 min I = NR F = 1x P = 1 day NA = no	**ED symptom s:** EDI-2. **Physical health:** BMI; **Mental health:** HAM-D; HAM-A; BAQ; TAS-20; SOQ; HR; Iac.
		NI (H)	*n* = 20 (100%), 28.59 (± 9.85) 21.23 (± 3.12)	0 (0%)	/				
Cook-Cottone et al. (71)	UT	ET + SC	*n* = 29 (100%), 20 (NR) 18.3 to 29.3, AN (100%)	5 (17%)	/	Outpatientt	Yoga, relaxation and meditation Individualized: yes I/P ratio = 1/1 and NR for group sessions	D = 120 min I = NR F = 1x/week P = 6-8 weeks NA = no	**ED symptoms:** EDI-2. **Physical health:** BMI; **Mental health:** subscales: drive for thinness*, body dissatisfaction*, and bulimia;
Hall et al. (72)	UT	ET + SC	*n* = 20 (100%), 12.61 (± 0.59) 17.28 (± 2.55), AN (15%), BN (5%), ARFID (5%), OSFED (75%)	9 (45%)	/	Outpatient	Yoga Individualized: NR I/P ratio = NR	D = 60-90min I = NR F = 1x/week P = 12 weeks NA = no	**ED symptoms:** EAT-26*; EDE-Q*. **Physical health:** BMI; **Mental health:** SOM*; STAI*.
Diers et al. (73)	UT	ET + SC	*n* = 91 (99%), age = NR BMI = NR, AN, BN, OSFED (%NR)	24 (26%)	/	Outpatient	Yoga Individualized: yes I/P ratio = NR (in group)	D = 90 min I = NR F = 1x/week P = 8 weeks NA = no	**Mental health:** Body image questionnaire* (constructed by the first author).

(Continued)

10.3389/fpsyt.2022.939856

TABLE 5 (Continued)

References	Study type	Type of therapy	Participants' characteristics Sample size (% female), mean age (SD) Mean BMI (SD) and ED type (%)	Post-intervention dropout, n (%)	Follow-up dropout, n (%)	Treatment settings	Intervention parameters		Outcomes
Martinez-Sanchez et al. (54) and Martinez-Sanchez et al. (55)	UT	ET + SC	n = 15 (100%), 14.6 (± 1.7) 19.6 (± 2.2), AN (100%)	3 (20%)		NR	Pilates Individualized: yes I/P ratio = NR (in group)	D = 60 min I = NR F = 3x/week P = 10 weeks NA = no	**ED symptoms:** EDI-3. **Physical health:** BMI, impedance analysis for body composition (total body water, body FM, LM, SMM, FFM,%body fat, bone mineral content); 34 measures from blood analysis (calcium* and follitropin*); Sedentary time, night sleep duration*, sleep latency, night perturbations* and sleep efficiency*. **Mental health:** CDRS*; K27*;

SD, standard deviation; ED, eating disorders; ET, exercise therapy; BMI, body mass index; ED, eating disorder; RCT, randomized controlled trial; NRCT, non-randomized controlled trial; UT, uncontrolled trial; SC, standard care; NI, no intervention; H, healthy community sample; NR, not reported; AN, anorexia nervosa; BN, bulimia nervosa; EDNOS, eating disorder not otherwise specified; ARFID, avoidant/restrictive food intake disorder; OSFED, other specified feeding or eating disorder; I/P ratio, Instructor/Patient ratio; D, session duration; I, intensity; F, frequency; P, period; NA, nutritional adjustment; EDI-2, eating disorder inventory 2; EDE-Q, eating disorder examination questionnaire; BDI-II, Beck depression inventory-II; STAI, state and trait anxiety inventory; BBAT, basic body awareness therapy; EDI, eating disorder inventory; EAT-40, eating attitude test 40-items; SF-36,medical outcomes study 36-items short-form health survey; BAT, body attitude test; PSDQ, physical self-description questionnaire; CDRS, contour drawing rating scale; RSES, Rosenberg self-esteem scale; SOM, state of mind questionnaire; EAT-26, eating attitudes test 26-Item; EAQ, emotional avoidance questionnaire; PANAS, positive and negative affect schedule; VET, visual estimation task; TET, tactile estimation task; HT, hoop task; FM, fat mass; SMM, skeletal muscle mass; FFM, fat free mass;%BF;% body fat; EDI-3, eating disorder inventor-3; K27, KIDSCREEN 27; TAS-20, Toronto alexithymia scale, MBSRQ, multidimensional body-self relations questionnaire; HAM-D, Hamilton rating scale for depression; HAM-A, Hamilton anxiety rating scale; BAQ, body-awareness questionnaire; SOQ, self-objectification questionnaire; HR, heart rate; **Iac**, interoception accuracy; *, significant improvement for the intervention group.

Catalan-Matamoros et al. (59) revealed a significant increase in the mental health score assessed by the SF-36 quality of life questionnaire after twelve weeks of one weekly session of basic body awareness therapy (59, 82). In the same way, Martinez-Sanchez et al. (55) showed a significant improvement in quality of life on the Kid Screen-27 questionnaire for young anorexic patients after 10 weeks of Pilates (54).

The study by Martinez-Sanchez et al. (54) revealed additional significant results. They found an increase in plasma calcium, involved in various functions of the body, and a decrease in plasma follitropin, involved in ovum production. In addition, results showed improvements in sleep parameters, such as a decrease in duration and number of night perturbations and an increase in sleep efficiency (55).

Seven studies assessed the BMI of participants, but none revealed any effect of MBPE (54, 55, 58, 60, 66, 67, 71, 72). Four studies reported no significant effect on any of their measures (8, 58, 65, 67). The study by Keizer et al. did not perform any statistical analyses (65).

Effects of combined physical exercise interventions

Over the identified period, eight studies from 1993 to 2020 have investigated the effect of combined PE interventions (i.e., composed of at least 2 different types of PE) in patients with AN (**Table 6**) (61–63, 68–70, 74, 75). Of these studies, three were RCTs (61–63), three were NRCTs (68–70) and two were UTs (74, 75). The combined PE interventions were carried out one (75), two (62, 70, 74), three (61, 63) or four times per week (69) depending on the study, with a session duration of 60 min (69), 90 min (75), 100 min (62, 74), 120 min (63, 70), or 180 min (68) depending on the study. Only one study did not report the frequency of sessions (68), and only one study did not mention the duration of the session (61). The durations were 4 weeks (62, 74), 6 weeks (68), 8 weeks (75) or 12 weeks (61, 63, 70) depending on the study. Only one study did not report the duration of the ET intervention (69). The intensity was not documented in all of these studies. To manage progression, two studies reported adaptations to regulate PE intensity and difficulty (61, 75). The summary of ET interventions parameters from these eight studies highlighted a mean session length of 98.33 minutes (± 22.28), a mean frequency of 2.28 (± 0.95) sessions per week, and a mean duration of 8.14 weeks (± 3.84).

Touyz et al. (68) were the first to examine the effect of a combined PE intervention (i.e., 180 min per week for 6 weeks of stretching, posture enhancement, weight training, social sport, and occasional aerobic activity) on the health of patients with AN. They did not reveal any significant differences in BMI or weight gain after the intervention (68). In the same way, Thien et al. (61) showed no increase in BMI or body

TABLE 6 Characteristics and main results of studies (RCT, NRCT, UT) conducted on effects of combined physical exercise interventions in patients with AN.

