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Peer Reviewer of *World Journal of Psychiatry*, Qing-Zhong Wang, PhD, Associate Professor, Institute of Chinese Materia Medica, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China. wangqingzhong3@gmail.com

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THERAPEUTIC AND DIAGNOSTIC GUIDELINES

Ultra-brief crisis interpersonal psychotherapy based intervention for suicidal children and adolescents

Anat Brunstein Klomek, Liat Haruvi Catalan, Alan Apter

ORCID number: Anat Brunstein Klomek 0000-0003-2588-0465; Liat Haruvi Catalan 0000-0002-2093-9563; Alan Apter 0000-0002-5568-0491.

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Anat Brunstein Klomek, Baruch Ivcher School of Psychology, Interdisciplinary Center, Herzliya 4610101, Israel

Liat Haruvi Catalan, Alan Apter, Depression and Suicide Clinic, Schneider Children's Medical Center, Petach Tikva 49202, Israel

Alan Apter, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv 69978, Israel

Corresponding author: Liat Haruvi Catalan, PhD, Director, Depression and Suicide Clinic, Schneider Children's Medical Center, Kaplan 14, Petach Tikva 49202, Israel.
liatcatalan@gmail.com

Abstract

Suicidal behaviors in adolescence are a major public health concern. The dramatic rise in self-injurious behaviors among adolescents has led to an overwhelming increase in the number of those presenting to the emergency rooms. The intervention described below was constructed on the basis of brief and focused interventions that were found to be effective among suicidal adults using an adaptation of interpersonal psychotherapy for adolescents. The intervention has four main objectives: first, a focused treatment for reducing suicide risk; second, a short and immediate response; third, building a treatment plan based on understanding the emotional distress and interpersonal aspects underlying suicidal behavior; and lastly, to generate hope among adolescents and their parents. The intervention includes intensive five weekly sessions, followed by 3 mo of email follow-up.

Key Words: Suicide; Depression; Adolescents; Crisis intervention; Interpersonal psychotherapy

Core Tip: Waiting time for treatment for adolescents who are at risk for suicide in Israel is unreasonably long. The purpose of the interpersonal psychotherapy based intervention for suicidal children and adolescents is to allow more children to receive an acute preventive intervention within a reasonable period of time. The initial phase

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includes building a safety plan, understanding the emotional and interpersonal aspects underlying the suicide risk and formulating a problem area. The middle sessions include learning and practicing emotional, behavioral and interpersonal skills. The termination session includes building a treatment plan for relapse prevention and providing hope.

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INTRODUCTION

Suicidal behaviors in adolescence are a major public health concern; recent elevation in adolescents suicidality highlight an increasing need for its prevention and treatment. The prevalence of non-fatal suicidal acts among children and adolescents is considerably high. In fact, suicide risk is the most frequent reason for presentation to psychiatric emergency rooms among this population[1]. Risk factors for suicide are numerous and utterly complex. Particularly, non-fatal self-injurious behaviors, which are generally recurring, constitute an especially elevated risk for suicide[2]. Unrecognized and/or untreated depression is the psychiatric disorder that is the most commonly associated with suicide[3]. Inappropriate management of depression may produce a range of adverse outcomes for children and adolescents, such as school failure and dropout, avoidance of friends, eating disorders, substance and alcohol abuse and of course the propensity to self-harm[3].

The dramatic rise in self-injurious behaviors among children and adolescents has led to an overwhelming increase in the number of those presenting to the emergency rooms worldwide[1]. In Israel each year, about 400 such incidents are accepted to our emergency room at Schneider Children's Medical Center, with about a hundred of these cases necessitating subsequent treatment[4]. As a result, the average waiting time for treatment before the current study was about 12-18 mo; such a lengthy delay often culminated in deterioration of the child's condition and led to an increased probability of adverse consequences. Evidently, the need to develop a brief and targeted intervention for this population is unequivocal. The need for emergency intervention has become even more important due to the coronavirus disease 2019 pandemic. Many countries reported an increase in suicide rates among children and adolescents during this period[5]. Studies among suicidal adults have demonstrated the efficacy of brief and focused treatments in reducing suicide risk[6]. For example, receiving postcards from a clinic was found to reduce suicidal behaviors over time[7].

Interpersonal psychotherapy for adolescents (IPT-A), a manualized, short-term (12 sessions) therapeutic intervention for adolescents with depression[8] is among the most common forms of therapy provided at our clinic. We decided to attempt to lessen the number of sessions even further in the hope of reducing our waiting list and enable a larger number of adolescents to receive therapeutic care. The rationale for selecting IPT-A specifically is based on present research linking interpersonal problems to suicide risk[9]. Previous studies found that individuals at risk for suicide suffer from significant challenges in their relationships[10]. Insecure attachment, in particular, has been identified as a major risk factor for adolescent suicidality[11]. In addition, difficulty expressing and sharing feelings with others has been found to significantly increase the risk of severe suicide attempts, above and beyond the contribution of depression and hopelessness[12].

IPT BACKGROUND

IPT is a commonly used, evidence-based, time-limited treatment for depression in adults[13] and adolescents (IPT-A)[8,14] as well as other psychiatric disorders (*e.g.*, anxiety disorders)[15]. IPT has demonstrated efficacy in reducing depressive symptoms and improving overall performance and social functioning[16]. IPT-A is an

adaptation of IPT tailored specifically for adolescents with depression[8]. Similar to the original adult version, IPT-A is time-limited and evidence-based[8]. IPT-A focuses on addressing the link between depressed mood and current interpersonal problems. The goal of IPT-A is to reduce depressive symptoms and improve interpersonal functioning by identifying an interpersonal problem area of focus and developing communication/interpersonal, emotional skills and problem-solving strategies[8].

Recently, a number of studies documented the potential for effectiveness of IPT in treating suicidal patients. Mufson *et al*[17] presented preliminary outcomes of a small sample of suicidal adolescents treated with IPT-A (IPT-A-Suicide Prevention). Tang *et al*[18] examined the effects of intensive interpersonal psychotherapy for adolescents with depression who were at risk for suicidal behavior and compared these adolescents with patients who received treatment as usual at schools. Results illus-trated lower post-intervention severity of depression, anxiety, suicidal ideation and hopelessness among those treated with intensive IPT-A compared to treatment as usual.

To the best of our knowledge, despite the tremendous service gap and devastating consequences of the global suicide epidemic among children and adolescents, no protocol exists that offers a very short, practical and feasible crisis intervention for children and adolescents who are at risk of suicide. The intervention described below was constructed on the basis of brief and focused interventions that were found to be effective among suicidal adults using an adaptation of IPT-A.

INTERPERSONAL PSYCHOTHERAPY BASED INTERVENTION FOR SUICIDAL CHILDREN AND ADOLESCENTS

The efficacy of IPT based intervention for suicidal children and adolescents has been recently published elsewhere[4]. The following is a thorough description of the intervention itself. The intervention has four main objectives: first, a focused treatment for reducing suicide risk; second, a short and immediate response to be able to deliver the intervention within a month from the date of referral; third, building a treatment plan based on understanding the emotional distress and interpersonal aspects underlying suicidal behavior and the associated, distinct difficulties of the patient (such as interpersonal skills deficits and emotion dysregulation); and lastly, to generate hope among patients and their parents. Our assumption is that achieving these four goals allows the patient and parents to feel that things can get better, which in turn helps to decrease the patient's suicide risk.

Structure of the intervention

The intervention is comprised of an intensive phase of five weekly sessions and a follow-up phase consisting of four emails across a 3 mo period. The emails are sent to both the adolescent and his/her parents. In the first month post-intervention, two emails are sent (one email every 2 wk). In the following 2 mo, two additional emails are sent (an email every month) for a total of four follow-up emails (Figure 1).

Parental involvement: The intervention is intended for children and adolescents ages 6-18-years-old. We require parental attendance at the first and final sessions and invite parents to attend additional sessions as needed. For children under 10 years of age we recommend that the parents be present during all five sessions.

The intensive phase: The intensive phase is based on IPT-A with the addition of some elements adapted from Cognitive Behavioral Therapy for Suicide Prevention[19] and Dialectical Behavioral Therapy[20].

The first and second sessions constitute the initial phase of the acute intervention and involve assessment and diagnosis of depression and suicide risk (risk assessment), interpersonal assessment and problem area formulation. The third and fourth sessions comprise the middle phase of the acute IPT-A intervention, which focuses on fostering emotional and interpersonal skills within the specific problem area. The termination phase includes the final fifth session in which the patient and therapist summarize the therapeutic process, and the therapist provides recommendations for further treatment. Below is a detailed description of each session.

First session

The first session should ideally include both patient and parents to establish initial rapport and commitment as well as focus on depression and suicidal risk. It is an

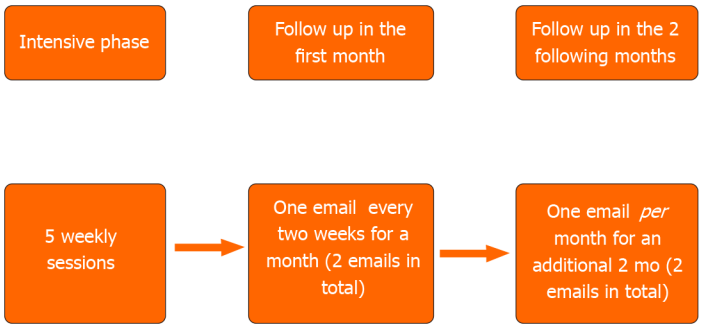

Figure 1 The intervention is comprised of an intensive phase of five weekly sessions and a follow-up phase consisting of four emails across a 3 mo period.

especially intensive meeting requiring an active therapeutic approach and should include:

(1) Risk assessment: A short risk assessment is conducted in addition to the initial risk assessment generally conducted at the intake. This portion of the first session includes an evaluation of depressive symptoms using scales like the Mood and Feelings Questionnaire[21] as well as an assessment of suicidality based on the Columbia Suicide Rating Scale[22] and/or Suicide Ideation Questionnaire[23].

(2) Safety plan[24]: In the event of suicidal risk, an interpersonal safety plan is constructed in collaboration with the patient and the parents. The safety plan includes a list of coping strategies arranged in a hierarchical order, available for the patient, should a suicidal crisis occur. The main purpose of the plan is to provide a predetermined course of action for potential coping strategies as well as a list of specific and relevant support resources. The plan includes internal strategies that a patient employs on his own (*e.g.*, self-talk) in addition to a list of contacts of individuals in the patient's life (*e.g.*, family members, healthcare providers) who can be contacted in real time to help reduce the risk of suicidal behavior. A collaborative approach is recommended between the therapist, the patient and the parents. The plan is a dynamic therapeutic program reviewed periodically by the patient and therapist to evaluate the need for any particular changes or additions.

(3) Chain analysis: A chain analysis is performed in order to outline and discern the events that occurred in the hours prior to the attempt. The chain analysis allows for better understanding of the context of the suicidal act and the emotional and interpersonal/social triggers preceding the attempt.

(4) Presenting the intervention to adolescents and their parents: A thorough explanation of the nature, structure and goals of the intervention is presented to the adolescent and parents. The need for parental cooperation is addressed directly, and the topic of confidentiality is discussed. Further, the obligation to share details of the patient's risk and needs with the school is discussed. The goal of collaboration with the school is to increase the support the patient receives from the school in the areas he struggles the most (*e.g.*, academic, social or emotional realms). Although the communication with the school is addressed in the first session, in practice the school is contacted only after the end of the second session, once we have gotten to know the patient better and have jointly delineated with the patient the main problem area that underlies his/her suicidality. Finally, the limitations of the intervention and the need for long-term psychological treatment and/or consultation about psychotropic medication are addressed. The family is accompanied throughout the intervention in the challenge of finding appropriate follow-up care after the acute IPT-A for suicidal children and adolescents intervention.

and (5) Psychoeducation: Extensive psychoeducation about depression, suicidality, adolescence, parenting and other patient-specific topics is provided. The patient is presented with an explanation of the concept that suicidal crises come in waves and that the purpose of the intervention is to prepare for the next wave. The underlying assumption is that it is likely there will be more crises in the future even if, at the moment, the patient is feeling better. We also use the IPT-A concept of a "Limited Sick Role," which is an aspect of the medical model of IPT. This role refers to the need to match expectations between functional requirements and the patient's mood. The patient is encouraged to function to the best of his ability, while adjusting the pace and progress to his mental state. The concept of the limited sick role is also explained to the patient's parents and teachers.

Second session

Each session begins with an evaluation of the patient's mood and suicidal risk on a scale of 0-10 and discussion about the changes needed in the safety plan. While the first session focuses on the depression and suicidal risk, the second session concentrates on interpersonal functioning. The purpose of the second session is to define the problem area that will be the main focus of the intervention. In order to achieve this, the therapist uses the Closeness Circle and the Interpersonal Inventory[25]. The Closeness Circle is a series of circles, one inside the other (Supplementary material 1). The therapist explains that the circles around the patient's name represents circles of closeness, and the goal is to place the patient's significant relationships within the appropriate circles according to the relevant degree of intimacy; the result is a visual representation of the patient's significant relationships. Then, the therapist and the patient discuss the patient's meaningful relationships using the Interpersonal Inventory. The Interpersonal Inventory includes questions related to facts, opinions, particular events and feelings about the relationships with the people outlined in the patient's circles. The goal of this session is to reach as deep of an understanding as possible of the patient's emotional and interpersonal world and to identify the most relevant emotional and interpersonal struggles that may be the underlying issues contributing to the patient's suicidal risk.

The first two sessions lead to the formulation of the main problem area that the patient is currently dealing with[25]. The problem area is a framework in which the patient and therapist learn and practice skills in the middle phase of the intervention. The line of questioning taken by the therapist in exploration of the various potential problem areas (*e.g.*, grief, conflicts, role transitions and interpersonal deficits) should be directed towards obtaining relevant information in order to ascertain which is currently most significant. There are four main problem areas: (1) grief: relates to actual death and refers to situations in which depression developed due to complicated grieving following the loss of a significant other; (2) interpersonal disputes: conflicts or problems managing expectations in significant relationships. With adolescents this is usually between the patient and his/her parents but may also occur with a teacher, sibling or friend; (3) role transitions: significant life events that may be positive or negative and can be identified as the point at which the patient became depressed such as entry to middle/high school, parental divorce or a diagnosis of an illness; and (4) interpersonal deficits: difficulties with interpersonal skills, leading to loneliness or social detachment. The problem can be in social/group settings or intimate/dyadic situations. It is important to establish an understanding of the specific hardships involved, such as asking for help, learning to forgive, dealing with disagreements in groups, *etc.*

During or after the second session, the therapist contacts and communicates with the school staff.

Sessions three and four

These sessions are focused on fostering and practicing interpersonal, emotional and behavioral skills. Each session begins with an examination of the patient's mood during the past week as well as his suicidal risk. The safety plan is reviewed and readjusted. These two sessions focus on skills learning and practicing within the formulated problem area.

As there is very little time within this brief intervention for skill learning, the therapist should choose one or two IPT-A skills that the patient exhibits the greatest deficits in and that are most relevant to his suicidal risk. These skills are typically related to mood and/or interpersonal relationships. There are three skill sets to choose from including emotional, behavioral and interpersonal. Emotional skills include an emphasis on emotional regulation techniques. The work on emotions with these at-risk children and adolescents include raising their awareness to the various emotions, cultivating their ability to label their emotions, monitoring their intensity and learning ways to regulate them in order to control behaviors associated with these feelings. This promotes the patient's realization and understanding that it is normal to feel lonely, sad or hopeless at times. Yet, when these emotions are intensive and overwhelming, the adolescent should act to control their behavior. Behavioral skills include decision analysis (interpersonal problem-solving), which are crucial in every type of interpersonal interaction. Lastly, enhancement of interpersonal skills incorporates communication analysis, in which the patient learns to identify maladaptive communication skills and learns flexible and adaptive alternatives. All skills are taught through role-play and entail interpersonal experiments intended to be conducted between sessions (*i.e.* in real life) and processed with the therapist during the sessions

themselves. Many of the parents benefit from these skills training as well and are therefore encouraged to attend these sessions as needed.

Session five

The concluding session of the intensive phase includes a summary of the interpersonal and emotional work that has taken place and recommendations for further treatment. In this session we re-emphasize that suicidal risk and behaviors occur in waves and address the possibility that the adolescent may feel suicidal again by discussing relapse prevention. We return to the safety plan devised together in the beginning of treatment in order to ensure its relevance and verify that the patient is familiar with it and willing to use it when needed.

Follow-up phase

Following the intensive phase, periodic emails are sent to the patient and his parents over a 3 mo timespan. During the first month following termination, an email is sent every 2 wk. Then, during the following 2 mo, one email is sent each month. The emails are sent to the patient's personal e-mail and/or his parent's email depending on the patient's age and preferences.

The email is written in a fixed format and is sent directly from the clinic. The email includes patient-specific information in order for it to be personalized (Supplementary material 2).

CASE STUDY

Background

Rona (pseudonym) is a 16-and-a-half-year-old, 11th grade student. She lives with her parents and two brothers in a city in the center of Israel. Her father is a software engineer, and her mother works as a teacher. Both parents were born in the Soviet Union and immigrated to Israel in their early 20s.

Rona presented with a significant suicide attempt in which she swallowed 50 pills with an intention to die. The psychiatric evaluation concluded that she was diagnosed with depression. She began anti-depressant medication and was simultaneously referred for IPT-A for suicidal children and adolescents.

First session

Assessment and psychoeducation: The first session took place with Rona and her parents. After taking Rona's history, psychoeducation was provided, focusing primarily on symptoms of depression and suicide prevention. Further, the intervention itself was explained in terms of its structure, content and goals and the need to find continued, psychological care post-treatment even though we just started.

The next step was performed with Rona alone. A clinical evaluation of depressive symptoms and suicidal risk was repeated, and Rona completed a few self-report questionnaires. In the clinical assessment, Rona denied current suicidality. She stated she understood she had made a mistake attempting suicide and declared she would avoid future attempts. She denied suicidal ideation and intent to die. She also reported significant improvement in her depressive symptoms. Her questionnaires indicated significant depression (Mood and Feelings Questionnaire = 29), moderate severity of suicidal ideation (Suicide Ideation Questionnaire = 33) and high suicide risk (Columbia Suicide Rating Scale = 5).

Safety plan: The next step included a collaborative drafting of a safety plan with Rona. Although Rona insisted it was unnecessary, the need to build a plan for handling potential suicidal waves was explained to her. Rona was cooperative, and the program seemed to be a good fit for her (Supplementary material 3). Despite the proper plan and the fact that Rona denied suicidal risk, we kept in mind the immense gap between the current circumstances and the serious suicide attempt she had made just a month prior to her referral. A substantial portion of the present therapeutic intervention focused precisely on this gap.

Chain analysis: From the chain analysis it became evident that the night before the suicide attempt, Rona was very stressed because of an exam she was supposed to take the next day at school. She knew that she had not studied properly and was extremely afraid that she would fail. She felt that she could not afford to fail this exam especially because she knew how much her failure would disappoint her father.

She tried not to think about it and watched TV, but she could not concentrate. She only imagined the reaction of her father when he finds out that she failed the exam. She was not able to sleep all night. When the day started the pressure increased, and there seemed to be no other solution. She felt stressed and helpless. She got ready for school as if she were planning on going, her parents wished her luck on the exam and left for work. She was left alone at home and finally decided she was not going to go to school. She felt desperate. She went to her shower and saw a packet of pills. She felt that she would rather die than face whatever would happen if she went on with her day as planned. She took all the pills in the container. Her mother found her half an hour later, in the bath with the pills next to her. When Rona recovered in the hospital and saw her parents, she was very disappointed to find that she was still alive and felt awfully guilty and ashamed.

After we conducted the chain analysis, we came back to the safety plan and addressed the need to use it whenever stressful events occur. Towards the end of the session, we invited the parents to rejoin and shared with them the safety plan; we clarified what was required from them when Rona approaches them in times of crisis.

Second session

The second session focused on the interpersonal assessment; to enhance this process we used the Closeness Circles and the Interpersonal Inventory. Rona had many people in the circles (Supplementary material 1), and it seemed she had many significant individuals in her life. She described close and meaningful relationships with her friends, juxtaposed to the fact that she recently moved away from them. Her father was in the closest circle to her. She described a special and close relationship with him that was different from her father's relationship with her brothers. She explained that her academic success was always important to her father and that when she was younger, he tutored her for many hours. However, Rona explained she was not invested in her studies and preferred to spend time with her friends; she described ongoing conflicts between her and her father about it. Rona felt that her dad did not understand her needs. In the last year she was less invested in her studies, and this negatively impacted her relationship with her father. Rona felt he was dissatisfied with her and believed he was distancing himself from her. She felt that the two were no longer as close as they used to be. Rona shared that she missed the closeness they had, and she felt she failed to be the daughter her father wanted her to be. Further, Rona shared her parents' relationship was deteriorating and that they quarreled often. In the past, Rona's father had shared with her some of his feelings about her mother, and Rona felt that she understood her father better than her mother did. She missed being the one her father trusted and confided with.

Rona's mother was in the second circle. Rona describes she was never very close to her mother and felt that her mother was unable to truly understand her. Rona described she did her best to help around the house whenever her mother asked her to, which she felt helped avoid arguments with her mother and assisted in maintaining a somewhat normal relationship between the two of them. There was no real closeness between Rona and her mother, but Rona insisted it did not bother her and that their relationship was this way as long as she could remember. The more we talked about their relationship, the more likely it seemed that Rona actually wished to be closer to her mother but that she was too afraid to expect intimacy with her and be disappointed.

In the third circle Rona wrote her ex-boyfriend. Rona shared she decided to break up with him 2 mo ago because she felt she was no longer fun to be around and that she would probably disappoint him soon as she disheartened others in her life. She felt she was changing; she was no longer in the mood to hang out with friends and found she mostly preferred to be alone. After the interpersonal inventory, we introduced Rona to the concept of problem areas and collaboratively chose the problem area of interpersonal disputes (surrounding her conflicting relationship with her father).

Session three and four

Learning skills: The third and fourth sessions focused on skill acquisition and rehearsal. The goal was to teach Rona skills that would help her communicate better with her father (communication skills) as well as skills that would help her respond differently if she felt similarly to how she felt prior to her suicide attempt (emotional regulation skills). We used communication analysis and identified the need to work on Rona's ability to speak more openly with her father and express her feelings to him without fearing she would be disappointing him. Through communication analysis we were able to uncover that Rona predominantly avoided discussing her school difficulties with her father or share with him that she wished to be more engaged in

other activities such as spending time with her friends.

Together, we brainstormed some goals Rona wished to achieve in a potential conversation with her father. Rona wanted to relieve stress from her studies and accomplishments without feeling she would be disheartening her father too much. We planned numerous possible scripts for the conversation and used the teen tips to promote effective communication. Between sessions, Rona practiced her communication skills with her father, eventually introducing a possibility for a different kind of dialogue between them.

Further, sessions centered on fostering Rona's emotional regulation skills. At first, Rona found it difficult to recognize the feelings she experienced before attempting suicide (*e.g.*, the fear of disappointing her father, hopelessness and loneliness, in particular). She was only able to describe she felt she was "under pressure." Through processing Rona's feelings prior to the attempt, we were able to elucidate Rona's explicit fear of disappointing her father, which led her to distance herself from him initially and avoid others subsequently, the latter behavior culminating in a detrimental increase in her feelings of loneliness and sadness. Between sessions Rona was requested to monitor the intensity of her negative emotions in various situations, and together we practiced numerous self-calming methods such as self-talk and relaxation techniques. Further, Rona was asked to practice additional soothing techniques at home, and these skills were added to her safety plan. Our intention was to teach Rona to recognize situations in which she would be likely to have a decreased ability to regulate her emotional state, so that once becoming aware of them she would have adaptive means of calming herself.

Fifth meeting

As described above, the objectives of the fifth session are to summarize the therapeutic process, focus on relapse prevention, provide recommendations for further treatment and review the safety plan. The meeting was divided into two parts; in the first half of the meeting we met Rona alone, and her parents joined us in the second part of the session. We addressed the focus of Rona's difficulties, her experiences and her needs in the relationships with her parents. Her parents were invited to express their desire for closeness in addition to their concern for her well-being. We repeated and reevaluated the safety plan with Rona and later with the parents to ensure each of them was knowledgeable of what to do should Rona feel suicidal again.

Although the need for continuous treatment for Rona had been discussed earlier in treatment, present difficulties of finding available individual psychotherapy in the community disabled her immediate transition into follow-up care. Rona was waitlisted for long-term treatment at our clinic, and in the meantime, the family began family therapy.

CONCLUSION

At the end of the intervention, there was a significant reduction in Rona's depressive symptoms, and she continued to deny current suicidal ideation. The family remained in family therapy for 8 mo, and treatment was found to be helpful and led to tremendous therapeutic gains. A year later, Rona began long-term treatment at our clinic. Of note, throughout this period, Rona refrained from further engagement in suicidal behaviors.

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REVIEW

Menopause and cognitive impairment: A narrative review of current knowledge

Délio Marques Conde, Roberto Carmignani Verdade, Ana L R Valadares, Lucas F B Mella, Adriana Orcesi Pedro, Lucia Costa-Paiva

ORCID number: Délio Marques Conde 0000-0003-2062-960X; Roberto Carmignani Verdade 0000-0002-8467-7267; Ana L R Valadares 0000-0002-8416-6096; Lucas F B Mella 0000-0002-4298-9553; Adriana Orcesi Pedro 0000-0003-0138-8935; Lucia Costa-Paiva 0000-0002-9088-6700.

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Délio Marques Conde, Department of Gynecology and Obstetrics, Federal University of Goiás, Goiânia 74605-050, Goiás, Brazil

Roberto Carmignani Verdade, Ana L R Valadares, Adriana Orcesi Pedro, Lucia Costa-Paiva, Department of Obstetrics and Gynecology, School of Medical Sciences, State University of Campinas, Campinas 13083-881, São Paulo, Brazil

Lucas F B Mella, Department of Medical Psychology and Psychiatry-Geriatric Psychiatry and Neuropsychiatric Division, State University of Campinas, Campinas 13083-887, São Paulo, Brazil

Corresponding author: Lucia Costa-Paiva, MD, PhD, Full Professor, Department of Obstetrics and Gynecology, School of Medical Sciences, State University of Campinas, Rua Alexander Fleming, 101, Cidade Universitária Zeferino Vaz, Barão Geraldo, Campinas 13083-881, São Paulo, Brazil. paivaepaiva@uol.com.br

Abstract

A severe impairment of cognitive function characterizes dementia. Mild cognitive impairment represents a transition between normal cognition and dementia. The frequency of cognitive changes is higher in women than in men. Based on this fact, hormonal factors likely contribute to cognitive decline. In this sense, cognitive complaints are more common near menopause, a phase marked by a decrease in hormone levels, especially estrogen. Additionally, a tendency toward worsened cognitive performance has been reported in women during menopause. Vasomotor symptoms (hot flashes, sweating, and dizziness), vaginal dryness, irritability and forgetfulness are common and associated with a progressive decrease in ovarian function and a subsequent reduction in the serum estrogen concentration. Hormone therapy (HT), based on estrogen with or without progestogen, is the treatment of choice to relieve menopausal symptoms. The studies conducted to date have reported conflicting results regarding the effects of HT on cognition. This article reviews the main aspects of menopause and cognition, including the neuroprotective role of estrogen and the relationship between menopausal symptoms and cognitive function. We present and discuss the findings of the central observational and interventional studies on HT and cognition.

Key Words: Menopause; Cognition; Dementia; Estrogens; Hot flashes; Cognitive decline

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Core Tip: Cognitive complaints are more common in postmenopausal women than in premenopausal women. Due to the reduction in ovarian function, a progressive decrease in serum estrogen levels occurs, leading to menopausal symptoms with an emphasis on vasomotor symptoms. In addition to these symptoms, cognitive impairment can affect postmenopausal women to varying degrees. Several aspects of the relationship between menopause and cognitive function were reviewed. We report the latest evidence on the topic. In this sense, considering current knowledge, we do not recommend the prescription of hormone therapy to prevent cognitive decline or dementia in postmenopausal women.

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INTRODUCTION

Approximately 50 million people worldwide live with dementia, with Alzheimer's disease (AD) being the most frequent cause[1]. Dementia is characterized by severe cognitive decline and subsequent functional disability[2]. It is the fifth leading cause of death and is responsible for 28.8 disability-adjusted life-years[3]. A few decades before the onset of Alzheimer's dementia, AD-related neuropathological changes are observed in the brain, which may be accompanied by subtle cognitive decline[4]. Accordingly, patients with early cognitive symptoms are at increased risk of dementia [5,6].

Mild cognitive impairment (MCI) is defined as individuals with objective cognitive deficits in neuropsychological tests (usually defined as a performance of 1.5 standard deviations below the mean established for age and education) and preserved functional independence for activities of daily life[2]. MCI is related to a nine-fold increase in the risk of dementia compared to the general population[5]. Subjective cognitive complaints with normal performance on neuropsychological tests are related to a two-fold increase in the risk of dementia compared to the general population[6]. Identifying and understanding the predisposing and triggering factors of the neurobiological mechanisms underlying early cognitive decline may contribute to the development of preventive interventions to mitigate the risk of dementia.

Female sex is a consistent risk factor for dementia, and the greater longevity of women does not fully explain this relation. In addition, estrogen plays an essential role in the neurobiology of cognitive processing and neuronal function, and the menopausal transition is associated with subtle cognitive decline. However, the relationships among decreased estrogen levels in menopause, the effects of hormone therapy (HT) on cognition, and the risk of dementia are still conflicting and puzzling.

Considering the relevance of the issue and seeking to contribute to the existing literature, several aspects of the relationship between menopause and cognitive function were reviewed in this paper. We describe the most recent evidence, presenting what we know and the gaps in knowledge on the subject.

SEARCH METHODS

A search was conducted in Medline and Embase for the period from 1980 to 2020. The search terms cognition, climacteric, cognitive decline, estrogen effects, menopause, menopausal symptoms, hot flashes, middle-aged women, perimenopause, neuropsychology, HT, progestogen, MCI, subjective cognitive decline, risk of dementia, neuroimaging, and vasomotor symptoms were used.

Original articles, systematic reviews, meta-analyses, narrative reviews, and consensus reports were evaluated. Both human and animal studies published in

English were considered. The bibliographies of the articles were searched to identify related studies. All articles were critically evaluated by the authors, including those more specifically related to the theme of this narrative review and those that resulted in agreement between the authors for their inclusion.

EVIDENCE OF THE RELATIONSHIP BETWEEN MENOPAUSE AND COGNITIVE DECLINE

Subjective cognitive decline is one of the most frequent complaints of women undergoing the menopausal transition, with a 44%-62% prevalence estimated in population-based studies[7,8]. Reports of memory problems are associated with the perimenopausal period compared to pre- or postmenopausal periods[9]. The incidence of MCI was 4.5% in 6376 postmenopausal women evaluated for 5.4 years in the Women's Health Initiative Memory Study (WHIMS)[10], but the relationship between MCI and menopausal factors has still been poorly studied. In contrast, changes in women's cognitive test performance, regardless of cognitive complaints or cognitive impairment, are consistently related to the reproductive period and menopausal transition.