References	Study type	Type of therapy	Participants' characteristics Sample size (% female), mean age (SD) Mean BMI (SD) and ED type (%).	Post-intervention dropout, n (%)	Follow-up dropout, n (%)	Treatment settings	Intervention parameters		Outcomes
Thien et al. (61)	RCT	ET + SC	n = 8 (100%), 29 (± 4.4) 20.26 (± 1.8), AN (100%)	3 (37.5%)	/	Outpatient	Stretching, resistance and aerobic exercise Individualized: Yes I/P ratio = NR	D = NR I = progressive intensity (7 levels) F = 3x/week P = 3 months NA = no	**Physical health:** BMI; %BF; **Mental health:** SF-36.
		SC	n = 8 (87.5%), 36.1 (± 7.9) 17.2 (± 1.6), AN (100%)	1 (12.5%)	/				
Dittmer et al. (62)	RCT	ET + SC	n = 112 (100%), 20.04 (± 5.7) 14.98 (± 1.96), AN (80%), EDNOS (20%)	24 (21%)	15 (13%)	Inpatient	CBT coupled with PE (yoga, recreational activity, body exploration, dual task exercises) Individualized: yes I/P ratio = 1/1 and NR for group sessions	D = 100 min I = NR F = 2x/week P = 4 weeks NA = no	**ED symptoms:** EDE-Q. **Physical health:** BMI; **Mental health:** CES*; CET*; BDI-II; BSI; DERS.
		SC	n = 95 (100%), 18.32 (± 5.19) 15.35 (± 1.86), AN (68%), EDNOS (22%)	21 (22%)	19 (20%)				
Zeeck et al. (63)	RCT	ET + SC	n = 15 (94%), 24.3 ± 3.4 20.3 ± 2.7, AN (33%), BN (60%), OSFED (7%)	3 (20%)	0 (0%)	Outpatient	Educational program and PE (45-60min playful activities, team sports, body-oriented exercises) (group) Individualized: yes I/P ratio = 1/1 and 1/5-8	D = 120 min I = NR F = 2x/week P = 12 weeks NA = no	**ED symptoms:** E DE-Q; EDI-2 subscales drive for thinness, bulimia and body dissatisfaction. **Physical health:** BMI; Exercise quantity with accelerometer; **Mental health:** CES; CET*; EDS; SCL-27; BDI-II; IPAQ;
		SC	n = 11 (100%), 27.2(± 8.8) 19.2 (± 2.1), AN (45.5%), BN (36.4%), OSFED (18.1%)	0 (0%)	0 (0%)				
Touyz et al. (68)	NRCT	ET + SC	n = 19 (100%), 15.94 (± 2.45) 14.82 (± 1.01), AN (100%)	NR	2 (10%)	Inpatient	stretching, posture enhancement, weight training, social sport and occasional aerobic activity with no impact (individually and group) Individualized: yes I/P ratio = 1/1 and NR for group sessions	D = 180 min I = NR F = NR P = 6 weeks NA = no	**Physical healt h:** BMI; Weight; Weight gain.
		SC	n = 20 (100%), 20 (± 5.28) 14.28 (± 1.32)	NR	0 (0%)				

(Continued)

10.3389/fpsyt.2022.939856

TABLE 6 (Continued)

References	Study type	Type of therapy	Participants' characteristics Sample size (% female), mean age (SD) Mean BMI (SD) and ED type (%).	Post-intervention dropout, n (%)	Follow-up dropout, n (%)	Treatment settings	Intervention parameters		Outcomes
Calogero& Pedrotty (69)	NRCT	ET + SC	n = 127 (100%), 22.49 (± 7.96), 18.45 (± 5.24), AN (50%), BN (33%), EDNOS (17%)	NR	/	Inpatient	stretching, yoga, Pilates, weight training, recreational activity, endurance activity (group) Individualized: yes I/P ratio = 1/1 and NR for group sessions	D = 60 min I = NR F = 4x/week P = length of the stay NA = no	**ED sympto ms:** items from EDE-Q. **Physical health:** BMI; Weight gain*; **Mental health:** OEQ*; OBC-AC; EDPEX.
		SC	n = 127 (100%), 23.14 (± 8.72) 20.54 (± 5.98), AN (41%), BN (37%), EDNOS (22%)	NR	/				
Schleg el et al. (70)	NRCT	ET + SC	n = 18 (89%), 24.8 (± 3.5) 21.7 (± 4.1), AN (33%), BN (56%), EDNOS (11%)	11 (34%)	/	Outpatient	Educational program and PE (45-60' playful activities, team sports, body-oriented exercises) (group) Individualized: yes 1/1 and NR for group sessions	D = 120 min I = NR F = 2x/week P = 12 weeks NA = no	**ED sympt oms:** EDI-2 subscales drive for thinness and body dissatisfaction; EDE-Q. **Physical health:** BMI; **Mental health:** CES*; SF-12.
		SC	n = 18 (94%), 26.1 (± 6.8) 21.3 (± 5.3), AN (33%), BN (56%), EDNOS (11%)		/				
Dittmer et al. (74)	UT	ET + SC	n = 32 (100%), 22.6 (± 8.25) 15.67 (± 1.54), AN (81%), BN (6%), EDNOS (13%)	9 (28%)	/	Inpatient	CBT coupled with PE (yoga, recreational activity, body exploration, dual task exercises) Individualized: yes 1/1 and NR for group sessions	D = 100 min I = NR F = 2x/week P = 4 weeks NA = no	**ED symptoms:** EDI-2*. **Physical health:** BMI*; **Mental health:** CES*; CET*; BDI-II*; BSI*; ERSQ*.
Kern et al. (75)	UT	ET + SC	n = 41 (100%), 16.35 (± 1.33) 16.76 (± 2.03), AN (100%)	12 (29%)	/	Inpatient	Resistance exercise and shadow boxing Individualized: yes 1/1 and NR for group sessions	D = 90 min I = low F = 1x/week P = 8 weeks NA = no	**ED symptoms:** EDE-Q*. **Physical health:** BMI*; **Mental health:** GLTEQ*; EDSR*; EDQ*; DUKE-HP*.

SD, standard deviation; ED, eating disorders; ET, exercise therapy; BMI, body mass index; ED, eating disorder; RCT, randomized controlled trial; NRCT, non-randomized controlled trial; UT, uncontrolled trial; SC, standard care; NR, not reported; AN, anorexia nervosa; BN, bulimia nervosa; EDNOS, eating disorder not otherwise specified; OSFED, other specified feeding or eating disorder; I/P ratio, Instructor/Patient ratio; D, session duration; I, intensity; F, frequency; P, period; NA, nutritional adjustment;%BF,%body fat; SF-36,medical outcomes study 36-items short-form health survey; EDE-Q, eating disorder examination questionnaire; OEQ, obligatory exercise questionnaire; OBC-AC, objectified body consciousness scale—appearance control subscale; EDPEX, eating disorder patient's expectations and experiences of treatment questionnaire; CES, commitment exercise scale; EDI-2, eating disorder inventory 2; CBT, cognitive behavioral therapy; PE, physical exercise; CET, compulsive exercise test; BDI-II, Beck depression inventory-II; BSI, brief symptom inventory; ERSQ, emotion regulation skills questionnaire; DERS, difficulties in emotion regulation scale; GLTEQ, Godin leisure-time exercise questionnaire; EDSR, exercise dependence scale-revised; EDQ, exercise dependence questionnaire; DUKE-HP, DUKE health profile; EDS, exercise dependence scale; SCL-27, symptom check list-27; IPAQ, international physical activity questionnaire; *, significant improvement for the intervention group.

10.3389/fpsyt.2022.939856

fat in patients with AN after a combined PE intervention including stretching, aerobic exercises and resistance training performed three times a week over three months. Nonetheless, their results revealed a trend in the improvement of quality of life in the intervention group compared to the control group (**Table 6**) (61).