After adjusting for age, cognitive performance during postmenopause tended to be lower than that during pre- and perimenopausal periods, particularly verbal delayed memory and executive function[11], which involve cognitive domains that are assumed to be more sensitive to changing estrogen levels[12]. The Study of Women's Health Across the Nation evaluated 2362 American women by repeated administration of neuropsychological tests for four years. Women's scores on delayed and immediate memory tests in the early and late perimenopausal periods did not improve over time with test repetition. However, the incremental changes in scores normalized in the postmenopausal period, returning to the pattern observed during premenopause[13]. Similarly, Kilpi *et al*[14] studied 2411 middle-aged United Kingdom women, verifying that processing speed and immediate and delayed verbal episodic memory decreased in the perimenopausal period; additionally, changes in verbal episodic memory tests correlated with follicle-stimulating hormone and luteinizing hormone levels.

Several studies have also reported that prolonged lifetime estrogen exposure results in better cognitive outcomes[15]. A younger age at first menses, older age at menopause, age at birth of a first child more than 20 years, and an extended reproductive period were related to a more remarkable performance on neuropsychological tests at postmenopause[16,17]. However, the data are conflicting regarding reproductive period factors and the risk of progressive cognitive decline or dementia. Although the meta-analysis by Georgakis *et al*[15] found that age at menopause and the reproductive period were not associated with the risk of dementia, two more recent population-based studies documented an increased risk of dementia by up to 23% with late menarche, early menopause and a short reproductive period[18,19]. Interestingly, patients who underwent bilateral oophorectomy before menopause had a higher risk of cognitive impairment over time than age-matched natural menopausal women; additionally, oophorectomy at ≤ 45 years of age was associated with an increased risk of dementia[20,21]. In women with Down syndrome, a condition with a higher incidence of AD than the general population, age at menopause was directly correlated with the age of dementia onset[22].

Evidence on AD biomarkers in middle-aged women strengthened the hypothesis that decreased estrogen levels in the menopausal transition explain cognitive decline during perimenopause and the greater risk of dementia related to the female sex. Rahman *et al*[23] compared 40- to 65-year-old women with age-matched men in terms of cerebral volumetry using structural magnetic resonance imaging, cerebral metabolism using 18F-fluorodeoxyglucose positron emission tomography, and the β-amyloid load using 11C-Pittsburgh compound B positron emission tomography. Women presented lower gray and white matter volumes, lower glucose metabolism, and higher deposition of β-amyloid; this neuroimaging pattern was consistent with an AD endophenotype. Menopause was the strongest predictor of these findings. Other studies reported a gradient of AD biomarkers, with the most remarkable abnormalities in menopausal women, an intermediate number of abnormalities in perimenopausal women, and the lowest number of abnormalities in premenopausal women[24,25]. In addition, cerebral glucose hypometabolism in AD-vulnerable regions of peri- and postmenopausal women correlated with reduced platelet mitochondrial cytochrome oxidase activity; mitochondrial cytochrome oxidase is an enzyme involved in

adenosine triphosphate (ATP) synthesis that is regulated by estrogen[24]. Based on these findings, the decrease in estrogen levels during the menopausal transition disrupts brain bioenergetics due to mitochondrial cytochrome oxidase dysfunction that is accompanied by reduced cerebral metabolism, β-amyloid deposition, synaptic loss, and cognitive decline.

PATHOPHYSIOLOGY

Estrogen and the brain

Accumulating evidence shows a significant neurotrophic and neuroprotective effect of estrogen on the central nervous system. Cognitive deficits have been described in women during the menopausal transition, particularly in cognitive domains such as working memory, attention, reduced processing speed, and reduced verbal memory. This review briefly describes the plausible biological functions of estrogens in aspects of cognitive function and the mechanisms involved[26].

The effects of estrogen on the brain include complex cellular mechanisms ranging from classical nuclear to nonclassical membrane-mediated actions. In classical mechanisms, estrogen modulates gene transcription by interacting with nuclear receptors. The estrogen receptors (ER) α and ERβ have distinct differences in their binding affinities for different ligands and selective ER modulators[27].

Through genomic mechanisms, steroids exert long-term effects on neurons, modulating the synthesis, release, and metabolism of many neuropeptides and neuroactive transmitters and the expression of their receptors. The nongenomic (nonclassical) estrogen action is probably mediated by receptors integrated or associated with the cell membrane and by the activation of distinct intracellular signaling cascades through the high-affinity membrane-associated G protein-coupled estrogen receptor GPR30/GPER1[28,29].

These effects of estrogens include rapid actions on the excitability of neuronal and pituitary cells, activation of cyclic adenosine monophosphate and mitogen-activated protein kinase pathways that affect the activity of targets such as kainite and insulin-like growth factor-1 receptors, modulation of G-protein coupling, modulation of calcium currents, modulation of calcium channels and calcium ion entry and protection of neurons from damage by excitotoxins and free radicals[30-33].

Decreases in estradiol levels may impact three systems. Researchers must determine how therapeutic modulation of estradiol levels may augment normal or disease-related cognitive decline. The three predominant systems postulated to be involved in cognitive aging concerning hypoestrogenism include the basal forebrain cholinergic system, the dopaminergic system, and the mitochondrial bioenergetic system[34].

Reduced nicotinic cholinergic binding sites in the cortex and reduced cholinergic acetyltransferase activity (a marker of cholinergic neurons) have been shown to correlate with reduced cognitive performance[35]. Choline acetyltransferase-expressing neurons are a marker for cholinergic neurons, and thus the expression of GPR30/GPER1 on cholinergic neurons provides increasing evidence for an interaction between estrogens and the cholinergic system. Clinical magnetic resonance imaging studies have shown that estradiol treatment also modulates anti-muscarinic and anti-nicotinic induced brain activity. Estradiol treatment alters anticholinergic-related brain activation during working memory in postmenopausal women[36].

The effects of estradiol on dopaminergic signaling have been less well characterized than its effects on the cholinergic system. *In vitro*, estradiol protects against 6-hydroxydopamine toxicity in dopamine neurons[37]. Magnetic resonance imaging evidence has shown that dopaminergic agonists increase working memory activity, suggesting that the dopaminergic system is responsive to pharmacological manipulation after the menopausal transition[38]. The potential mechanism by which estradiol exerts its neuroprotective effects on dopaminergic neurons is to modulate the neurotoxic effects of the renin-angiotensin system[39].

The mitochondrial aging hypothesis is related to increased mitochondrial DNA damage, leading to increased reactive oxygen species-mediated damage and a reduction in mitochondrial activity[40]. Clinical studies support the postulated role for estradiol in maintaining appropriate mitochondrial bioenergetics; clinical studies also support the hypothesis that decreasing estradiol levels are correlated with reduced synaptic plasticity, an indicator of cognitive performance, suggesting that a failure of glucose metabolism might influence cognitive deficits. As glucose uptake decreases, ATP production also decreases, consistent with aerobic cellular respiration[41].

Finally, low-grade inflammation has also been identified as a potential cause of cognitive decline. Postmenopausal women present an increase in the levels of inflammatory markers such as interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha. These increases in inflammatory markers appear to be normalized following treatment with sex HT, exerting a relevant anti-inflammatory effect[42,43].

Neuroprotective effect of estrogen

A reasonable hypothesis is that estrogen might exert an important protective effect on the deterioration of cognitive functions that occurs with normal aging. The potential mechanisms involved in the neuroprotective effects of estrogens include modulation of neuropeptides, neurotransmitters, and neurosteroid synthesis and activity[44,45]; reduced cell apoptosis[46]; modulation of neuronal growth and synaptic plasticity[47] and mitochondrial activity[48]; antioxidant properties[49]; modulation of the brain immune system[50]; and reduced formation of β-amyloid[51].

Importantly, the effects of treatment with sex hormones on cognitive symptoms appear to be more evident during the menopausal transition or in the first years of menopause when the levels of estradiol and estrogen receptors are initially decreasing [52].

Moreover, some selective estrogen receptor modulators, such as tamoxifen and raloxifene, have shown promising effects by interacting with ERα, ERβ, and GPR30[53] and exert neuroprotective effects[54]. Selective estrogen receptor modulators have shown efficacy in reducing anticholinergic effects on cognitive performance in some cognitive domains by reducing proinflammatory cytokine levels[55].

Findings from primary studies have shown that testosterone also exerts neuroprotective and anti-inflammatory effects on the brain. Testosterone protects against oxidative stress, serum deprivation-induced apoptosis, and soluble amyloid β (Aβ) toxicity; this effect is mediated by estrogen. Aβ toxicity induced by testosterone appears to involve an androgen receptor-dependent mechanism that leads to the upregulation of the Aβ-catabolizing enzyme neprilysin[56,57].

Notably, testosterone studies in women have yielded differing findings according to the women's ages, the testosterone dose administered, and the study duration. Observational and interventional studies have shown an association between verbal learning and memory and physiological concentrations of testosterone administered to postmenopausal women exogenously. The effects of testosterone on verbal learning and memory in postmenopausal women do not seem to rely on the aromatization of estradiol. The statistically significant improvements in verbal memory following testosterone therapy in postmenopausal women suggest that further investigations of the ability of testosterone to enhance cognitive performance or delay cognitive decline are warranted, but the results currently do not justify using testosterone for this purpose[58].

In conclusion, increasing evidence linking menopausal hormone changes and cognition has revealed a complex biological mechanism. A better understanding of this mechanism is fundamental to enable earlier and personalized pharmacological treatment with the potential to delay the onset of cognitive decline during the menopausal transition.

CLIMACTERIC FACTORS AND COGNITIVE DECLINE

The climacteric period often involves problematic symptoms, including vasomotor symptoms, vaginal dryness, decreased libido, insomnia, and fatigue[59]. In clinical practice, cognitive changes are also frequently observed during this period, with subjective reports of "cerebral fog" affecting daily cognitive performance. Some of the most common symptoms are deficits in attention, processing speed, and memory, which subsequently manifest as lack of focus, slow thinking, and forgetfulness[60].

In the Study of Women's Health Across the Nation with 16065 women between the ages of 40 and 55, 31% of premenopausal women reported complaints of forgetfulness, compared to 44% of women in early perimenopause, 41% of women in late perimenopause, and 41% of postmenopausal women[61]. This study later reported a compromise in cognitive performance, mainly in learning skills during the menopausal transition, with a subsequent improvement in the postmenopausal period. Cognitive changes that occur late after menopause are associated with aging and not with the last menstrual period[8].

In the Kinman women's health investigation, a longitudinal study, the cognitive performance of 694 premenopausal Chinese women was evaluated. Verbal memory,

mental flexibility, verbal fluency, and processing speed were measured at baseline and after 18 mo. An improvement in cognitive test scores was observed, which was expected due to the learning effect of repetition of neuropsychological tests. However, perimenopausal women recorded worse results than those who remained in the premenopause group[62].

Studies indicate that this decreased cognitive performance during perimenopause appears to normalize in postmenopause[8,62]. If this pattern of change in memory during the menopausal transition is valid, the decreases in estradiol levels alone are not likely solely responsible for cognitive changes, as memory appears to recover while decreases in estradiol levels persist[13,63].

Although self-reported vasomotor symptoms (VMSs) are generally not related to memory performance[64], when this relationship was observed using 24-h monitoring to measure physiological VMSs, verbal memory differences were found. Among middle-aged women, moderate to severe VMSs related to worse verbal memory were recorded with ambulatory skin conductance monitors and not self-reported VMSs[65,66].

Another cross-sectional study was performed with women with moderate to severe VMSs. Researchers recorded physiological VMSs using ambulatory monitors associated with or without a diary to record subjective VMSs and performed a battery of neuropsychological tests. A higher frequency of physiological VMSs, but not subjective VMSs, particularly during sleep, was associated with poor verbal memory testing performance[67]. Recently, a study evaluating the association between VMSs and worse memory was replicated in breast cancer survivors, confirming evident associations only with physiological VMSs[68].

Thus, in addition to being passive predictors of depressed mood, sleep problems, and worse quality of life during menopausal transition, VMSs also appear to be linked to the leading indices of physical and neurocognitive health[65,68].

HT AND COGNITION

Although many questions remain about the effects of HT on cognitive function, two factors seem to be consistently involved: Age and time of exposure concerning menopause. Researchers have postulated that a critical window exists that explains the more evident effects of HT when administered early when symptoms manifest and when administered to young women. However, published studies have reported conflicting results in this regard and are presented and discussed below.

Contradictory evidence presented to date

Although a considerable number of studies have examined the effects of HT on cognitive function in postmenopausal women, the results are still conflicting. Some studies showed benefits[69-71], others showed a lack of effect[72-74], and worsening of cognitive function was observed in some, including a more significant risk of MCI and various types of dementia[75,76]. Importantly, observational studies are prone to biases, such as selection bias, type, time of HT use, and age at HT initiation, which are often not controlled. These biases may at least partially explain the divergence between the findings of observational and interventional studies.

Many investigators presented their results for different aspects of HT and cognition at the same time. Because the same study published data on global cognitive function, MCI, and dementia, we chose to discuss the best evidence available, presenting the data jointly, as in the original articles of the critical observational and interventional studies on this topic.

Observational studies

Evidence from older women: The Cache County Study (CCS), a longitudinal, population-based study, investigated the association between HT and global cognitive function. The modified Mini-Mental State Examination (MMSE) was administered to 2073 women over 65 years old with no prior diagnosis of dementia. After three years of follow-up, HT was associated with an apparent benefit in global cognitive function and reduced cognitive decline, especially in older women (75 years or older) and even more so in women older than 85 years[77]. In another CCS publication, the relation between HT and AD was evaluated in 1889 women with an average age of 74.5 years. Compared to nonusers, women who received HT for more than ten years presented a 2.5-fold lower risk of AD incidence[78]. With seven more years of follow-up, the CCS cohort verified that starting HT (any type) within five years of menopause was

associated with a 30% reduction in the risk of developing AD. However, if HT was initiated after five years of menopause, no associations were observed.

Furthermore, if HT was initiated within five years of menopause and used for ten years or more, the reduction observed in AD risk was 37%. Additionally, the use of estrogen alone within five years of menopause reduced the risk of AD by 35%[79], which supports the critical window hypothesis. The main information obtained from the observational studies is shown in Table 1.

In a recent 12-year update of the follow-up of the CCS cohort, which included 2,114 women, a longer HT duration was associated with better cognitive function. Additionally, women who initiated HT within five years of menopause presented better cognitive performance than those who initiated it six or more years after menopause, once again supporting the critical window hypothesis. However, another interesting finding in the CCS was that even women who initiated HT after six years of menopause still presented cognitive benefits compared to women who never used HT [71].

In a French longitudinal study, the Three-City Study, 3310 postmenopausal women aged 65 years and over were followed every two years and were subjected to a series of cognitive tests to examine the association of HT with dementia and some specific cognitive domains. After a 4-year follow-up period, no associations were observed between HT and dementia or AD. Additionally, active HT users had significantly better performance on verbal fluency, working memory, and psychomotor speed tasks than those who never used HT. These associations varied according to the type and duration of HT. The findings of this study suggest that transdermal estrogen combined with progestogen and a lengthier HT duration are better at improving cognitive function. Notably, current HT users exhibited a reduction in the detrimental effect of apolipoprotein E (ApoE) E4, a known risk factor for dementia, on the incidence of dementia and AD. Moreover, starting HT near menopause had no relation to improved cognition[69], potentially refuting the critical window hypothesis.

In another longitudinal study with 5504 postmenopausal women conducted at the Kaiser Permanente Medical Care Program of Northern California, women who used HT only during their midlife period presented a 26% reduced risk of dementia than women who never used HT. Those who used HT in late life experienced detrimental effects, with a 48% higher risk of dementia in the 8-year follow-up[80]. These findings support the critical window hypothesis.

The largest longitudinal study was the Nurses' Health Study, a prospective cohort study that included a subgroup of 13087 participants aged 70 or older to evaluate global cognitive function, attention, verbal memory, and category fluency. Generally, few differences were observed between average cognitive decline when comparing current users or former users of HT and those who had never used it. On the other hand, the data suggest an increased risk of cognitive decline in long-term users (*i.e.*, 5 to 10 years) of estrogen alone or estrogen combined with progestogen, with a greater risk identified in women who initiated HT at an older age than in those who never received HT [relative risk: 1.74; 95% confidence interval (CI): 1.08-2.81]. The authors also did not identify a relation between HT and the ApoE E4 allele. The authors concluded that postmenopausal HT provides no relevant cognitive benefit in older women[76].

In a population-based nested case-control study that included 59 women with AD and 221 controls, no relationship was observed between the use of HT (estrogen with or without progestogen) and AD risk[72], corroborating the findings from a previous case-control study[81]. The Multi-Institutional Research in Alzheimer's Genetic Epidemiology case-control study included 971 postmenopausal women from different countries (426 patients with AD and 545 nondemented patients). HT was associated with a 30% reduction in the AD risk. The ApoE genotype did not influence the relationship between HT and AD. The protective effect of HT was modified by age, as it was observed only in younger women aged between 50 and 63 years, who presented a 65% reduction in the AD risk[82].

These findings suggest that HT use during the first years after the last menstrual period, named the critical window, may protect cognitive function. In another case-control study conducted in Finland, 84739 women diagnosed with AD and 84739 women without an AD diagnosis were included. Systemic HT was associated with a 9% to 17% increased risk of AD, with no significant difference between those who used estrogen alone and those who used estrogen and progestogen in combination. The exclusive use of vaginal estradiol did not increase the risk of AD. Moreover, the age at which HT was initiated (younger than 60 years or older than 60 years) had no effect on the AD risk. Notably, in women who initiated HT before 60 years of age, the increase in the AD risk was associated with the use of HT for ten years or more. The

Table 1 Observational studies on hormone therapy and cognition in women

Ref.	Study	Country	Design	*n* (%)	Age (yr)	Hormone therapy	Main findings
Carlson *et al* [77], 2001	Cache County Study	United States	Longitudinal	2073	≥ 65	ET or EPT	HT reduced cognitive decline
Seshadri *et al* [72], 2001		United Kingdom	Case-control	AD: 59. Controls: 221	Mean: 66.7	ET or EPT	HT was not associated with AD
Kang *et al*[76], 2004	Nurses' Health Study	United States	Longitudinal	13807	≥ 70	ET or EPT	HT was not associated with relevant cognitive benefits
Henderson *et al* [82], 2005	Mirage Study	United States, Canada, Germany	Case-control	AD: 426. Controls: 545	Mean: 71.1	ET or EPT	HT reduced the AD risk by 30%
Ryan *et al*[69], 2009	Three City Study	France	Longitudinal	3130	≥ 65	ET or EPT	HT was not associated with dementia or AD, but current users had better cognitive performance in specific domains
Shao *et al*[79], 2012	Cache County Study extended	United States	Longitudinal	1768	≥ 65	ET or EPT	HT initiated within five years of menopause decreased the AD risk by 30%
Whitmer *et al* [80], 2011	Kaiser Permanente Medical Care Program of Northern California	United States	Longitudinal	5504	Mean in midlife: 48.7	ET or EPT	The use of HT only in midlife reduced the dementia risk. On the other hand, the use of HT in late-life increased this risk
Imtiaz *et al*[70], 2017	Kuopio Osteoporosis Risk Factor and Prevention study	Finland	Longitudinal	8195	46 a 56	ET or EPT	Long-term HT users (> 10 yr) exhibited a 47% reduction in the AD risk
Savolainen-Peltonen *et al* [83], 2019		Finland	Case-control	AD: 84739. Controls: 84739	Mean age at onset of systemic HT: 52	ET or EPT	HT increased the AD risk by 9%-17%, regardless of the age of onset of use and the type of HT

ET: Estrogen-only therapy; EPT: Estrogen-progestogen therapy; HT: Hormone therapy; AD: Alzheimer's disease.

authors concluded that prolonged use of systemic HT might be accompanied by an increased risk of AD, which is not related to the type of progestogen or the age of HT initiation[83].

Few observational studies have evaluated the effects of HT exclusively in younger women. A recent prospective study conducted in Finland with 8195 women between 47 and 56 years of age with a 20-year follow-up showed little evidence of the protective effect of HT on dementia or AD, as only women who reported long-term (*i.e.*, more than ten years) use of HT presented a significant reduction in the AD risk of 47% compared to nonusers[70].

Interventional studies and the critical window hypothesis

As previously stated, the critical window hypothesis postulates that the effects of HT vary according to the moment of exposure, as related to menopause. According to this theory, estrogen administered closer to menopause would exert neuroprotective effects, whereas no benefit or harm would be observed when HT was administered years later[80]. Similarly, an ideal moment would exist to start HT and obtain cognitive benefits. Table 2 shows the main findings from the pertinent randomized clinical trials.

Evidence from older women

Due to possible biases regarding HT in observational studies, clinical trials were conducted to clarify these doubts. The WHIMS is an ancillary study of the Women's Health Initiative (WHI). The WHIMS included women aged 65 years or older. The effect of HT on the incidence of MCI and all-cause dementia (Alzheimer's, vascular and other types) was evaluated in hysterectomized women treated with conjugated equine estrogen (CEE), nonhysterectomized women treated with CEE plus medroxyprogesterone acetate (MPA), and the placebo group.

Table 2 Randomized clinical trials on hormone therapy and cognition in women

Ref.	Study	Country	*n* (%)	Age (yr)	Hormone therapy	Main findings
Shumaker *et al*[75], 2003	Women's Health Initiative Memory Study-WHIMS	United States	HT users: 2229. Placebo: 2303	≥ 65	CEE + MPA	HT increased the dementia risk
Shumaker *et al*[84], 2004	Women's Health Initiative Memory Study-WHIMS	United States	HT users: 1464. Placebo: 1483	65 to 79	CEE alone	Estrogen alone did not decrease the incidence of mild cognitive impairment or dementia
Greenspan *et al*[85], 2005		United States	HT users: 187. Placebo: 186	≥ 65	CEE with or without MPA	HT did not affect cognitive function
Yaffe *et al* [86], 2006		United States	HT users: 208. Placebo: 209	60 to 80	Ultra–low dose unopposed transdermal estradiol	Transdermal estradiol did not affect cognitive function
Espeland *et al*[87], 2010	Women's Health Initiative Study of Cognitive Aging-WHISCA	United States	HT users: 1125. Placebo: 1179	65 to 80	CEE with or without MPA	HT was associated with worsening global cognitive function and some specific cognitive domains. This worsening persisted after the interruption of HT
Espeland *et al*[73], 2013	Women's Health Initiative Memory Study of Younger Women-WHIMSY	United States	HT users: 696. Placebo: 630	50 to 55	CEE with or without MPA	HT did not alter global cognitive function or specific cognitive domains
Gleason *et al* [74], 2015	Cognitive and Affective Study-KEEPS-Cog	United States	HT users: 431. Placebo: 262	Mean: 52.6	CEE + micronized progesterone ortransdermal estradiol + micronized progesterone	HT did not affect cognition
Henderson *et al*[92], 2016	Early *vs* Late Intervention Trial with Estradiol Cognitive endpoints-ELITE-Cog	United States	HT users: 284. Placebo: 283	Early postmenopause: 55.6. Late postmenopause: 64.9	Estradiol with or without micronized progesterone	HT did not affect verbal memory, executive function and global cognition, regardless of whether it was started < 6 yr or ≥ 10 yr after menopause
Espeland *et al*[91], 2017	WHIMSY extended + Women's Health Initiative Memory Study of the Epidemiology of Cognitive Health Outcomes (WHIMS-ECHO	United States	WHIMSY-HT users: 701. Placebo: 635. WHIMS-ECHO-HT users: 1402. Placebo: 1478	Two groups: 50 to 54; 65 to 79	CEE with or without MPA	HT prescribed to younger women had no significant effect on cognitive function in the long term. HT administered to older women produced decreased global cognitive function, executive function, and working memory

CEE: Conjugated equine estrogen; MPA: Medroxyprogesterone acetate; HT: Hormone therapy.

In the CCE/MPA arm of the study, in which 4532 women participated (CEE/MPA group: 2.229; placebo group: 2.303), the hazard ratio (HR) for dementia was 2.05 (95%CI: 1.21-3.48; 45 *vs* 22 *per* 10000 person-years; $P = 0.01$), resulting in 23 additional cases of dementia *per* 10000 women *per* year. AD was the most common dementia type in both groups. The effects of treatment on the risk of MCI did not differ between groups (HR: 1.07; 95%CI: 0.74-1.55; 63 *vs* 59 cases *per* 10000 person-years; $P = 0.72$). The authors concluded that HT with the combination of estrogen and progestogen increased the risk of probable dementia in postmenopausal women aged 65 years older. These data indicate a lack of protection from MCI in these women receiving HT [75].

In the WHIMS arm with CEE alone, 2947 participants were included (CEE group: 1464; placebo group: 1483), with ages ranging from 65 to 79 years. No significant differences in the dementia risk (HR: 1.49; 95%CI: 0.83-2.66) and MCI risk (HR: 1.34; 95%CI: 0.95-1.89) were observed between groups. However, the joint analysis of the MCI or dementia risk showed a greater risk for women who received CEE alone than the placebo group (HR: 1.38; 95%CI: 1.01-1.89; $P = 0.04$)[84]. Isolated estrogen therapy did not reduce the incidence of MCI or dementia. Based on the combination of WHIMS data, HT with estrogen alone and CEE/MPA resulted in an increased risk of dementia or MCI in women aged 65 or older, and HT was not recommended to prevent cognitive decline[84].

In two randomized clinical trials with a smaller population of older postmenopausal women, including a study with 373 women and a 3-year follow-up period[85] and another with 417 women and a 2-year follow-up period[86], HT had no significant effect on cognitive function. The WH Study of Cognitive Aging, another ancillary study of the WHI, had two arms, CEE alone and CEE/MPA with matching placebos, and included 2304 women. HT initiated after 65 years of age was associated with worsening global cognitive function and changes in a few cognitive domains; notably, this reduction persisted after the interruption of HT. The authors highlighted that this difference in cognitive function was small and might have no clinical meaning[87].

A meta-analysis that included 16 clinical trials with 10114 women reported no beneficial effect of HT (estrogen with or without progestogen) administered in the short or long term (up to five years) on the cognitive function of older postmenopausal women. Moreover, the authors were unable to establish definitive conclusions on the effects of different administration routes and HT dosages on women's cognitive function[88]. Another meta-analysis concluded that HT is not indicated to prevent cognitive decline or dementia in postmenopausal women[89].

Evidence from younger women

Since younger women more frequently receive HT, its effects on cognitive function when used precociously must be clarified. Clinical trials on this topic are rare.

A systematic review included data from nine randomized, double-blind, placebo-controlled clinical trials of HT with estrogen alone and two with estrogen combined with progestogen, in which cognitive tests were administered to women aged less than 65 years, although the sample size was small. Seven of nine studies reported a small advantage for estrogen treatment in at least one cognitive test, particularly in verbal memory and attention. Only two studies assessed the effect of combined HT (estradiol valerate and dienogest), showing some benefit only on verbal memory[90]. Thus, although scarce, evidence from HT in younger women suggests potentially beneficial effects on specific cognitive domains, particularly in symptomatic women and women who recently underwent menopause, as well as inadequate evidence of damage. Studies examining the cognitive effects of estrogen combined with progestogen on younger women are scarce[90].

In the WHIMS of Younger Women (WHIMSY), an ancillary study of the WHI study, the effect of HT (CEE/MPA, CEE-alone, and placebo) on cognition was evaluated in 1326 postmenopausal women aged 50 to 55 years. Cognitive testing was performed, on average, 7.2 years after the end of the WHI study, when participants had an average age of 67.2 years at their first evaluation. HT did not alter global cognitive function or the specific domains of cognition (verbal memory, working memory, verbal fluency, attention, and executive functions). WHIMSY data indicated that CEE-based HT administered to younger women in the initial postmenopausal period had no long-term beneficial or harmful effects[73]. Afterward, the authors published data from the extended follow-up accomplished through WHIMSY and WHIMS-Epidemiology of Cognitive Health Outcomes, in which HT was prescribed to women aged 65 to 79 years. The use of HT by younger women for up to 6 years had no significant effect on cognitive function in the long term. On the other hand, the use of HT for five years by older women was related to a decline in global cognitive function, executive functions, and working memory, which persisted for more than ten years after administration [91].

Another investigation that included younger women was the Cognitive Affective Study (KEEPS-Cog)[74], an ancillary study of the Kronos Early Estrogen Prevention Study (KEEPS). The KEEPS-Cog studied the effects of HT administered for up to four years on cognition (global cognitive function, mental flexibility, verbal learning/memory, auditory attention, and executive functions) and humor in recently postmenopausal healthy women. In this randomized, double-blinded, placebo-controlled clinical trial, 0.45 mg of CCE was administered orally, plus 200 mg of micronized progesterone or 50 mcg of transdermal estradiol, plus 200 mg of micronized progesterone, as well as a placebo. Participants had a mean age of 52.5 years and were tested at an average of 1.4 years after menopause. HT did not affect cognition, and the use of oral CEE combined with micronized progesterone reduced anxiety and depressive symptoms, changes that were not observed in the group receiving transdermal therapy[74]. The KEEPS-Cog results regarding the lack of effect of HT on cognition are consistent with the WHIMSY findings.

The Early *vs* Late Intervention Trial with Estradiol (ELITE) was a randomized clinical trial in which participants received oral estradiol, micronized progesterone, or a matched placebo. The ELITE-Cog evaluated the effects of HT on cognition in postmenopausal women who were divided into two groups according to time since

menopause: early (less than six years, mean age of 55.6 years) or late (ten years or more, the mean age of 64.9 years). After an average of 57 mo of treatment, no significant differences in verbal memory, executive function, or global cognition were observed among women who initiated estradiol use within six years or ten years or more after menopause. These data suggest that estradiol has no beneficial or harmful effect on the evaluated cognitive domains, regardless of time elapsed since menopause; hence, the authors did not confirm the critical window hypothesis for cognitive function[92].

CONSIDERATIONS FOR CLINICAL PRACTICE

Clinical management of cognitive symptoms in perimenopausal women should consider that cognitive impairment does not appear to be frequent in this population [10], and an increased risk of dementia due to menopause is not well established[15,16, 18,19]. Nevertheless, patients with cognitive complaints and no objective impairment exhibited worse performance on cognitive tests than women without complaints[93]. Hence, some perimenopausal women might perceive the decline in verbal memory and learning performance compared to their ability during their premenopausal period, although they performed within normal parameters on neuropsychological tests[13]. Therefore, clinicians must validate the concerns about the cognitive decline of perimenopausal patients and evaluate their cognitive performance. Cognitive screening tests such as the MMSE[94] and the Montreal Cognitive Assessment (MoCA) [95], functional tests such as the Functional Assessment Questionnaire (FAQ)[96], and neurological examinations should comprise routine clinical evaluations. Due to the menopausal transition, cognitive symptoms are not expected to coincide with alterations on the MMSE, MoCA, FAQ, or neurological examination[97]. In these cases, patients should be advised that cognitive complaints are probably due to the menopausal transition associated with a subtle and transient cognitive decline[13]. Women with early menopause or those undergoing surgical or chemotherapy-induced menopause should be evaluated more carefully with repeated cognitive assessments during follow-up since these characteristics are more strongly associated with worse cognitive outcomes at older ages[15,20,21]. Scores less than 28 on the MMSE and less than 26 on the MoCA, indicating functional decline in daily activities (FAQ > 0), or altered neurological examinations are associated with cognitive impairment[98-100]. Notably, lower educational levels may bias cognitive tests, impairing their accuracy [101].