Calogero and Pedrotty conducted the largest inpatient interventional study with 254 patients with ED. In this study, 127 patients underwent one month of ET intervention including four weekly sessions of 60 minutes of stretching, yoga, Pilates, strength training, balance and coordination practice and aerobic exercise, and were compared to 127 no-exercise patients (69). The results showed a significant increase in weekly weight gain, as well as total post-program weight regain in the intervention group compared to the control group. There was also a significant reduction in dysfunctional exercise (e.g., compulsiveness, physical hyperactivity), as assessed by questionnaire, for the intervention group (**Table 6**).

Schlegel et al. developed the Freiburg sport therapy program, designed for outpatients with ED (70). This program was conducted over 12 weeks with two 120-minute sessions per week. Each session was composed of an educational program focused on good practices and healthy behaviors concerning PE, coupled with team sports and body-oriented and playful PE. For the intervention group, the results showed a significant reduction in obligatory and excessive exercising assessed using the commitment to exercise scale (CES) (83). Based on this pilot study, Zeeck et al. conducted an outpatient RCT using the Freiburg sport therapy program (63). They found a significant reduction in unhealthy exercise behaviors assessed using the compulsive exercise test (CET) for the intervention group (84).

Two other studies obtained similar results with another ET intervention. The uncontrolled pilot study by Dittmer et al. assessed the effect of cognitive behavioral therapy (CBT) focused on changing practice behavior and attitude toward exercise, coupled with various PE (i.e., yoga, recreational activities, dual-task training, and body exploration) (74). After four weeks of two 100-min sessions per week, the results showed a significant increase in BMI, as well as a significant decrease in dysfunctional exercise behavior, desire for thinness, perfectionism, and depression level. Regarding this pilot study, Dittmer et al. carried out an RCT using the same protocol with a larger inpatient sample of 207 ED patients, including a majority of patients with AN (62). The results showed a significant reduction in compulsive exercise behavior measured using the CET and CES for the intervention group, after ET intervention and at the 6-month follow-up (**Table 6**).

The UT by Kern et al. examined the effects of one 90-minute session per week of resistance training and shadow boxing for 8 weeks (75). They found a significant increase in BMI and quality of life, as well as a significant decrease in exercise dependence, physical activity level, and specific symptoms of AN, such as eating, weight and shape concerns (**Table 6**).

Quality assessment of the studies

Overall, according to the PEDro scale criteria, the 27 studies presented a fair quality with a mean score of 4.29 ($\pm$ 1.66), ranging from 2 to 7 on a scale of 0 to 10 (**Table 7**). The PEDro mean score was slightly higher when only RCTs were considered (i.e., 5.61 $\pm$ 0.96), but still reflected a fair quality of the methodological procedures. When only NRCTs were considered, mean score was 3.86 ($\pm$ 0.90) which was between fair and poor quality. When only UTs were considered, mean score was 2.28 ($\pm$ 0.75) which revealed a poor quality. Among the 27 studies, seven studies (26%) were considered to be of good quality (score = 6–8), twelve studies (44%) were considered to be of fair quality (score = 4–5), and eight (30%) studies were considered to be of poor quality (score $\leq$ 3). The only study that examined the effect of aerobic exercise alone in patients with AN had a score of 4, indicating a fair methodological quality for this study. Concerning the studies including resistance exercises (RCTs), the mean score was 5.71 ($\pm$ 1.11) which revealed good quality. The 11 studies based on MBPE (3 RCT, 4 NRCT and 4 UT) obtained a mean score of 3.63 ($\pm$ 1.75) indicating fair quality. When only RCTs were considered for MBPE studies, the PEDro mean score was 6 ($\pm$ 0), indicating good methodological quality. The mean score obtained for the eight studies based on combined PE intervention (3 RCT, 3 NRCT and 2 UT) was 4 ($\pm$ 1.41), or fair quality. Regarding combined PE, when only RCTs were considered, the PEDro mean score was 5 ($\pm$ 1), reflecting the same level of quality.

Discussion

This systematic review reveals that ET supervised by exercise professionals does not adversely affect the health of patients with AN, either in outpatient or inpatient settings; therefore, PE cannot be systematically contraindicated. Furthermore, beneficial effects have been identified both on the symptomatology of AN and on physical and mental health. In most of the controlled studies presented in this review, patients with ET intervention in addition to their usual care showed similar (49, 58, 61, 67, 68) or even greater improvements (50–53, 56, 57, 59, 60, 62–64, 66, 69, 70) than the control group in all the dimensions assessed. We examined comparable studies for differences in observed effects between inpatients and outpatients and found little or no difference. For example, all studies investigating the impact of combined PE interventions, with the exception of Dittmer et al. (74),

TABLE 7 PEDro scale scores.

		Random assignment	Concealed allocation	Baseline group similarity	Blind subjects	Blind therapists	Blind assessors	Less than 15% dropout	Intention-to-treat analysis	Between-group comparisons	Estimating the effect and its variability	Total
A. Studies conducted on effects of aerobic exercise in patients with AN												
1	Tokumura et al. (64)*	0	0	1	0	0	0	0	1	1	1	**4**
	Mean score RCT = 0/10; Mean of NRCTs scores = 4/10; Mean of UTs scores = 0/10										*Mean score (A)*	**4**
B. Studies conducted on effects of resistance exercise in patients with AN												
1	Szabo & Green (49)**	1	0	1	0	0	0	0	1	1	1	**4**
2	Chantler et al. (50)**	1	0	1	0	0	0	0	1	1	1	**5**
3	Fernandez-del-Valle et al. (56)**	1	1	1	0	0	0	1	1	1	1	**7**
4	Fernandez-del-Valle et al. (51)**	1	0	1	0	0	0	1	1	1	1	**6**
5	Fernandez-del-Valle et al. (52)**	1	0	1	0	0	1	1	1	1	1	**7**
6	Fernandez-del-Valle et al. (53)**	1	0	1	0	0	0	0	1	1	1	**5**
7	Martin et al. (57)**	1	0	1	0	0	0	1	1	1	1	**6**
	Mean score RCT = 5,71/10; Mean of NRCTs scores = 0/10; Mean of UTs scores = 0/10										*Mean score (B)*	***5, 71***
C. Studies conducted on effects of mind-body physical exercise interventions in patients with AN												
1	Cook-Cottone et al. (71)	0	0	0	0	0	0	0	1	0	1	**2**
2	Carei et al. (58)**	1	0	1	0	0	0	1	1	1	1	**6**
3	Moscone et al. (8)*	0	0	0	0	0	0	1	1	1	1	**4**
4	Catalan-Matamoros et al. (59)**	1	1	1	0	0	0	0	1	1	1	**6**
5	Hall et al. (72)	0	0	0	0	0	0	0	1	0	1	**2**
6	Pacanowski et al. (60)**	1	0	1	0	0	0	1	1	1	1	**6**
7	Keizer et al. (65)*	0	0	0	0	0	0	1	1	0	0	**2**
8	Diers et al. (73)	0	0	0	0	0	0	0	1	0	1	**2**
9	Martinez-Sanchez et al. (54, 55)	0	0	0	0	0	0	0	1	0	1	**2**
10	Savidaki et al. (66)*	0	0	0	0	0	0	1	1	1	1	**4**
11	Demartini et al. (67)*	0	0	0	0	0	0	1	1	1	1	**4**
	Mean score RCT = 6/10; Mean of NRCTs scores = 3.50/10; Mean of UTs scores = 2/10										*Mean score (C)*	***3, 63***

(Continued)

10.3389/fpsyt.2022.939856

10.3389/fpsyt.2022.939856

TABLE 7 (Continued)

		Random assignment	Concealed allocation	Baseline group similarity	Blind subjects	Blind therapists	Blind assessors	Less than 15% dropout	Intention-to-treat analysis	Between-group comparisons	Estimating the effect and its variability	Total
D. Studies conducted on effects of combined physical exercise interventions in patients with AN												
1	Touyz et al. (68)*	0	0	0	0	0	0	1	1	1	1	**4**
2	Thien et al. (61)**	1	0	0	0	0	0	0	1	1	1	**4**
3	Calogero & Pedrotty (69)*	0	0	1	0	0	1	0	1	1	1	**5**
4	Schlegel et al. (70)*	0	0	1	0	0	0	0	1	1	1	**4**
5	Dittmer et al. (74)	0	0	0	0	0	0	0	1	0	1	**2**
6	Dittmer et al. (62)**	1	0	1	0	0	0	0	1	1	1	**5**
7	Kern et al. (75)	0	0	0	0	0	0	0	1	0	1	**2**
8	Zeeck et al. (63)**	1	0	1	0	0	0	1	1	1	1	**6**
						Mean score RCT = 5/10; Mean of all NRCTs scores = 3.86/10; Mean of all UTs scores = 2/10					*Mean score (D)*	**4**
						Mean of all RCTs scores = 5.61/10; Mean of all NRCTs scores = 3.87/10; Mean of all UTs scores = 2/10					*Mean of all scores*	**4, 29**

**Randomized controlled trial; * non-randomized controlled trial; PEDro score 9-10 = high quality; PEDro score 6-8 = good quality; PEDro score 4-5 = fair quality; PEDro score ≤ 3 = poor quality.

found no increase in BMI post-program, regardless of whether patients were hospitalized. In the same way, among these studies, the three that examined the effect of combined PE interventions on compulsive exercise in patients with AN using the CET questionnaire found a significant increase in CET score after the program for inpatients (59) as well as outpatients (60, 73).

The study by Tokumura et al. (64) was, to our knowledge, the only study to investigate the effectiveness of exclusively aerobic exercise on patients with AN, which is unsurprising given that this type of PE is generally avoided in the care of patients with AN. Overly intensive exercise, particularly aerobic exercise modes such as running and swimming, may seem inappropriate for patients with severe undernutrition due to its high energy expenditure requirement, which could lead to even greater weight loss or other medical risks (85). Nevertheless, their results revealed increase in cardiorespiratory capacity and BMI. Thus, this specific cardiorespiratory training program of 30 minutes of stationary bicycling at the anaerobic threshold five times per week appears to be beneficial for patients with AN.

In most studies that included resistance exercise program, interventions parameters were from low-to-high intensity, 2-3 times per week for at least 8 weeks. They revealed significant increases in muscle strength, no adverse effect on bone density and a faster stabilization of vital signs. The four studies conducted by Fernandez-del-Valle et al. (51–53, 56) made an important contribution to this topic. Their results first revealed that resistance exercise was not harmful to patients' health (48) and further showed that higher intensity and frequency contributed to enhanced effects on strength and anthropometric parameters (51–53). The findings of the studies assessing resistance exercise interventions suggest that this type of PE is suitable for patients with AN to improve muscle strength and size (50–53, 56), and restore bone mineralization (57). Finally, it is important to mention that in all of these studies, additional caloric intake was given to the intervention group to counterbalance the energy expenditure, except for the study of Fernandez-del-Valle et al. (56) and the study of Martin et al. (57).

Almost half of the studies that included MBPE showed significant improvements in specific symptoms of AN and psychological associated disorders, such as body shape and body concerns, body dissatisfaction, depression, anxiety and quality of life (54, 59, 60, 66, 71–73). MBPE such as yoga or Pilates offers patients the opportunity to be physically active while avoiding weight loss and excessive caloric expenditure (33). In addition, the mobilization of an often-rejected body leads patients to develop more positive feelings about their body image and a healthier relationship with their body (8). One study also revealed the positive impact of MBPE on the sleep quality and sleep efficiency of patients (55). All of

these results tend to provide evidence of the effectiveness of this type of PE in patients with AN. However, they must be taken with caution because most of these studies are NRCTs or UTs, only three RCTs were carried out (58–60) and two showed significant improvements (59, 60) (i.e., ED symptoms, quality of life, body attitude and negative affects).

Finally, most studies that examined the effects of ET intervention using combined PE showed positive effects in patients with AN, especially on dysfunctional exercise behaviors, with a reduction of compulsive exercise and exercise dependence (62, 63, 69, 70, 74, 75). In addition, a few studies revealed that combined PE contributed to the increase of weight (69, 74, 75), and reduction in specific symptoms of AN (74, 75), as well as anxiety and depression (74). These findings are congruent with the primary goals of AN treatment. Therefore, ET intervention including various types of PE seems promising for clinical practice and future research. However, once again, results must be taken we caution as there were only three RCTs (61–63) and only two revealed significant improvements (62, 63) (i.e., compulsive exercise and commitment to exercise). It is worth to mention that other than BMI, physical and biological parameters such as muscle strength, muscle endurance, respiratory capacities, and blood analysis have never been assessed for this type of PE intervention in AN patients.

Taken together, all these results suggest that, despite the heterogeneity of the results (especially regarding MBPE), ET may have multiple benefits for patients with AN, which depend on the type of PE practiced. Therefore, it seems difficult to limit recommendations for PE within clinical management to a single type of PE, unless one type of PE is targeted according to the primary therapeutic goals. For example, if the main therapeutic goal is to improve the patient's muscle mass and strength, resistance training could be the best choice according to data from the literature. Indeed, the majority of studies that examined the effects of a resistance training protocol in anorexic patients have shown significant gain in muscle mass and strength in these patients. However, as studies that examined the benefits of other types of PE in patients with AN have not measured effects on muscle function, it is not possible to state that other types of PE are not equally effective in improving muscle mass and strength. Thus, even if this systematic review could be useful for clinicians to make informed choices about which type of PE to recommend, further studies are needed to explore and compare the effects of each type of PE on the same health outcomes.

Moreover, it can be assumed that the benefits achieved may also vary depending on the ET intervention parameters. Results of the present review support the argument that for any given PE, some specific parameters such as the period or frequency of PE sessions could be more effective than others in reducing the symptoms of AN, or in improving the physical and psychological health of patients. However, it is difficult to make precise recommendations regarding specific ET intervention parameters to improve the therapeutic strategy of AN treatment. Indeed, results revealed that the duration, as well as the frequency and length of the sessions, varied greatly between different types of PE and within similar intervention types. In ET intervention including resistance exercise, patients were commonly asked to engage in an 8-week program, with two or three 60-minute sessions per week. Concerning MBPE intervention, the frequency of sessions usually varied from one to two per week, for 8–12 weeks, with sessions ranging from 60 to 120 minutes. It is in the ET intervention including combined PE that can be observed the higher heterogeneity in parameters, with a period of four to twelve weeks, a frequency ranging from one to four per week and length varying from for 60–180 minutes per session.

As a consequence and in agreement with the collective expertise report on the health effects of PE in patients with chronic diseases, coordinated by the French National Institute of Health and Medical Research (86), the major public health issue is now to determine the most efficient ET intervention parameters and to adapt them to the patients' individual needs.

Limitations and future directions

In recent years, there has been an increasing interest in clinical research focusing on the feasibility and effectiveness of ET intervention as a therapeutic strategy for patients with AN, or more broadly for patients with ED. Indeed, most of the studies included in the present review (67%) were published in the last decade. However, this systematic review reveals that the quality of the studies remains too small to obtain a good level of evidence. Indeed, the overall quality of the studies included, measured using the PEDro scale, was fair with a total mean score of 4.29 ($\pm$ 1.66). The most common methodological weaknesses were the absence of randomization, the lack of concealed allocations, the non-blinding of therapists and assessors, and a high dropout rate. However, in the case of PE interventional research, given the near impossibility of blinding subjects (87), it was not surprising that all studies scored 0 for this criterion.