Suppose that screening tests indicate cognitive impairment in perimenopausal women. In that case, a comprehensive neuropsychiatric and neuropsychological assessment would be required to confirm the diagnosis of MCI or dementia in addition to a laboratory workup, neuroimaging examination, and, eventually, other tests to investigate underlying causes of cognitive decline. Thyroid hormones disturbances, vitamin B12 or folic acid deficiency, anemia, decompensated diabetes or hypoglycemia, electrolyte disturbances, renal or hepatic impairment, neurosyphilis or other infection of the central nervous system, and the use of benzodiazepines or medications with anticholinergic effects are potentially modifiable causes of cognitive impairment that should be excluded. Depression and other affective symptoms, such as anxiety, sleep disturbances, and attention deficit hyperactivity disorder, may exacerbate cognitive decline due to the menopausal transition, causing MCI in middle-aged women. In addition, presenile dementias such as familial AD, frontotemporal lobar degeneration, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy are uncommon neurocognitive disorders that may affect perimenopausal women.

Concerning the relationship between HT and cognition in postmenopausal women, the literature reports conflicting data. Notably, research differs in terms of the study design, age of the studied population, starting moment of HT, type, route of administration, and HT duration, among other aspects. An analysis of these studies allows us to verify dissonant findings, even among observational studies. Generally, observational studies have suggested some beneficial effects of HT on cognition, although some researchers, as previously described, have identified cognitive decline or an increased risk of dementia associated with HT. Regarding interventional studies, the findings are also not uniform concerning whether HT exerts detrimental or no effects on cognition. Overall, the results of interventional studies indicated detrimental effects of HT on older women, leading to cognitive decline and a greater risk of dementia, including AD.

Data on HT and cognition in younger postmenopausal women are scarce. Although observational studies suggest that HT may protect against future cognitive impairment in the early years of postmenopause, data from the WHIMSY trial[73,91], KEEPS-Cog trial[74], and ELITE-Cog trial[92] showed no benefits of HT in terms of the cognitive function of postmenopausal women compared to that of younger women. In younger symptomatic women, for whom benefits of using HT for symptom improvement have been reported, limited evidence suggests that these women do not appear to have a more significant risk of developing future cognitive problems.

Building big data and using data-driven approaches such as machine learning would help resolve conflicting data regarding the role of the menopausal transition in the risk of dementia and the effect of HT. In this context, big data may contribute to the prevention and early diagnosis of cognitive impairment in women undergoing the menopausal transition and facilitate evidence-based decision-making.

Based on the best available evidence, no robust data have been published that indicate that the use of HT with estrogen alone or combined with progestogen prevents cognitive decline or dementia in postmenopausal women. Thus, the prescription of HT is not recommended for this purpose.

CONCLUSION

The increasing number of people living with dementia will significantly impact life in years to come. Its effects will be felt individually, as it decreases the quality of life, both in patients and caregivers and at a population level, as it overburdens the health system and influences policies worldwide.

Being at greater risk of developing dementia, women are a target group of great interest for future studies. The link between sex and the risk of dementia still must be better understood. Along these lines, the menopausal transition is important, as it is a period of intense hormonal changes and symptomatic stress, which may be related to cognitive decline. Estrogen may play an essential role as a neuroprotective agent, although numerous other aspects are also relevant. A better understanding of the physiology involved in the cognitive impairment in this population, as well as the aspects of this decrease in cognition–which functions are affected and to what extent–may contribute to the elaboration of preventive measures and eventually may contribute to better treatment strategies, focusing on this possibly reversible cause of the cognitive decline.

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REVIEW

Clozapine resistant schizophrenia: Newer avenues of management

Subho Chakrabarti

ORCID number: Subho Chakrabarti 0000-0001-6023-2194.

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Subho Chakrabarti, Department of Psychiatry, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

Corresponding author: Subho Chakrabarti, MD, Professor, Department of Psychiatry, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh 160012, India. subhochd@yahoo.com

Abstract

About 40%-70% of the patients with treatment-resistant schizophrenia have a poor response to adequate treatment with clozapine. The impact of clozapine-resistant schizophrenia (CRS) is even greater than that of treatment resistance in terms of severe and persistent symptoms, relapses and hospitalizations, poorer quality of life, and healthcare costs. Such serious consequences often compel clinicians to try different augmentation strategies to enhance the inadequate clozapine response in CRS. Unfortunately, a large body of evidence has shown that antipsychotics, antidepressants, mood stabilizers, electroconvulsive therapy, and cognitive-behavioural therapy are mostly ineffective in augmenting clozapine response. When beneficial effects of augmentation have been found, they are usually small and of doubtful clinical significance or based on low-quality evidence. Therefore, newer treatment approaches that go beyond the evidence are needed. The options proposed include developing a clinical consensus about the augmentation strategies that are most likely to be effective and using them sequentially in patients with CRS. Secondly, newer approaches such as augmentation with long-acting antipsychotic injections or multi-component psychosocial interventions could be considered. Lastly, perhaps the most effective way to deal with CRS would be to optimize clozapine treatment, which might prevent clozapine resistance from developing. Personalized dosing, adequate treatment durations, management of side effects and non-adherence, collaboration with patients and caregivers, and addressing clinician barriers to clozapine use are the principal ways of ensuring optimal clozapine treatment. At present, these three options could the best way to manage CRS until research provides more firm directions about the effective options for augmenting clozapine response.

Key Words: Clozapine-resistance; Augmentation; Medications; Electroconvulsive therapy; Psychosocial treatments; Schizophrenia

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Core Tip: About 40%-70% of patients develop clozapine-resistant schizophrenia, which has serious health, economic, and social consequences. Research on clozapine-resistant schizophrenia has provided little support for the efficacy of psychotropics, electroconvulsive therapy, and cognitive-behavioural therapy in augmenting clozapine non-response. Therefore, newer approaches are needed including a clinical consensus about using the most effective of the currently available augmentation strategies. Augmentation with long-acting antipsychotic injections or multi-component psychosocial interventions could also be tried. Finally, the best option at present may be to prevent clozapine resistance from developing by optimizing clozapine treatment and collaborating with patients and caregivers to ensure its continuation.

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INTRODUCTION

Although antipsychotic treatment is one of the principal options for the management of schizophrenia, about a third of the patients with schizophrenia do not respond well to first- or second-generation antipsychotics[1,2]. People with treatment-resistant schizophrenia (TRS) continue to have psychotic symptoms and functional impairment despite adequate antipsychotic use. TRS is associated with greater severity of symptoms, more frequent relapses, repeated hospitalizations, poorer socio-occupational functioning, and poorer quality of life(QOL). Consequently, it imposes a substantial economic and social burden on patients, families, and healthcare services[1,3]. Despite some contrary opinions, there is a widespread consensus that clozapine is the treatment of choice for patients with TRS[4,5]. However, even with optimal clozapine treatment, 40%-70% of the patients with TRS do not benefit from monotherapy with clozapine[6-9]. Patients with clozapine-resistant schizophrenia (CRS) are probably among the most severely ill of all patients with this disorder. A study comparing TRS and CRS found that the overall severity of the illness and positive and negative symptoms were significantly higher, while the QOL score was significantly lower among patients with CRS[10] Moreover, symptom severity among patients with CRS did not improve much over 6 mo of follow-up. Other estimates have suggested that apart from the greater symptom severity, patients with CRS are likely to be more frequent users of healthcare services and more likely to have multiple and prolonged hospitalizations[11].

Consequently, the cost of their care and the adverse impact of CRS on patients and their caregivers is also likely to be substantially greater than TRS[7,12]. Such serious consequences of CRS often compel clinicians to try new and different strategies to treat these patients. The option most commonly adopted is to add another psychotropic agent to clozapine to enhance its effects[9,11]. However, the evidence to date indicates that augmentation with medications or other treatments yields little or no additional benefits for these patients[13]. The treatment of CRS thus continues to pose a formidable challenge for clinicians. Moreover, the size of this group of patients will increase as the use of clozapine for TRS increases. Therefore, newer ways of managing CRS have to be explored. Accordingly, this review attempts to briefly summarize the research in this area, followed by a discussion of certain treatment options and strategies that appear promising.

DEFINING AND CONCEPTUALIZING CRS

The key elements of the current definitions of CRS are depicted in Table 1. These include a diagnosis of schizophrenia, moderate baseline severity, and non-response and persistence of symptoms, and functional impairment despite adequate treatment with clozapine[12,14-16]. Though these operationalized definitions of CRS represent an improvement, it is also apparent that the majority of clinical trials of patients with

Table 1 Key components of the current definitions of clozapine-resistant schizophrenia[12,14-16]

Diagnosis	Diagnosis of schizophrenia using standardized criteria and after ruling out psychosis due to substance use or medical conditions
Adequate clozapine treatment	
Dose	200-500 mg/d
Blood levels	≥ 350 ng/mL
Treatment duration	2-3 mo[1]
Treatment adherence	≥ 80% of prescribed doses for the duration of treatment
Response to clozapine	
Baseline symptom severity and functional impairment	Moderately severe illness either globally or in positive and negative symptom domains assessed using standardized scales (CGI, BPRS, PANSS, SAPS, SANS). Moderate levels of functional impairment assessed using standardized scales (GAF, SOFAS)
Non-response	< 20% reduction in symptoms and minimal response in levels of functional impairment during an adequate trial of clozapine treatment
Persistence	Moderately severe illness and functional impairment should persist following an adequate trial of clozapine treatment

[1]It has been proposed that duration of clozapine trials should be 2 mo for patients with aggression or self-harm, 3 mo for those with positive symptoms, and 4 mo for those with negative and cognitive symptoms[13].

BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impression scale; GAF: Global Assessment of Functioning scale; PANSS: Positive and Negative Syndrome Scale; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms; SOFAS: Social and Occupational Functioning Scale.

CRS have not utilized such definitions. Moreover, a major criticism of the current constructs of CRS is that they rely excessively on positive symptoms of schizophrenia [11,17,18]. Other domains such as negative, cognitive, or depressive symptoms, or QOL have not received sufficient attention. This gives rise to substantial heterogeneity in the CRS groups selected using such definitions, which further hinders research. Although measures such as more precise delineation of target symptoms and differentiating between "minimum and optimal criteria" required for CRS have been proposed [15,16], the current definitions are still far from perfect[11,15,18,19]. Finally, from a clinical perspective there are many practical difficulties in determining adequate doses, estimating blood levels, judging adherence, and conducting prospective observation of patients during treatment with clozapine[15,16].

AUGMENTATION STRATEGIES FOR CRS: A BRIEF REVIEW

Medication augmentation

In routine clinical practice, the commonest strategy to deal with CRS is augmentation with another antipsychotic[9,11,20,21]. Mood stabilizer or antidepressant augmentation is used less frequently. Some treatment guidelines also endorse augmentation with antipsychotics[13]. Over the past 25 years, many trials of clozapine augmentation with medications and other treatments have been conducted. Additionally, more than 50 reviews on the subject including narrative and systematic reviews, individual meta-analyses, and reviews of different meta-analyses have been published.

Antipsychotic augmentation: Some of the recent reviews of augmentation of clozapine with a second antipsychotic in CRS are included in Table 2[22-44].

Among all augmentation trials, the largest number has involved antipsychotic augmentation of clozapine non-response. Risperidone, aripiprazole, and amisulpride are the most commonly evaluated augmenting agents. Despite the size of the evidence, the majority of reviews have concluded that adding a second antipsychotic to clozapine does not have any significant impact on clinical response, overall symptom severity, or severity of positive symptoms[7,8,20,45,46]. Though some benefit has been noted when all trials are included, there appear to be no significant effects when only high-quality trials are considered[2,18]. Even when benefits are evident in well-designed randomized controlled trials (RCTs), the combined effect sizes are small to moderate casting doubts on the clinical significance of these findings. The effect of antipsychotic combinations with clozapine on negative and depressive symptoms has

Table 2 Reviews of antipsychotic augmentation strategies in clozapine-resistant schizophrenia[1]

Ref.	Type of review	Details	Effect on positive or psychotic symptoms	Effect on negative or depressive symptoms
Wagner *et al* [2], 2019	Systematic review	14 meta-analyses of FGA and SGA augmentation of clozapine.	Some evidence of benefits based on low-quality studies (SIGN grade B).	
Roerig *et al* [8], 2019	Systematic review	4 meta-analyses and 1 naturalistic study of FGA and SGA augmentation of clozapine.	No benefits of antipsychotics when high-quality RCTs were considered.	
Bartoli *et al* [22], 2019	Meta-analysis	12 RCTs of SGA augmentation of clozapine-risperidone (n = 5) and aripiprazole (n = 3).	No difference between SGA augmentation and placebo in improving positive symptoms.	A small benefit of SGA augmentation for negative and depressive symptoms.
Siskind *et al* [23], 2018	Meta-analysis	19 RCTs of FGA and SGA augmentation of clozapine-aripiprazole (n = 7), risperidone (n = 3), and amisulpiride (n = 2).	Evidence for benefit with aripiprazole, but effects were lost when low-quality studies were excluded.	
Correll *et al* [24], 2017	Meta-analysis	Meta-analysis of 29 previous meta-analyses of antipsychotic combinations-5 clozapine combinations examined.	Clozapine combinations no different from clozapine monotherapy for positive symptoms.	Clozapine combinations no different from clozapine monotherapy for negative symptoms.
Galling *et al* [25], 2017	Meta-analysis	20 RCTs of FGA and SGA augmentation of clozapine-risperidone (n = 6) and aripiprazole (n = 6).	No evidence for additional benefits of augmentation in double-blind, high-quality RCTs.	Improvement in negative symptoms with aripiprazole augmentation. No effect of augmentation on depressive symptoms.
Ortiz-Orendain *et al*[26], 2017	Meta-analysis	31 RCTs and quasi-RCTs of augmentation with SGAs (n = 26) and FGAs (n = 5) including clozapine augmentation.	Low-quality evidence that augmentation improves global clinical response. No specific effects on positive symptoms.	No effect of augmentation on negative symptoms.
Barber *et al* [27], 2017	Meta-analysis	5 RCTs of clozapine augmentation with SGAs or haloperidol.	Low-quality evidence that augmentation may improve global clinical response. Effects on positive symptoms not clear.	Effects on negative symptoms not clear.
Jiménez-Cornejo *et al* [28], 2016	Meta-analysis	17 prior meta-analyses and reviews of FGA and SGA augmentation (62 studies) of clozapine.	Little evidence that augmentation improves clinical response (> 20% reduction in PANSS/BPRS scores).	
Taylor *et al* [29], 2012	Meta-analysis	14 RCTs of FGA and SGA augmentation of clozapine.	A small benefit in overall symptom reduction with augmentation.	
Sommer *et al* [30], 2012	Meta-analysis	10 RCTs of FGA and SGA augmentation of clozapine.	One RCT showed that sulpiride augmentation led to overall symptom reduction. No specific effects on positive symptoms.	No specific effects on negative symptoms.
Porcelli *et al* [31], 2012	Systematic review and meta-analysis	Systematic review of 25 studies of SGA augmentation of clozapine - risperidone (11 trials) and aripiprazole (6 trials). Meta-analysis of 5 RCTs of risperidone augmentation of clozapine.	Low quality evidence indicated benefits for aripiprazole and amisulpiride augmentation. No benefit of risperidone augmentation.	Some benefit of aripiprazole in reducing negative symptoms from 1 RCT.

[1]Several other systematic reviews[9,12,14,32,33] and meta-analyses[17,34-37] have been unable to find significant benefits, while others have reported modest benefits for antipsychotic augmentation of clozapine[38-44].

BPRS: Brief Psychiatric Rating Scale; FGA: First-generation antipsychotic; RCT: Randomized controlled trial; PANSS: Positive and Negative Syndrome Scale; SGA: Second-generation antipsychotic; SIGN: Scottish Intercollegiate Guidelines Network.

been examined less frequently. A similar inconsistency is apparent with some meta-analyses showing modest benefits, while others report no effects on these symptoms.

Antidepressant and mood stabilizer augmentation: As depicted in Table 3, the number of RCTs examining the augmentation of clozapine with antidepressants and mood stabilizers is comparatively less. Moreover, the trials are more often of poorer quality. Consequently, there is little evidence of the benefits of antidepressant augmentation on the severity of symptoms[23,24,30,37]. When some evidence of a positive effect has been found, it is usually based on single, high-quality RCTs[23,24,30,37]. Similarly, though mood stabilizer augmentation is reported to be beneficial in some meta-analyses[47,48], others have either found no benefit[7,24,46,49] or evidence of significant symptom reduction only in low-quality trials[2,8,23,30,50].