Moreover, we identified some methodological limitations that should be taken into consideration in the interpretation of the findings. First, only 13 of the 27 studies were RCTs, which may partly explain a low overall score on the PEDro scale. In addition, 13 of the 27 studies were pilot studies. Regarding the number of RCT conducted for each type of PE, the level of evidence was different with a higher level for resistance exercise (i.e., 7 RCT) and a lower level for MBPE (i.e., 3 RCT, 4 NRCT, and 4 UT), combined PE (i.e., 3 RCT, 3 NRCT, 2 UT) and aerobic exercise (i.e., 1 NRCT). Further, most of the studies did not report sample size

calculation and other major statistical lacks can be reported: 16 studies did not report a primary outcome while some studies reported multiple outcomes, but no formal adjustments were made for multiple comparisons. Only two studies performed a Bonferroni correction for multiple comparisons (51, 53). These different limitations underscore the need for caution in interpreting the results, particularly for studies without a control group, and should be addressed in future studies to provide greater methodological rigor and greater confidence in the research findings.

Other methodological limitations should be pointed out, such as the vast diversity of tools used to measure identical variables. This was particularly true for the measurement of body composition, which differed from one study to another. For example, while in studies by Fernandez-del-Valle's team (51–53), body composition was assessed by BMI calculation coupled with a measure of fat mass (FM), in the study by Martinez-Sanchez et al. (55), it was assessed by using a bioelectrical impedance analysis. Other studies simply assessed body composition using BMI calculation. However, it is now accepted that BMI, although a quick way to assess if a patient is underweight or overweight, remains an imprecise measure of body composition and actual metabolic risk, as its calculation considers weight as a whole and does not distinguish between fat and lean mass. For a more accurate and reliable measurement of body composition, some authors suggest the use of bioelectrical impedance analysis or dual x-ray absorptiometry (DEXA) measurement (88). Therefore, more direct assessments of body composition are needed in future research. In addition, the present review highlighted a diversity of measures used to assess the specific symptoms of AN (or ED) and their level of severity, which limits interpretation of the results and comparisons among studies. Thus, seven of the studies used the eating disorder examination questionnaire (EDE-Q), five used the eating disorder inventory 2 (EDI-2), two used the eating disorder inventory 1 (EDI), one used the eating disorder inventory 3 (EDI-3), one used the eating attitude test 40 (EAT-40), and one used the eating attitude test 26 (EAT-26). The same heterogeneity can be reported for other outcomes (for example, quality of life, exercise dependence, body dissatisfaction, PE time).

It is also important to note that the studies included very few men, with a total of 16 men out of the 27 studies included, compared to 1300 women. This small sample can be explained by the ratio usually reported in AN with only 1 man for 10 women. It can also raise the question of whether the findings of this systematic review apply to male participants regarding their low representativeness. Hence, a study including only male participants would be a first and major contribution to this field.

Although the main ET intervention parameters were usually reported (i.e., session duration, frequency and period), individualization, instructor to patient ratios, exercise intensity and adjustment of caloric intake were not always indicated, as well as the content of ET intervention was poorly detailed in most of the studies. Indeed, only a few studies mentioned the level of exercise intensity and only six detailed how progression was managed through the program (51–53, 56, 61, 75). According to these authors, the intensity of PE for patients with AN should be systematically controlled and graded. Indeed, a lack of gradation may result in anorexic patients exercising at a very high intensity, and therefore lead to further weight loss. In addition, this review showed that only a few authors described the delivery method (71) and the structure of the program (54, 55, 60, 61, 69, 71). Overall, the ET interventions were poorly described in the majority of studies, which makes reproducibility and comparability difficult.

Another bias can be identified. Indeed, among the studies, four included ET intervention coupled with another type of therapy (educational program or cognitive behavioral therapy) and did not allow to isolate the effects of ET intervention, which alone cannot completely explain the improvements observed in patients. Moreover, especially for studies conducted with inpatients (i.e., 10 studies among all selected studies), it is common for patients to receive other therapies in addition to ET intervention as part of their protocol of care (e.g., psychotherapy, nutritional follow-up). These treatments, which are rarely mentioned in studies, may also play a role in improving patients' health and may represent a bias in the results. Finally, it is unfortunate that in studies that included a majority of AN patients among other ED, results were not extracted, presented and analyzed separately for AN. Indeed, it would be interesting to have access to detailed results by type of ED, in order to examine the differences in effect according to pathology and to better target potential clinical applications.

Conclusion

This systematic review provides an overview of existing evidence regarding the effect of ET intervention in patients with AN. Specific benefits have been emphasized according to the type of PE intervention and can be considered for future research or clinical implications. Nevertheless, this review does not allow us to affirm that the effects obtained are related exclusively to a type of PE. For example, resistance training exercise revealed significant increase in muscular strength, which could also be achieved through the practice of a yoga or Pilates program. To our knowledge, this has not been examined in any previous study.

In addition, this review highlights several limitations of the existing literature, such as inconsistent results, a

fair methodological quality or heterogeneity of measures, which greatly contribute to lowering the quality of evidence of the studies and make it difficult to establish specific recommendations for patients with AN. However, ET intervention seems to be emerging as a therapeutic strategy that can contribute to the well-being and the recovery of patients with AN and does not induce deleterious effects as long as it is adapted to patients' profiles and supervised by exercise professionals. Further work is needed in this field of research to determine whether, in addition to being accepted and not limited, the integration of ET intervention within the management of patients with AN is truly effective, on what health outcomes and to what extent.

Data availability statement

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

Author contributions

MT, PL, and AG planned the research. MT and PL conducted the review. AG checked the search strategy and results. All authors contributed to write and read the manuscript, and approved the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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

References

1. Treasure J. Eating disorders. *Medicine.* (2016) 44:672–8. doi: 10.1016/j.mpmed.2016.08.001

2. Nandrino JL. *L'anorexie mentale.* Paris: Dunod (2015). doi: 10.3917/dunod.nandr.2015.01

3. van Eeden AE, van Hoeken D, Hoek HW. Incidence, prevalence and mortality of anorexia nervosa and bulimia nervosa. *Curr Opin Psychiatry.* (2021) 34:515–24. doi: 10.1097/YCO.0000000000000739

4. Eddy KT, Tabri N, Thomas JJ, Murray HB, Keshaviah A, Hastings E, et al. Recovery from anorexia nervosa and bulimia nervosa at 22-year follow-up. *J Clin Psychiatry.* (2017) 78:184–9. doi: 10.4088/JCP.15m10393

5. Frostad S, Rozakou-Soumalia N, Dârvariu Ş, Foruzesh B, Azkia H, Larsen MP, et al. BMI at discharge from treatment predicts relapse in anorexia nervosa: a systematic scoping review. *J Pers Med.* (2022) 12:836. doi: 10.3390/jpm12050836

6. Arcelus J, Mitchell AJ, Wales J, Nielsen S. Mortality rates in patients with anorexia nervosa and other eating disorders. A meta-analysis of 36 studies. *Arch Gen Psychiatry.* (2011) 68:724–31. doi: 10.1001/archgenpsychiatry.2011.74

7. American Psychiatric Association. *Diagnostics and Statistical Manual of Mental Disorders (DSM-5).* Fifth Edn. Washington, DC: American Psychiatric Association (2015).

8. Moscone AL, Leconte P, Le Scanff C. Self-perception and adapted physical activity in anorexia nervosa. *Sci Sports.* (2011) 26:225–8. doi: 10.1016/j.scispo.2011.04.006

9. Brusset B. *Psychopathologie de l'anorexie mentale*. Paris: Dunod (2008). doi: 10.3917/dunod.bruss.2009.01

10. Cros G, Sznajder M, Meuric S, Mignot C, Chevallier B, Stheneur C. Dénutrition rapide au cours de l'anorexie mentale: expérience d'un service de pédiatrie générale. *Arch Pédiatrie.* (2010) 17:112–7. doi: 10.1016/j.arcped.2009.10.026

11. El Ghoch M, Calugi S, Bernabè J, Pellegrini M, Milanese E, Chignola C, et al. Sleep patterns before and after weight restoration in females with anorexia nervosa: a longitudinal controlled study. *Eur Eat Disord Rev J Eat Disord Assoc.* (2016) 24:425–9. doi: 10.1002/erv.2461

12. Crenn P, Melchior JC. Bilan somatique et critères de gravité dans l'anorexie mentale. *Nutr Clin Métab.* (2007) 21:155–8. doi: 10.1016/j.nupar.2008.03.002

13. HAS. *Anorexie mentale: prise en charge [Internet].* (2010). Available online at: https://www.has-sante.fr/jcms/c_985715/fr/anorexie-mentale-prise-en-charge (accessed Oct 10, 2021).

14. Kass AE, Kolko RP, Wilfley DE. Psychological treatments for eating disorders. *Curr Opin Psychiatry.* (2013) 26:549–55. doi: 10.1097/YCO.0b013e328365a30e

15. Melchior JC, Hanachi M, Crenn P. Quand et comment conduire une nutrition entérale au cours de l'anorexie mentale ? *Nutr Clin Métab.* (2007) 21:201–8. doi: 10.1016/j.nupar.2008.03.007

16. Chakraborty K, Basu D. Management of anorexia and bulimia nervosa: an evidence-based review. *Indian J Psychiatry.* (2010) 52:174–86. doi: 10.4103/0019-5545.64596

17. Fogarty S, Smith CA, Hay P. The role of complementary and alternative medicine in the treatment of eating disorders: a systematic review. *Eat Behav.* (2016) 21:179–88. doi: 10.1016/j.eatbeh.2016.03.002

18. Foroughi N, Zhu KCY, Smith C, Hay P. The perceived therapeutic benefits of complementary medicine in eating disorders. *Complement Ther Med.* (2019) 43:176–80. doi: 10.1016/j.ctim.2019.01.025

19. Veerbeek JM, van Wegen E, van Peppen R, van der Wees PJ, Hendriks E, Rietberg M, et al. What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. *PLoS One.* (2014) 9:e87987. doi: 10.1371/journal.pone.0087987

20. Ashdown-Franks G, Firth J, Carney R, Carvalho AF, Hallgren A, Koyanagi M, et al. Exercise as medicine for mental and substance use disorders: a meta-review

of the benefits for neuropsychiatric and cognitive outcomes. *Sports Med Auckl N Z.* (2020) 50:151–70. doi: 10.1007/s40279-019-01187-6

21. Hausenblas HA, Cook BJ, Chittester NI. Can exercise treat eating disorders? *Exerc Sport Sci Rev.* (2008) 36:43–7. doi: 10.1097/jes.0b013e31815e4040

22. Hechler T, Beumont P, Marks P, Touyz S. How do clinical specialists understand the role of physical activity in eating disorders? *Eur Eat Disord Rev.* (2005) 13:125–32. doi: 10.1002/erv.630

23. Bratland-Sanda S, Sundgot-Borgen J, Rø Ø, Rosenvinge JH, Hoffart A, Martinsen EW. Physical activity and exercise dependence during inpatient treatment of longstanding eating disorders: an exploratory study of excessive and non-excessive exercisers. *Int J Eat Disord.* (2010) 43:266–73. doi: 10.1002/eat.20769

24. Bratland-Sanda S, Mathisen TF, Sundgot-Borgen J, Rosenvinge JH. Defining compulsive exercise in eating disorders: acknowledging the exercise paradox and exercise obsessions. *J Eat Disord.* (2019) 7:8. doi: 10.1186/s40337-019-0238-2

25. Rizk M, Lalanne C, Berthoz S, Kern L, Godart N, Grp E. Problematic exercise in anorexia nervosa: testing potential risk factors against different definitions. *PLoS One.* (2015) 10:143352. doi: 10.1371/journal.pone.0143352

26. Rizk M. *Implications of Hyperactivity in Anorexia Nervosa: From Redefinition to Clinical Research*. Ph.D. thesis. Paris: Université Sorbonne Paris (2015).

27. Schlegl S, Dittmer N, Hoffmann S, Voderholzer U. Self-reported quantity, compulsiveness and motives of exercise in patients with eating disorders and healthy controls: differences and similarities. *J Eat Disord.* (2018) 6:17. doi: 10.1186/s40337-018-0202-6

28. Davis C, Kaptein S. Anorexia nervosa with excessive exercise: a phenotype with close links to obsessive-compulsive disorder. *Psychiatry Res.* (2006) 142:209–17. doi: 10.1016/j.psychres.2005.11.006

29. Davis C, Katzman D, Kaptein S, Kirsh C, Brewer H, Kalmbach K, et al. The prevalence of high-level exercise in the eating disorders: etiological implications. *Compr Psychiatry.* (1997) 38:321–6. doi: 10.1016/S0010-440X(97)90927-5

30. Klein DA, Mayer LES, Schebendach JE, Walsh BT. Physical activity and cortisol in anorexia nervosa. *Psychoneuroendocrinology.* (2007) 32:539–47. doi: 10.1016/j.psyneuen.2007.03.007

31. Bratland-Sanda S, Sundgot-Borgen J, Ro O, Rosenvinge JH, Hoffart A, Martinsen EW. "I'm Not Physically Active - I Only Go for Walks": physical activity in patients with longstanding eating disorders. *Int J Eat Disord.* (2010) 43:88–92. doi: 10.1037/e522322010-004

32. Achamrah N, Coëffier M, Déchelotte P. Physical activity in patients with anorexia nervosa. *Nutr Rev.* (2016) 74:301–11. doi: 10.1093/nutrit/nuw001

33. Borden A, Cook-Cottone C. Yoga and eating disorder prevention and treatment: a comprehensive review and meta-analysis. *Eat Disord.* (2020) 28:400–37. doi: 10.1080/10640266.2020.1798172

34. Bratland-Sanda S, Rosenvinge JH, Vrabel KAR, Norring C, Sundgot-Borgen O, Ro J, et al. Physical activity in treatment units for eating disorders: clinical practice and attitudes. *Eat Weight Disord-Stud Anorex Bulim Obes.* (2009) 14:E106–12. doi: 10.1007/BF03327807

35. Quiles Marcos Y, Zarceño EL, López López JA. Effectiveness of exercise-based interventions in patients with anorexia nervosa: a systematic review. *Eur Eat Disord Rev.* (2020) 29:3–19. doi: 10.1002/erv.2789

36. Mathisen TF, Sundgot-Borgen J, Bulik CM, Bratland-Sanda S. The neurostructural and neurocognitive effects of physical activity: a potential benefit to promote eating disorder recovery. *Int J Eat Disord.* (2021) 54:1766–70. doi: 10.1002/eat.23582

37. Davies S, Parekh K, Etelapaa K, Wood D, Jaffa T. The inpatient management of physical activity in young people with anorexia nervosa. *Eur Eat Disord Rev J Eat Disord Assoc.* (2008) 16:334–40. doi: 10.1002/erv.847