Table 3 Meta-analyses of antidepressant and mood stabilizer augmentation in clozapine-resistant schizophrenia

Ref.	Type of review	Details	Results
Antidepressants			
Siskind *et al* [23], 2018	Meta-analysis	10 RCTs of fluoxetine, paroxetine, duloxetine, and mirtazapine augmentation	Some evidence for fluoxetine augmentation in reducing in overall symptom severity based on 1 high-quality RCT.
Correll *et al* [24], 2017	Meta-analysis	Analysis based on the earlier meta-analysis of Veerman *et al*[37]	No benefit of antidepressant augmentation on reduction in overall, positive, and negative symptom severity.
Veerman *et al* [37], 2014	Meta-analysis	4 RCTs of mirtazapine, duloxetine, and fluoxetine augmentation	No benefit of antidepressant augmentation on reduction in overall, positive, and negative symptom severity.
Sommer *et al* [30], 2012	Meta-analysis	4 RCTs of mirtazapine, citalopram, and fluoxetine augmentation	Some evidence for citalopram augmentation in reducing overall and negative symptom severity based on 1 RCT.
Mood stabilizers			
Siskind *et al* [23], 2018	Meta-analysis	5 RCTs of valproate (n = 2), lamotrigine (n = 2), lithium (n = 1), and topiramate(n = 1) augmentation	Low-quality evidence for valproate and lithium augmentation in reducing total symptom severity. Reduction of positive and negative symptom severity by topiramate augmentation based on1 RCT.
Correll *et al* [24], 2017	Meta-analysis	Analysis based on the earlier meta-analysis of Veerman *et al*[37]	No benefit of lamotrigine and topiramate augmentation on reduction in overall, positive, and negative symptom severity.
Zheng *et al* [50], 2017	Meta-analysis	22 RCTs of valproate (n = 9), lamotrigine (n = 8), and topiramate (n = 4) augmentation	Significant benefits for valproate and topiramate in reducing total and positive symptom severity but based on low-quality studies. No effects on clinical response.
Zheng *et al* [48], 2016	Meta-analysis	4 RCTs of topiramate augmentation	Significant benefits of topiramate augmentation in reducing overall, positive, and negative symptom severity.
Veerman *et al* [49], 2014	Meta-analysis	6 RCTs of lamotrigine and 4 RCTs of topiramate augmentation	No benefit of lamotrigine and topiramate augmentation on reduction in overall, positive, and negative symptom severity.
Sommer *et al* [30], 2012	Meta-analysis	7 RCTs of lamotrigine (n = 4) and topiramate (n = 3) augmentation	Benefits of lamotrigine and topiramate augmentation for total and positive symptoms based on single RCTs that did not persist on further analysis.
Tiihonen *et al* [47], 2009	Meta-analysis	5 RCTs of lamotrigine augmentation	Evidence for benefit of lamotrigine augmentation in reducing overall, positive, and negative symptom severity.

RCT: Randomized controlled trial.

Methodological lacunae: One of the principal reasons for the inability to find effective medication augmentation options for CRS is the methodological shortcomings of current research. Even in the better quality RCTs, there is considerable heterogeneity in terms of the definitions used, the types and numbers of patients included, the duration of trials, and the outcomes examined. The methodological lacunae of the RCTs have in turn affected the methodological quality of meta-analytic examinations of the evidence. For example, in a systematic review of 21 meta-analyses only one was judged to have "very little risk of bias;" 7 had "low risk of bias," and the rest had "high risk of bias"[2]. Therefore, there is considerable uncertainty even about the findings of meta-analytic studies.

Augmentation with electroconvulsive therapy and recurrent transcranial magnetic stimulation

Some of the more recent reviews have concluded that electroconvulsive therapy (ECT) is an effective augmentation strategy, especially when medications fail to decrease persistent positive symptoms[2,8,20,46,51]. However, this conclusion appears to be based on a single meta-analysis of 18 RCTs[52], which showed that the ECT-clozapine combination was better than clozapine alone in reducing positive symptoms. Then again, 17 of these RCTs were conducted in China and are not easily accessible[53]. As shown in Table 4, there are only two small RCTs of ECT augmentation of clozapine response. The first showed that the clozapine-ECT combination was more effective than clozapine alone in TRS[54], whereas the second did not find the combination to be more effective in CRS[55]. The rest of the evidence consists of non-randomized trials[56] and case studies. Thus, the higher response rates of the clozapine-ECT combination reported in systematic reviews[57-61] and other meta-analyses[62-64] are largely based on low-quality evidence, obtained mainly among patients with TRS, and

Table 4 Electroconvulsive therapy and recurrent transcranial magnetic stimulation augmentation in clozapine-resistant schizophrenia

ECT			
Ref.	**Study/review**	**Details**	**Results**
Masoudzadeh *et al*[56], 2007	Controlled trial, (non-randomized, non-blinded)	18 patients with TRS; 3 groups of clozapine-ECT treatment, only clozapine and only ECT treatment (n = 6 each)	Significant differences between the clozapine- ECT combination and monotherapy groups in reduction of PANSS scores.
Petrides *et al*[54], 2015	Single-blind cross-over RCT	39 patients with TRS randomized to clozapine-ECT (n = 20) and clozapine only treatment (n = 19)	Significantly greater response on BPRS psychosis & CGI scores in the clozapine-ECT combination group.
Melzer-Ribeiro *et al*[55], 2017	Single-blind sham-controlled RCT	23 patients with CRS randomized to treatment with clozapine-ECT (n = 13) and clozapine-sham ECT (n = 10)	No significant differences between the groups on PANSS total and positive symptom scores and CGI scores.
Kupchik *et al*[57], 2000	Systematic review	Case reports of 36 patients with TRS and clozapine non-responders	67% of the patients on the clozapine-ECT combination showed good response.
Braga *et al*[58], 2005	Systematic review	12 case reports or chart reviews of patients with TRS and clozapine non-responders	The clozapine-ECT combination was efficacious.
Havaki-Kontaxaki *et al*[59], 2006	Systematic review	One open trial and 6 case studies of patients with CRS	73% patients on the clozapine-ECT combination showed marked improvement.
Pompili *et al*[60], 2013	Systematic review	31 studies examining indications for ECT in schizophrenia	The clozapine-ECT combination was efficacious in patients resistant to medications.
Grover *et al*[61], 2015	Systematic review	40 studies, mainly case reports of patients with CRS	Short-term response rates of the clozapine-ECT combination varied from 37%-100%.
Lally *et al*[62], 2016	Systematic review and meta-analysis	Pooled analysis of patients with TRS treated with clozapine and ECT based on 4 open trials, 2 controlled trials (1 RCT)[1], 2 chart reviews, 6 case series, and 15 case reports	Pooled response rate with the clozapine-ECT combination was 54% on meta-analysis. Systematic review showed 76% overall response rate with clozapine-ECT treatment and a relapse rate of 32%.
Manubens *et al*[63], 2016	Systematic review and meta-analysis	6 systematic reviews of ECT in TRS including 6 controlled trials of the clozapine-ECT combination in clozapine non-responders (1 RCT)[1]	Modest effect of ECT in augmenting clozapine response with low certainty of evidence.
Ahmed *et al*[64], 2017	Systematic review and meta-analysis	9 studies of the clozapine-ECT combination in TRS including 2 controlled trials (1 RCT)[1], 3 open trials, and 4 case series/chart-reviews *vs* 9 studies of ECT-non-clozapine antipsychotic combination	The ECT-clozapine combination was significantly better than the ECT-non-clozapine antipsychotic combinations in reducing positive symptoms on the PANSS and the BPRS.
Wang *et al*[52], 2018	Meta-analysis	18 RCTs of clozapine augmentation in CRS (17 from China and 1 from the United States[1])	Adjunctive ECT was superior to clozapine monotherapy in reducing positive symptoms after 1–2 wk but with moderate effect size.
rTMS			
Wagner *et al*[66], 2020	Meta-analysis	Pooled data from 10 RCTs for 131 patients with persistent positive and negative symptoms being treated with clozapine	No differences between active and sham rTMS in improving clinical response and reducing PANSS scores. No benefit of rTMS augmentation for patients with persistent symptoms on clozapine.

[1]The RCT from United States is by Petrides *et al*[54].

BPRS: Brief Psychiatric Rating Scale; CGI: Clinical Global Impression scale; CRS: Clozapine-resistant schizophrenia; ECT: Electroconvulsive therapy; PANSS: Positive and Negative Syndrome Scale; RCT: Randomized controlled trial; rTMS: Recurrent transcranial magnetic stimulation; TRS: Treatment resistant schizophrenia.

limited to the short-term efficacy of ECT augmentation. Though the combination appears to be relatively safe, about 20% of the patients develop adverse effects, and there is some evidence of greater cognitive impairment[52,57,59,62,63]. Nevertheless, augmentation with ECT may result in a faster response, which is particularly useful among patients with high risks of aggression or self-harm[9,11,60,65]. Therefore, though the evidence is still inconclusive, the effects of ECT augmentation certainly merit further examination. On the other hand, augmentation with recurrent transcranial magnetic stimulation appears to be largely ineffective in CRS despite promising results from recent trials[66,67].

Psychosocial augmentation strategies

Two systematic reviews of psychosocial interventions have concluded that CBT can be effective among patients with poor response to clozapine[33,68]. As shown in Table 5, the evidence-base for CBT until recently had consisted of a few trials with small

Table 5 Psychosocial augmentation strategies in clozapine-resistant schizophrenia

Ref.	Study/participants	Interventions	Results
Studies			
Pinto *et al*[69], 1999	Single-blind RCT of 41 patients with TRS started on clozapine	CBT and social skills training *vs* supportive therapy for 6 mo.	Significant reductions in positive and negative symptom severity in the CBT group.
Buchain *et al*[70], 2003	Single-blind RCT of 41 patients with TRS started on clozapine	Occupational therapy and clozapine *vs* clozapine alone for 6 mo.	Significant improvements in the occupational performance and interpersonal relationships with OT.
Barretto *et al*[71], 2009	Single-blind RCT of 21 patients with CRS	CBT *vs* supportive treatment ("befriending") for 21 wk.	Significant reductions in overall symptom severity and improvement in quality of life with CBT.
Morrison *et al*[75], 2018	Double-blind RCT of 425 patients with CRS	CBT *vs* usual treatment for 9 mo. Follow-up for 21 mo.	Significant reductions in PANSS scores with CBT at 9 mo but no differences at 21 mo.
Sensky *et al*[72], 2000; Valmaggia *et al*[73], 2005; Edwards *et al*[74], 2011	RCTs of patients with TRS (n = 48-90) including patients on clozapine or clozapine non-responders	CBT *vs* supportive treatment or clozapine alone or comparisons with combinations of CBT with other antipsychotics.	Significant reductions in positive, negative, and depressive symptom severity, improvement in clinical response and functioning with CBT; benefits at end of treatment usually maintained during follow-up.
Reviews			
Ranasinghe *et al*[33], 2014	Systematic review	Review of the 2 CBT and 1 OT trial mentioned above.	Benefits of psychosocial interventions noted for overall symptom severity, quality of life, and social functioning.
Polese *et al*[68], 2019	Systematic review & meta-analysis	Review of all the above trials and meta-analysis of 4 RCTs including Morrison *et al*[75].	Benefits of psychosocial interventions noted for overall and positive symptom severity.

CBT: Cognitive-behavioural therapy; CRS: Clozapine resistant schizophrenia; PANSS: Positive and Negative Syndrome Scale; OT: Occupational therapy; TRS: Treatment resistant schizophrenia; RCT: Randomized controlled trial.

numbers and inadequate study designs[69-71] or RCTs that included some patients with CRS[72-74]. However, interest in the effects of CBT augmentation has been re-awakened with a large, well-designed RCT among patients with CRS[75]. This was the largest trial among all RCTs of clozapine augmentation. It employed standardized definitions of CRS and trained therapists who administered manual-based CBT to patients from routine clinical settings. After 9 mo of active treatment, the total Positive and Negative Symptom Scale scores, positive symptoms, emotional distress, and excitement had reduced significantly in the CBT group compared to the usual treatment group. However, at the end of 21 mo, there were no significant differences in the Positive and Negative Symptom Scale scores between the two groups, leading to the conclusion that CBT augmentation was not effective in CRS. Nevertheless, other indices suggested that CBT might be useful for a proportion of patients, and patients' ratings of recovery were greater in the CBT group at 21 mo. Other noteworthy advantages of CBT were the high adherence rates, negligible adverse effects, high acceptability, and effect sizes comparable to medication augmentation. Therefore, others have interpreted these results differently to emphasize the positive effects of CBT augmentation[2,66,76]. Moreover, it has been pointed out that the persistence of positive effects beyond the active treatment period is not the best indicator of the efficacy of CBT[76]. Thus, if the standards for medication trials were to be applied to this RCT, the conclusion would be that CBT was an effective augmentation strategy for CRS after 9 mo of treatment.

AUGMENTATION STRATEGIES FOR CRS: FROM EVIDENCE TO PRACTICE

Relying on clinical consensus

This brief update of the existing literature shows that augmentation of clozapine response in CRS with medications, ECT, or CBT is largely ineffective. Any favourable outcome for augmentation is usually based on low-quality or limited evidence, and the clinical significance of the small effects obtained in some meta-analyses is unclear. Moreover, because of the inconsistent results and methodological uncertainties, the

evidence offers no definite conclusions about the most effective augmentation strategies. Nevertheless, it has been suggested that the lack of evidence should not discourage clinicians from trying out these strategies in individual patients. This advice appears to be based on two assumptions. First, the lack of significant benefits applies only to entire groups of patients being evaluated in RCTs, whereas there may be considerable variability in individual responses of the patients comprising these groups[18,25,29,40]. Thus, there is a possibility that some patients may benefit from augmentation, though at present there is no way to identify these potential responders. Moreover, given the widespread adverse impact of CRS, even modest benefits are considered acceptable in clinical settings[7,22,46]. Therefore, the sequential use of different augmentation strategies is considered to be a realistic option in clinical practice.

To reduce the disparity between the evidence-based findings and clinical practice, researchers have been increasingly relying on clinical consensus to guide the management of complex and burdensome conditions such as CRS. A recent effort on these lines arrived at the following recommendations for augmentation of clozapine non-response: personalizing doses to reach plasma levels ≥ 350 ng/mL; a 3 mo trial for patients with positive symptoms; shorter treatment trials for those with violence or self-harm (2 mo) and longer periods (4 mo) for patients with negative or cognitive symptoms[13]. For persistent positive symptoms, adding aripiprazole, amisulpride, or ECT was suggested. Augmentation with antidepressants was recommended for negative symptoms while adding antidepressants, antipsychotics, mood stabilizers, or ECT to clozapine was proposed for CRS with increased risks of aggression or self-harm. Lastly, CBT or other psychosocial interventions were also felt to be useful. It was apparent that these clinicians were going beyond the current evidence while making some of these recommendations.

For example, though there is little support in the literature for augmentation of clozapine with a second antipsychotic, low-quality evidence or single RCTs have suggested that risperidone, aripiprazole, and amisulpride may be beneficial (Table 2). The group also relied on naturalistic studies showing that the clozapine-aripiprazole combination may have positive effects[77]. Similarly, for recommendations about antidepressants, positive evidence for antidepressant augmentation in schizophrenia was cited[78,79], though the evidence for similar effects of antidepressant augmentation in CRS is limited (Table 3).