38. Zhao J, Jiang W, Wang X, Cai Z, Liu Z, Liu G. Exercise, brain plasticity, and depression. *CNS Neurosci Ther.* (2020) 26:885–95. doi: 10.1111/cns.13385

39. Moscone AL, Leconte P, Scanff CL. L'anorexie et l'activité physique, une relation ambiguë. *Mov Sport Sci – Sci Mot.* (2014) 84:51–9. doi: 10.1051/sm/2013084

40. Kolnes LJ. Exercise and physical therapy help restore body and self in clients with severe anorexia nervosa. *J Bodyw Mov Ther.* (2016) 21:481–94. doi: 10.1016/j.jbmt.2016.09.005

41. Scott L, Blyderveen SV. Physical activity recommendations for adolescents with anorexia nervosa: An existing protocol based on physical activity risk. *Ment Health Phys Act.* (2014) 7:163–70. doi: 10.1016/j.mhpa.2014.09.001

42. Ostermann T, Vogel H, Boehm K, Cramer H. Effects of yoga on eating disorders—A systematic review. *Complement Ther Med.* (2019) 46:73–80. doi: 10.1016/j.ctim.2019.07.021

43. Vancampfort D, Vanderlinden J, De Hert M, Soundy A, Adámkova L-H, Skjaerven M, et al. A systematic review of physical therapy interventions for patients with anorexia and bulemia nervosa. *Disabil Rehabil.* (2013) 36:628–34. doi: 10.3109/09638288.2013.808271

44. Zunker C, Mitchell JE, Wonderlich SA. Exercise interventions for women with anorexia nervosa: a review of the literature. *Int J Eat Disord.* (2011) 44:579–84. doi: 10.1002/eat.20862

45. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* (2021) 372:n71. doi: 10.1136/bmj.n71

46. Charrois TL. Systematic reviews: What do you need to know to get started? *Can J Hosp Pharm.* (2015) 68:144–8. doi: 10.4212/cjhp.v68i2.1440

47. Herbert R, Jamtvedt G, Mead J, Hagen KB. Finding the evidence. In: Herbert R, Jamtvedt G, Mead J, Hagen KB editors. *Practical Evidence-Based Physiotherapy [Internet]*. (Chap. 4), Edinburgh: Butterworth-Heinemann (2005).

48. Moseley AM, Elkins MR, Van der Wees PJ, Pinheiro MB. Using research to guide practice: the physiotherapy evidence database (PEDro). *Braz J Phys Ther.* (2020) 24:384–91. doi: 10.1016/j.bjpt.2019.11.002

49. Szabo CP, Green K. Hospitalized anorexics and resistance training: impact on body composition and psychological well-being. a preliminary study. *Eat Weight Disord EWD.* (2002) 7:293–7. doi: 10.1007/BF03324975

50. Chantler I, Szabo CP, Green K. Muscular strength changes in hospitalized anorexic patients after an eight week resistance training program. *Int J Sports Med.* (2006) 27:660–5. doi: 10.1055/s-2005-865812

51. Fernandez-del-Valle M, Larumbe-Zabala E, Villasenor-Montarroso A, Cardona Gonzalez C, Diez-Vega LM, Lopez Mojares I, et al. Resistance training enhances muscular performance in patients with anorexia nervosa: a randomized controlled trial. *Int J Eat Disord.* (2014) 47:601–9. doi: 10.1002/eat.22251

52. Fernandez-del-Valle M, Larumbe-Zabala E, Graell-Berna M, Perez-Ruiz M. Anthropometric changes in adolescents with anorexia nervosa in response to resistance training. *Eat Weight Disord EWD.* (2015) 20:311–7. doi: 10.1007/s40519-015-0181-4

53. Fernandez-del-Valle M, Larumbe-Zabala E, Morande-Lavin G, Perez Ruiz M. Muscle function and body composition profile in adolescents with restrictive anorexia nervosa: does resistance training help? *Disabil Rehabil.* (2016) 38:346–53. doi: 10.3109/09638288.2015.1041612

54. Martinez-Sanchez SM, Martinez-Garcia C, Martinez-Garcia TE, Munguia-Izquierdo D. Psychopathology, body image and quality of life in female children and adolescents with anorexia nervosa: a pilot study on the acceptability of a pilates program. *Front Psychiatry.* (2020) 11:503274. doi: 10.3389/fpsyt.2020.503274

55. Martinez-Sanchez SM, Martinez-Garcia TE, Bueno-Antequera J, Munguia-Izquierdo D. Feasibility and effect of a Pilates program on the clinical, physical and sleep parameters of adolescents with anorexia nervosa. *Complement Ther Clin Pract.* (2020) 39:101161. doi: 10.1016/j.ctcp.2020.101161

56. Fernandez-del-Valle M, Perez M, Santana-Sosa E, Fiuza-Luces C, Bustamante-Ara C, Gallardo N, et al. Does resistance training improve the functional capacity and well being of very young anorexic patients? A randomized controlled trial. *J Adolesc Health.* (2010) 46:352–8. doi: 10.1016/j.jadohealth.2009.09.001

57. Martin SPK, Bachrach LK, Golden NH. Controlled pilot study of high-impact low-frequency exercise on bone loss and vital-sign stabilization in adolescents with eating disorders. *J Adolesc Health Off Publ Soc Adolesc Med.* (2017) 60:33–7. doi: 10.1016/j.jadohealth.2016.08.028

58. Carei TR, Fyfe-Johnson AL, Breuner CC, Brown MA. Randomized controlled clinical trial of yoga in the treatment of eating disorders. *J Adolesc Health.* (2010) 46:346–51. doi: 10.1016/j.jadohealth.2009.08.007

59. Catalan-Matamoros D, Helvik-Skjaerven L, Labajos-Manzanares MT, Martínez-de-Salazar-Arboleas A, Sánchez-Guerrero E. A pilot study on the effect of basic body awareness therapy in patients with eating disorders: a randomized controlled trial. *Clin Rehabil.* (2011) 25:617–26. doi: 10.1177/0269215510394223

60. Pacanowski CR, Diers L, Crosby RD, Neumark-Sztainer D. Yoga in the treatment of eating disorders within a residential program: a randomized controlled trial. *Eat Disord.* (2017) 25:37–51. doi: 10.1080/10640266.2016.1237810

61. Thien V, Thomas A, Markin D, Birmingham CL. Pilot study of a graded exercise program for the treatment of anorexia nervosa. *Int J Eat Disord.* (2000) 28:101–6. doi: 10.1002/(SICI)1098-108X(200007)28:1<101::AID-EAT12>3.0.CO;2-V

62. Dittmer N, Voderholzer U, Mönch C, Cuntz U, Jacobi C, Schlegl S. Efficacy of a specialized group intervention for compulsive exercise in inpatients with anorexia nervosa: a randomized controlled trial. *Psychother Psychosom.* (2020) 89:161–73. doi: 10.1159/000504583

63. Zeeck A, Schlegel S, Jagau F, Lahmann C, Hartmann A. The Freiburg sport therapy program for eating disorders: a randomized controlled trial. *J Eat Disord.* (2020) 8:31. doi: 10.1186/s40337-020-00309-0

64. Tokumura M, Yoshiba S, Tanaka T, Nanri S, Watanabe H. Prescribed exercise training improves exercise capacity of convalescent children and adolescents with anorexia nervosa. *Eur J Pediatr.* (2003) 162:430–1. doi: 10.1007/s00431-003-1203-1

65. Keizer A, Engel MM, Bonekamp J, Van Elburg A. Hoop training: a pilot study assessing the effectiveness of a multisensory approach to treatment of body image disturbance in anorexia nervosa. *Eat Weight Disord-Stud Anorex Bulim Obes.* (2019) 24:953–8. doi: 10.1007/s40519-018-0585-z