Augmentation with mood stabilizers and ECT was recommended despite the acknowledgement that the evidence for these strategies is insufficient (Tables 3 and 4). The recommendation for using CBT if other treatments failed was based on the recent CBT trial[75], which concluded that certain individuals with CRS may benefit from a practical trial of CBT augmentation. Clozapine augmentation was preferred over a switch to a different antipsychotic because of the consistent evidence of adverse outcomes following cessation of clozapine[8,11,80-82]. Switching to high-dose olanzapine has been suggested as an alternative, but this option is not supported by evidence[81,83]. Finally, though most of the evidence indicates that these augmentation strategies are safe and well-tolerated[22,25,26,29], the possibility of new side effects arising during combined treatment could not be discounted[9,12,18,28,32]. Therefore, cautious monitoring of all patients for the duration of the augmentation trial was also recommended.

Trying newer options for augmentation

Augmentation with long-acting antipsychotic injections: Apart from problems of resistance, non-adherence is a major hindrance to effective treatment with clozapine. Although non-adherence with clozapine may be lower than other antipsychotics, rates of intentional non-adherence vary from 23%-55% during treatment[84-88]. In such situations initiating a long-acting antipsychotic injection (LAI) remains the only option [89]. Intramuscular clozapine appears to have some benefits in enhancing adherence, but it has not been used frequently[90,91]. Recent studies suggest that apart from reducing non-adherence, LAI augmentation of clozapine may also have a role in enhancing clozapine response in CRS. As shown in Table 6, this evidence is still preliminary and consists mostly of series of patients and observational studies[92-102]. However, mirror-image studies that are considered the current standard for evaluating LAI efficacy[103,104] have also been conducted. Taken together, this body of evidence suggests that the combination of clozapine with LAIs leads to a reduction in all types of symptoms and behavioural problems such as aggression and suicidality as well as improvements in social functioning. The lowered risk of relapses and reduction in the number and length of hospitalizations has also been replicated consistently. Lastly, it appears that lower doses of both medications are required,

Table 6 Augmentation of clozapine with long-acting antipsychotic injections in clozapine-resistant schizophrenia

Ref.	Study details	Results
Kim *et al*[92], 2010	4 patients treated with clozapine and risperidone LAI for 1 yr	Reduction in number and length of hospitalizations and improvement in social skills after LAI addition. Fewer side effects with the combination.
Malla *et al*[93], 2013	One patient with poor response to clozapine treated with clozapine and an LAI	Improvement in symptoms and social functioning without any increase in side effects with combination treatment.
Baruch *et al* [94], 2014	8 patients, 6 with TRS. Treated with olanzapine LAI and clozapine or other antipsychotics up to 2 yr	Reduction in aggression in all 8 patients and in symptom severity in 6 patients.
Maia-de-Oliveira *et al* [95], 2015	2 patients with CRS treated with clozapine and paliperidone LAI for 9-10 mo	Remission of positive symptoms after LAI augmentation.
Kasinathan *et al* [96], 2016	9 patients with TRS and comorbid personality disorders/substance use and violence; 1 on clozapine but non-adherent treated with olanzapine LAI combination	1 yr of retrospective pre- and post-LAI comparisons showed significant improvements in psychotic symptoms, violence, and reduction in number and length of hospitalizations and emergency visits.
Sepede *et al* [97], 2016	One patient with poor response to clozapine treated with clozapine and aripiprazole LAI for 1 yr	Symptoms reduced by 50% with the combination without any increase in side effects.
Oriolo *et al*[98], 2016	Retrospective observational of 23 patients with TRS in whom paliperidone LAI was added toclozapine	Significant reductions in severity of global, positive, negative, depressive, and cognitive symptoms with the combination. Significantly lower doses of clozapine and paliperidone LAI required with combination treatment *vs* monotherapy.
Souaiby *et al* [99], 2017	Retrospective observational study with a mirror-image design of 20 patients with TRS treated with clozapine and LAIs for 32 mo	Significant reductions in number and length of hospitalizations during 32 mo of combination treatment *vs* 1 yr of monotherapy. No increase in side effects with the combination.
Grimminck *et al* [100], 2020	Retrospective observational study with a mirror- image design of 20 patients with poor response to clozapine or LAIs treated with clozapine and LAI combinations for 2 yr	Significant reductions in hospital admissions and emergency visits during 2 yr of combination treatment *vs* 2 yr of monotherapy. Overall improvement in behaviour and social functioning but no change in symptoms.
Bioque *et al* [101], 2020	Retrospective observational study with a mirror- image design of 50 patients with TRS treated with clozapine and paliperidone LAI for 6 mo	Significant reductions in BPRS scores, emergency visits, number and length of hospitalizations, and number and severity of adverse effects as well as significant improvements in social functioning during 6 mo of combination treatment *vs* 6 mo of monotherapy.
Caliskan *et al* [102], 2021	Retrospective observational study with a mirror- image design in 29 patients with TRS treated with clozapine and LAI combinations for 1 yr	Significant reductions in number of relapses and number and length of hospitalizations during 1 yr of combination treatment *vs* 1 yr of monotherapy. No differences in side effects with the combinations.

BPRS: Brief Psychiatric Rating Scale; CRS: Clozapine resistant schizophrenia; LAI: Long-acting antipsychotic injection; TRS: Treatment resistant schizophrenia.

while side effects are either less, or no more common with the combination than with clozapine monotherapy.

Indirect evidence for the effectiveness of clozapine-LAI combinations also comes from several Scandinavian nationwide cohort studies of antipsychotic treatment summarized in Table 7[77,82,105-109]. These provide the strongest support for the notion that clozapine and LAIs are the two most effective treatments for patients with both first episode and chronic schizophrenia. Incidentally, some of these studies have also shown that the combination of clozapine and aripiprazole is more effective than clozapine monotherapy[77]. Therefore, the combination of clozapine and LAIs appears to be a promising option that needs to be examined further for its usefulness in the management of CRS.

A re-evaluation of psychosocial augmentation strategies: Although the evidence reviewed in Table 5 suggests that augmentation with CBT does not yield consistent benefits in CRS, there are several reasons to re-examine the usefulness of psychosocial augmentation strategies. To begin with, CBT augmentation appears to be effective for persistent positive symptoms in TRS[20,68,75,76]. Moreover, the largest and most meticulously conducted CBT trial has shown a small but significant benefit for patients with CRS following the active intervention phase[66,75,76]. The same trial has suggested that CBT is one of the safest and acceptable augmentation options for patients with CRS. The evidence from this study and other trials shows that CBT augmentation has added benefits such as improvements in socio-occupational functioning and QOL. Moreover, symptomatic remission appears to be faster with CBT augmentation, and the benefits obtained may persist longer[71,72,74]. CBT augmentation early in the course of clozapine treatment may further enhance its benefits[68-70,74].

Table 7 Scandinavian nationwide cohort studies of antipsychotic treatment

Ref.	Study details	Results
Tiihonen *et al* [105], 2006, Finland	2230 inpatients followed up for 3.6 yr	Significantly lower risks of rehospitalization or treatment discontinuation in patients on perphenazine LAI, clozapine, or olanzapine *vs* those on oral haloperidol.
Tiihonen *et al* [106], 2009, Finland	66881 outpatients followed up for 11 yr	Clozapine was associated with a substantially lower mortality than any other antipsychotics singly or in combination, with perphenazine as a comparator.
Tiihonen *et al* [107], 2011, Finland	2588 inpatients followed up for 2 mo after discharge	Significantly lower risks of rehospitalization with LAIs than oral medications. Clozapine and olanzapine were associated with significantly lower risk of rehospitalization than risperidone.
Tiihonen *et al* [108], 2017, Sweden	29823 patients followed up for 5.7 yr	Significantly lower risks of rehospitalization and of treatment failure[1] with LAIs and clozapine *vs* no antipsychotic treatment.
Taipale *et al* [109], 2018, Finland	62250 inpatients followed up for 20 yr	Significantly lower risks of rehospitalization with LAIs and clozapine *vs* no antipsychotic treatment in first episode and chronic schizophrenia.
Tiihonen *et al* [77], 2019, Finland	62250 inpatients on antipsychotic monotherapy or antipsychotic combinations followed up for 14 yr	Combination of clozapine and aripiprazole was associated with significantly lower risk of rehospitalization and mortality than clozapine alone in first episode and chronic schizophrenia. Clozapine monotherapy was associated with the most favourable outcomes compared to other antipsychotics.
Luykx *et al*[82], 2020, Finland	2250 patients on clozapine treatment followed up for more than 1 yr before discontinuation	Compared to no antipsychotic treatment, significantly lower risks of rehospitalization with re-institution of clozapine alone, oral olanzapine, and antipsychotic combinations. Significantly lower risks of treatment failure**1**with aripiprazole LAI, re-institution of clozapine alone, and oral olanzapine.

[1]Treatment failure included re-hospitalization, suicide attempt, treatment discontinuation, medication switch, or death.
LAI: Long-acting antipsychotic injection.

Further, it has been proposed that rather than using only CBT, multi-component psychosocial interventions using different techniques might be more effective in enhancing clozapine response[33,110,111]. Though CBT is the most common psychosocial treatment used in patients with TRS, there is evidence to suggest that other types of interventions might be equally effective[68,112]. Psychoeducation and family interventions are also effective for schizophrenia[113], but they have not been tried out as augmenting strategies in TRS or CRS[20,68]. Lastly, psychosocial aug-mentation might be useful in other ways, for example in improving adherence to clozapine. An RCT that compared CBT with psychoeducation among patients with TRS on clozapine showed that both treatments led to improvements in patient empowerment, treatment alliance, and medication persistence[114]. Thus, while there may be no compelling evidence in favour of psychosocial augmentation strategies in CRS, there is scope for further evaluation of these potentially useful treatments.

PREVENTING RESISTANCE TO CLOZAPINE TREATMENT

The relative ineffectiveness of the different augmentation strategies suggests that a more fruitful option could be to try and prevent resistance to clozapine treatment from developing.

Predicting clozapine resistance

Predicting who among patients with TRS will not respond adequately to clozapine may be helpful because augmentation strategies could be instituted early in such patients to mitigate the adverse effects of clozapine resistance. However, despite over 300 studies of prediction of clozapine response, consistent predictors of response have not been found. Some reviews have concluded that there are no reliable predictors of clozapine response because of the inconsistent results and methodological uncertainties of existing research[115,116]. On the other hand, an older systematic review and a more recent meta-analysis have found that older age, greater severity of symptoms, especially negative symptom severity, poorer functioning, and non-paranoid subtypes could predict clozapine non-response[117,118]. Low cerebrospinal homovanillicacid to 5-hydroxyindoleacetic acid ratios and normal structure and

function of the prefrontal cortex have also emerged as reliable predictors of good response in some studies[117,119]. Consequently, because of the inconclusive nature of this evidence, currently the only way to predict clozapine resistance is to carry out an adequate trial of clozapine treatment under optimal conditions[20,115].

Optimizing clozapine treatment

Ensuring adequate treatment with clozapine may thus be the best option to prevent clozapine resistance. The necessary steps for optimizing clozapine treatment are listed in Table 8. Personalized dosing is a key component because of the wide variations in dose-blood level ratios between individuals and because many patients respond at lower doses[120,121].

Data on gender differences in clozapine treatment are scarce, and results are often inconsistent[122]. This is particularly true for response to clozapine treatment. Though the response is usually poorer in women[116,117,122], research on clozapine's effectiveness has also found better outcomes among women, although these differences in their favour are often of doubtful clinical significance[115,117,123]. Others have found no differences in outcome between the two genders[118].

In contrast, differences in pharmacokinetics are reported more consistently[122,124,125]. Women have lower renal clearance of clozapine than men because of differences in the activity of cytochrome P450 enzymes such as CYP1A2. Most studies have found higher plasma levels of clozapine in women, and some have also found higher levels of its metabolite norclozapine. Higher dose-blood level ratios have also been found in women. Therefore, women usually require lower doses of clozapine[124]. These pharmacokinetic differences also increase the risk of dose-dependent side effects in women, particularly metabolic side effects[122,126]. Accordingly, most of the evidence on gender differences in side effects of clozapine relates to metabolic disturbances [122]. However, findings are not consistent, and both genders appear to have increased risk of metabolic syndrome in different reports[122,126-128]. Hypertension, elevated triglycerides, lower high-density lipoprotein levels, and cardiac abnormalities appear to be more common in men[122]. Women are more likely to develop hyperglycaemia and diabetes and increases in weight and body mass index[122,126]. There is very little evidence of gender differences in other side effects, though certain studies have found haematological abnormalities and constipation to be commoner among women[122,125,128,129].

Unlike the influence of gender, ethnicity does not appear to have any impact on treatment response obtained with clozapine[115,130]. On the other hand, there are ethnic differences in pharmacokinetic profiles of clozapine[122]. More specifically, several studies among Asian patients have consistently indicated that they require about half the standard dose of clozapine due to their lowered clozapine metabolism [131-135]. The dose of clozapine required for adequate response among Asians varies from 150mg/d among women to 300 mg/d for men who smoke. Therefore, Asian patients need lower doses at the start of treatment and slower upward titration to reach their optimum dose. Despite these pharmacokinetic dissimilarities, ethnic differences seem to have minimal impact on the prevalence of adverse effects of clozapine[129]. Nevertheless, non-White ethnicity is a risk factor for metabolic syndrome, and certain studies have found a higher prevalence of hypertension and weight gain in Asians[127,136]. Others have found a higher risk of agranulocytosis in Asian patients[137]. This again emphasizes the fact that the best way to individualize clozapine doses is to base them on blood levels. Doing so has the added advantages of lessening side effects and allowing adherence to be monitored. However, facilities for blood levels are not always available. Standardized dosing schedules could be used in such instances[132].

Many of the side effects encountered with clozapine are dose-dependent including sedation, tachycardia, hypersalivation, enuresis, constipation, delirium, obsessive-compulsive symptoms, seizures, and orthostatic hypotension[81,120,138] Among all antipsychotics, the prevalence of metabolic dysfunction or metabolic syndrome is the highest for clozapine and olanzapine[81,126,127,132,139]. Whether metabolic side effects are also dose-dependent is not clear[81,138]. However, systematic reviews and meta-analyses have indicated a dose-outcome association between clozapine and metabolic side effects, particularly with lipid levels and weight gain[140,141]. Risk factors for metabolic syndrome include higher baseline weight or body mass index, gender, non-White, possibly Asian ethnicity, and several genetic and peptide markers [126,127,136,139,142]. Somewhat paradoxically, metabolic disturbances are also associated with a reduction in symptoms[126,127].

Table 8 Steps for ensuring optimal clozapine treatment[65,81,110,111,120,123,132]

Steps for ensuring optimal clozapine treatment	
Adequate assessment	Diagnosis should be established properly. Comorbid conditions should be looked for. Adherence should be determined. Symptoms and other outcome domains should be preferably rated using validated instruments. Caregiver burden and coping should be assessed. Stressors and adverse circumstances should be evaluated.
Proper dosing	Inter-individual and ethnic variability in optimal doses should be considered. If facilities for serum levels are available, doses should be titrated to ensure plasma levels > 350 ng/mL. Doses should be increased slowly with careful monitoring of side effects to reduce the burden of dose-dependent side effects.
Adequate duration	A minimum of 2-3 mo is considered necessary. Durations could be shorter in those with high risk of aggression or self-harm. Durations could be longer in those with negative or cognitive symptoms and in partial responders.
Managing side effects	Many of the common side effects of clozapine can be managed by slow titration, using the least effective dose, reducing doses when side effects develop, adding medications, or adopting lifestyle changes to counter side effects. Additionally, careful monitoring should be carried out for the more serious and idiosyncratic adverse reactions such as agranulocytosis and cardiopulmonary complications.
Managing non-adherence	Careful monitoring of adherence based on multiple sources is necessary. Managing side effects, educating patients to deal with negative attitudes to clozapine, developing a trusting alliance to improve motivation, caregiver education and support to increase their involvement in the patient's care may help. These measures should ideally be initiated right at the beginning of treatment. Use of long-acting antipsychotic injections may be considered.
Collaboration with patients and caregivers	Both patients and caregivers should be the focus of treatment. Measures should be tailored according to their needs. Goals of treatment should be reduction of symptoms and distress, improving support, forging effective alliances, and promoting patient and caregiver engagement. Simple psychosocial measures including cognitive or behavioural strategies, psychoeducation, and emotional and practical support should be implemented at the start of treatment or as early as possible. More structured interventions can be tried depending on availability of resources and expertise.
Addressing clinician related barriers	Clinicians' lack of awareness and experience of clozapine treatment and negative attitudes towards clozapine use should be addressed by proper education, dissemination of information, and dedicated facilities.

Optimizing clozapine doses is the principal way of managing most dose-dependent side effects. Using the lowest effective dose, slow increase in doses, and dose adjustments to minimize side effects is always recommended[81,120,123]. Discontinuation of concomitant medications that might not be essential also reduces the side effect burden[120]. Only serious and life-threatening adverse reactions such as agranulocytosis and some cardiopulmonary complications require abrupt discontinuation of clozapine[81,120]. Some side effects such as neuroleptic malignant syndrome, thromboembolism, or diabetic ketoacidosis may require temporary discontinuation followed by re-initiation of clozapine[81]. In most other situations, the dose of clozapine should be reduced very gradually to avoid worsening of clinical state or emergence of withdrawal symptoms[120]. When side effects persist despite optimizing the dose of clozapine, the options include adding other medications, instituting non-pharmacological measures to manage side effects, or combining clozapine with another antipsychotic[120,138]. In the case of metabolic syndrome, adequate treatment of risk factors and metabolic derangements is essential[143].

Meta-analyses of interventions for metabolic side effects have shown that adjunctive metformin is the most effective strategy[144,145]. Behavioural weight management strategies are also recommended though the evidence for their efficacy is uncertain [120,138,144]. Adding aripiprazole to clozapine to reduce both the clozapine dose and metabolic disturbances has also been suggested, but the evidence for this option is limited[120,144].

Minimizing the side effect burden is necessary because about 40% of the patients (range 21%-67%) stop taking clozapine in the first few years of treatment[82,84,86,87,146]. In 20%-30% of them, discontinuation is because of intolerable side effects, though intentional non-adherence appears to be somewhat more common[84,85,87,88,147]. Managing non-adherence requires open and non-judgmental discussions about medication-taking with patients, monitoring of adherence based on all available methods including caregiver reports, education to deal with misconceptions about treatment, and building trusting alliances with patients and families to ensure continued treatment. A collaboration with the patient and the family is an essential part of optimizing clozapine treatment that is often overlooked[65,110,111,120]. Shared decision-making about treatment, education, stress-management, support, and involvement of caregivers are ways of ensuring truly collaborative alliances.

Lastly, increasing evidence indicates substantial underutilization and delayed use of clozapine[148,149]. Clinician's lack of awareness and experience with clozapine, their misplaced concerns about its use, and the discrepancy between clinicians' and patients' attitudes regarding clozapine are among the main causes of inappropriate use

of clozapine[150,151]. Therefore, dealing with these clinician-related barriers is also necessary to ensure the proper use of clozapine.

CONCLUSION

Clozapine resistance is probably one of the most difficult conditions that clinicians treating patients with schizophrenia are likely to encounter. Unfortunately, the existing research evidence does not provide any firm guidelines about treatment options once clozapine fails. However, because of the seriousness of the condition and the widespread negative impact of CRS, clinicians need to look beyond the evidence and rely on consensus-based recommendations. At present, effective ways to deal with CRS are to optimize clozapine treatment, choose among the best available options judiciously, explore newer ways of augmentation, and adopt a holistic approach to treatment that includes simple psychosocial measures in addition to pharmacological ones. Finally, cautious optimism, commitment to treatment, patience, and persistence from clinicians, patients, and caregivers are almost always required for the effective use of clozapine.

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ORIGINAL ARTICLE

Case Control Study

Impact of spiritual care on the spiritual and mental health and quality of life of patients with advanced cancer

Xiang-Hong Sun, Xing Liu, Bo Zhang, Yu-Mei Wang, Ling Fan

ORCID number: Xiang-Hong Sun 0000-0001-8574-9413; Xing Liu 0000-0002-8075-5846; Bo Zhang 0000-0002-2814-3957; Yu-Mei Wang 0000-0003-2489-2181; Ling Fan 0000-0002-9649-4089.

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Xiang-Hong Sun, Intensive Care Unit, Shengjing Hospital of China Medical University, Shenyang 110004, Liaoning Province, China

Xing Liu, Department of Urology, Shaanxi Provincial People's Hospital, Xi'an 710000, Shaanxi Province, China

Bo Zhang, Department of Oncology, Shengjing Hospital of China Medical University, Shenyang 110004, Liaoning Province, China

Yu-Mei Wang, Hospice Care Unit, Shengjing Hospital of China Medical University, Shenyang 110004, Liaoning Province, China

Ling Fan, Nursing Department, Shengjing Hospital of China Medical University, Shenyang 110004, Liaoning Province, China

Corresponding author: Ling Fan, PhD, Chief Nurse, Full Professor, Nursing Department, Shengjing Hospital of China Medical University, No. 36 Sanhao Street, Shenyang 110004, Liaoning Province, China. fanl@sj-hospital.org

Abstract

BACKGROUND

Cancer is a growing threat to human health. Due to the double torment of cancer and cancer treatment, patients with advanced cancer generally have a low quality of life. At present, there is a lack of systematic spiritual care plans for patients with advanced cancer as well as systematic guidance plans on the specific clinical application of spiritual care for advanced cancer patients. We hypothesized that our care plan would be effective in improving the spiritual and mental health and quality of life of patients with advanced cancer.

AIM

To construct a spiritual care plan suitable for Chinese patients with advanced cancer through literature analysis.

METHODS

From February to December 2018, through purpose sampling, we selected 100 advanced cancer patients from the Oncology Department and Hospice Ward of a tertiary hospital in Liaoning Province who met the study standards. Patients were randomly divided into experimental and control groups, with 50 cases in each

group. The control group received the current routine care, while the experimental group received the advanced cancer spiritual care intervention in addition to routine care.

RESULTS

After the intervention, the overall spiritual health score for the experimental group was higher than that of the control group (4.68 ± 1.36 *vs* 3.63 ± 1.71). The difference between the groups was statistically significant ($P < 0.05$). The proportion of anxiety-free patients in the experimental group was 95.45%, which was significantly higher than the 60.98% in the control group. Moreover, the proportion of non-depressed patients in the experimental group was 97.73%, which was significantly higher than the 85.37% in the control group ($P < 0.05$). The overall quality of life score for the experimental group was significantly higher than that of the control group (5.36 ± 1.16 *vs* 4.39 ± 1.36, $P < 0.05$).

CONCLUSION

Our spiritual care plan for patients with advanced cancer could improve their spiritual health and quality of life and reduce negative mental health symptoms.

Key Words: Cancer; Spiritual care; Depression; Anxiety; Spiritual health; Quality of life

Core Tip: We constructed a spiritual care program for advanced cancer patients suitable for Chinese culture and national conditions, and carried it out for advanced cancer patients. Results showed that the spiritual health status and quality of life of advanced cancer patients were improved, and their anxiety and depression reduced.

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INTRODUCTION

As the environment is deteriorating, human health is facing a growing number of threats. One such threat that has grown increasingly significant is cancer. It has been estimated that the number of cancer patients worldwide had risen to 3 million in 2020, two-thirds of which are advanced cancers with low chances of cure[1]. Patients with advanced cancer generally have a low quality of life. Due to the double torment of cancer and cancer treatment, their psychological, physical, social, familial, and other aspects of their lives are all negatively affected in varying degrees[2]. Spiritual care is a complex and multidimensional concept with different definitions[3] and refers to patients seeking the meaning of life, gaining peace and comfort, obtaining emotional support from family members, and alleviating the fear of death during illness with the help of professional medical service teams, social groups, families, volunteers, and religious personnel, thereby improving the quality of life of patients with advanced cancer[4]. Global research on the spiritual care of patients with advanced cancer is relatively novel. A relatively mature care model that includes a professional care team and complete tools for evaluating the spiritual needs of patients with advanced cancer has been created. At present, the spiritual care model in China is based on the four-in-one holistic care model of body-mind-community-spirit. Intervention measures are embodied in several aspects, such as peaceful, holistic, special, hospice, overall nursing care, palliative treatment, death education, *etc*. However, there is a lack of systematic spiritual care plans for patients with advanced cancer as well as a lack of systematic guidance plans on the specific clinical application of spiritual care for them, which greatly reduces the effectiveness of care. The purpose of spiritual care is to pay attention to the patient's attitude towards the disease. This means that the patient's

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spiritual care is more important than their physical care[5]. We used advanced global spiritual care guidelines as references and combined them with information around the Chinese setting to construct a spiritual care plan that was suitable for Chinese culture. Our care plan achieved good results when applied to advanced cancer patients.

MATERIALS AND METHODS

Construction of a spiritual care plan for patients with advanced cancer

We searched the Chinese Biological Medicine Database, China National Knowledge Infrastructure, Wanfang Database, and VIP Information Resource System using Chinese search terms such as cancer, tumor, advanced stage, spirituality, spiritual care, spiritual intervention, *etc.* We also searched the PubMed, Science Citation Index Expanded, and Web of Science databases. To collect data as comprehensively as possible, we combined the aforementioned keywords in Chinese and English and included references from the retrieved literature. We invited nine experts in oncology and its related fields to revise the constructed spiritual care plan for advanced cancer patients through meetings with experts[6]. The selection criteria for the experts were as follows: (1) working in the fields of advanced cancer clinical nursing, nursing management, nursing education, advanced cancer clinical medicine, psychology, and other related disciplines; (2) having an under graduate degree or higher; (3) having a medium-grade professional title or higher; (4) having 10 or more years of work experience in their professional fields and being familiar with the content of our study; and (5) participating in our study voluntarily.

Evaluative research on the spiritual care plan for patients with advanced cancer

From February to December 2018, cancer patients from the Oncology Department and Hospice Ward of a tertiary hospital in Liaoning Province who qualified for our study were selected through objective sampling. Patients were stratified according to the different departments to which they were admitted. In each ward, 20% of the actual number of hospitalizations were sampled. We sampled a total of 100 patients and used randomized grouping to separate them into our study groups. The inclusion criteria were as follows: (1) a histological or cytological diagnosis of a tumor node metastasis stage III or IV malignant tumor; (2) age >18 years; (3) being able to communicate and understand; (4) being able to provide informed consent and participate voluntarily; and (5) being aware of their condition. The exclusion criteria were as follows: (1) impaired consciousness; and (2) being unable to understand or fill in the scale correctly.

Research tools

General information survey form: This included details of the patient's age, gender, education, family income, medical expense payments, *etc.*

Clinical data questionnaire: This questionnaire was self-designed and based on the literature review. It included information such as the patient's cancer diagnosis and stage, as well as whether there was metastasis.

The Chinese version of the European Organization for Cancer Research and Treatment Quality of Life Questionnaire-Spiritual Well-Being 32 (EORTC QLQ-SWB32)[7] scale: The original English scale was developed and validated by the EORTC QOL Group in 2017 for the assessment of the spiritual health status of patients with advanced cancer. EORTC QLQ-SWB32 consists of 32 items, with 22 items forming four multiitem scales: Existential; Relationship with Self; Relationships with Others; and Relationship with Someone or Something Greater. The first 31 items were scored using a four-point Likert Scale with answers ranging from "not at all" to "very". Item 32 was mainly used to reflect the patient's overall spiritual health status: 0 point, did not know or was unable to answer; 1 point, very poor; 7 points, very good. As the score increased, the patient's overall spiritual health improved[8]. In 2017, the author translated the scale into Chinese version[9] (it is not an official EORTC translation), and the total Cronbach α coefficient of the scale was 0.808.

The General Hospital Anxiety and Depression Scale: This scale was created by Zigmond *et al*[10] in 1983 and translated into Chinese by Ye *et al*[11] in 1993 to form its Chinese version. It is used in general hospitals to assess patients' anxiety and depression. Cronbach's α for the Chinese version of the scale was 0.870.

The Chinese version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative (EORTC QLQ-C15-PAL): The EORTC QLQ-C15-PAL was based on the EORTC QLQ-C30 and created by Groenvold *et al*[12] in 2005. It was translated into Chinese by Luo *et al*[13] in 2014 and was used to assess the quality of life of cancer patients in palliative care. Excluding the emotional function dimension, Cronbach's α values for the other dimensions were all > 0.7.

Research content

Intervention plan for the control group: The control group received routine care plans, including general and symptomatic care; tumor chemotherapy, radiotherapy, biotherapy, intracavitary therapy care, and psychological care.

Intervention plan for the experimental group: Based on routine care implementation and guided by the "Spiritual Care Plan for Patients with Advanced Cancer", we provided spiritual care for patients with advanced cancer. This included the following services: (1) Admission evaluation: For the patients who met the inclusion criteria, after informed consent was obtained from the patient and their caregivers, the research participant's basic information was collected and their spiritual care needs and spiritual health status were evaluated; (2) Spiritual care intervention: From 2–3 d after admission, based on the "Spiritual Care Plan for Advanced Cancer Patients" that we created, the researchers and oncology specialist nurses from each department worked together to carry out the intervention. Interventions included participating in activities and watching face-to-face guidance videos or targeted explanations and were implemented in a small conference room or ward in the Oncology Department. Patients' examination, treatment, nursing, and meal times were avoided, and their free and rest times were designated as the times when the interventions could take place; this was usually between 3:00 pm and 5:00 pm. A total of five interventions were carried out, each 30–60 min long. The patients' psychological and emotional states were closely monitored during each intervention. If the patient felt unwell, they could choose to take a break or have their session at another time; and (3) Post-intervention evaluation: After the intervention, patients' self-expression was asked in time. They were also asked to fill in the spiritual health assessment scale and other questionnaires to analyze quantitatively the effects of the spiritual care plan on patients with advanced cancer.

Data collection and analysis

The researchers collected data before and after the intervention. Before collection, our study's purpose, requirements, and precautions were explained, and patients were reassured of the confidentiality of the questionnaire and their data. After the patients' consent was obtained, they were asked to fill in a questionnaire to ensure objectivity. EpiData 3.1 was used for data entry, and the database was established using the Chinese version of SPSS version 21 (SPSS Inc., IBM Corp., Armonk, NY, United States). General data were depicted using statistics: Count data were expressed using the rate and composition ratio; and measurement data were expressed using the mean ± SD and comparison using a *t*-test and non-parametric test. Frequency, percentage, and the χ^2 square test was used for count data. A P value < 0.05 was considered statistically significant.

RESULTS

Construction of a spiritual health care intervention plan for patients with advanced cancer

A total of 10 articles that met the requirements were included and analyzed in our study. Nine experts in oncology and its related fields were invited to revise the constructed spiritual care plan for patients with advanced cancer. Finally, a final version of the spiritual health care intervention plan was developed.

Evaluation of the effect of application of the spiritual health care intervention plan for patients with advanced cancer

The effective sample sizes for the experimental and control groups were 41 and 44 cases, respectively, and the final effective sample size was 85 cases. The age range for

the experimental group was 28–83-years-old (50.05 ± 12.44-years-old), and for the control group it was 27–79-years-old (54.88 ± 13.78-years-old). The independent sample *t*-test results showed that there was no significant difference in age when the two groups were compared (t = 0.059, P = 0.953). The general demographic characteristics of the two groups were count data, such as gender, ethnicity, living conditions, religious beliefs/cultural beliefs, highest education, *etc.* Pearson's χ^2 test was used for the comparison, and the differences were not statistically significant (P > 0.05). The general data of the two groups were comparable (Table 1).

Clinical data

The differences in the research participants' clinical data were not statistically significant (P > 0.05), indicating two groups were comparable (Table 2).

Spiritual health

Before the spiritual care intervention, there was no significant difference in the spiritual health scores between the two groups (P > 0.05). The spiritual health scores of the two groups were comparable (Table 3).

After the spiritual care intervention, there were no significant differences in the existence (EX) and relationship with self (RS) scores when the