66. Savidaki M, Demirtoka S, Rodriguez-Jimenez R. Re-inhabiting one's body: a pilot study on the effects of dance movement therapy on body image and alexithymia in eating disorders. *J Eat Disord.* (2020) 8:22. doi: 10.1186/s40337-020-00296-2

67. Demartini B, Goeta D, Marchetti M, Bertelli S, Anselmetti A, Cocchi S, et al. The effect of a single yoga class on interoceptive accuracy in patients affected by anorexia nervosa and in healthy controls: a pilot study. *Eat Weight Disord-Stud Anorex Bulim Obes.* (2021) 26:1427–35. doi: 10.1007/s40519-020-00950-3

68. Touyz SW, Lennerts W, Arthur B, Beumont PJV. Anaerobic exercise as an adjunct to refeeding patients with anorexia nervosa: Does it compromise weight gain? *Eur Eat Disord Rev.* (1993) 1:177–82. doi: 10.1002/erv.2400010306

69. Calogero RM, Pedrotty KN. The practice and process of healthy exercise: an investigation of the treatment of exercise abuse in women with eating disorders. *Eat Disord.* (2004) 12:273–91. doi: 10.1080/10640260490521352

70. Schlegel S, Hartmann A, Fuchs R, Zeeck A. The Freiburg sport therapy program for eating disordered outpatients: a pilot study. *Eat Weight Disord EWD.* (2015) 20:319–27. doi: 10.1007/s40519-015-0182-3

71. Cook-Cottone C, Beck M, Kane L. Manualized-group treatment of eating disorders: Attunement in Mind, Body, and Relationship (AMBR). *J Spec Group Work.* (2008) 33:61–83. doi: 10.1080/01933920701798570

72. Hall A, Ofei-Tenkorang NA, Machan JT, Gordon CM. Use of yoga in outpatient eating disorder treatment: a pilot study. *J Eat Disord.* (2016) 4:38. doi: 10.1186/s40337-016-0130-2

73. Diers L, Rydell SA, Watts A, Neumark-Sztainer D. A yoga-based therapy program designed to improve body image among an outpatient eating disordered population: program description and results from a mixed-methods pilot study. *Eat Disord.* (2020) 28:476–93. doi: 10.1080/10640266.2020.1740912

74. Dittmer N, Voderholzer U, von der Mühlen M, Marwitz M, Fumi C, Mönch M, et al. Specialized group intervention for compulsive exercise in inpatients with eating disorders: feasibility and preliminary outcomes. *J Eat Disord.* (2018) 6:27. doi: 10.1186/s40337-018-0200-8

75. Kern L, Morvan Y, Mattar L, Molina E, Tailhardat A, Peguet L, et al. Development and evaluation of an adapted physical activity program in anorexia nervosa inpatients: a pilot study. *Eur Eat Disord Rev.* (2020) 28:687–700. doi: 10.1002/erv.2779

76. Garner DM, Garfinkel PE. The eating attitudes test: an index of the symptoms of anorexia nervosa. *Psychol Med.* (1979) 9:273–9. doi: 10.1017/S0033291700030762

77. Garner DM, Olmsted MP, Bohr Y, Garfinkel PE. The eating attitudes test: psychometric features and clinical correlates. *Psychol Med.* (1982) 12:871–8. doi: 10.1017/S0033291700049163

78. Garner DM, Olmstead MP, Polivy J. Development and validation of a multidimensional eating disorder inventory for anorexia nervosa and bulimia. *Int J Eat Disord.* (1983) 2:15–34. doi: 10.1002/1098-108X(198321)2:2<15::AID-EAT2260020203>3.0.CO;2-6

79. Garner DM. *Eating disorder inventory-2: professional manual.* Odessa: Psychological Assessment Resources (1991).

80. Garner DM. *EDI 3: eating disorder inventory-3: professional manual.* Lutz, FL: Psychological Assessment Resources (2004).

81. Cooper Z, Fairburn C. The eating disorder examination: a semi-structured interview for the assessment of the specific psychopathology of eating disorders. *Int J Eat Disord.* (1987) 6:1–8. doi: 10.1002/1098-108X(198701)6:1<1::AID-EAT2260060102>3.0.CO;2-9

82. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. conceptual framework and item selection. *Med Care.* (1992) 30:473–83. doi: 10.1097/00005650-199206000-00002

83. Davis C. Excessive exercise and anorexia nervosa: addictive and compulsive behaviors. *Psychiatr Ann.* (1999) 29:221. doi: 10.3928/0048-5713-19990401-09

84. Taranis L, Touyz S, Meyer C. Disordered eating and exercise: development and preliminary validation of the compulsive exercise test (CET). *Eur Eat Disord Rev J Eat Disord Assoc.* (2011) 19:256–68. doi: 10.1002/erv.1108

85. Heinl K. *The Influence of Physical Activity or Exercise Interventions on Physiological and Psychological Conditions of People with Anorexia Nervosa [Internet].* (2018). Available online at: https://www.grin.com/document/452114 (accessed june 30, 2022).

86. INSERM. *Activité physique: Prévention et traitement des maladies chroniques.* France: EDP Sciences (2019).

87. Hecksteden A, Faude O, Meyer T, Donath L. How to construct, conduct and analyze an exercise training study? *Front Physiol.* (2018) 9:1007. doi: 10.3389/fphys.2018.01007

88. El Ghoch M, Alberti M, Milanese C, Battistini NC, Pellegrini C, Capelli M, et al. Comparison between dual-energy X-ray absorptiometry and skinfolds thickness in assessing body fat in anorexia nervosa before and after weight restoration. *Clin Nutr Edinb Scotl.* (2012) 31:911–6. doi: 10.1016/j.clnu.2012.03.009

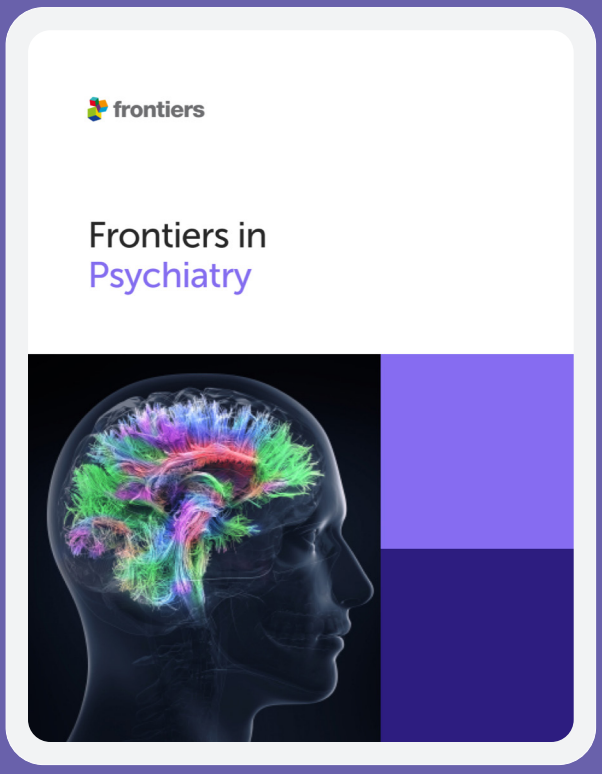
Frontiers in Psychiatry

Explores and communicates innovation in the field of psychiatry to improve patient outcomes

The third most-cited journal in its field, using translational approaches to improve therapeutic options for mental illness, communicate progress to clinicians and researchers, and consequently to improve patient treatment outcomes.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact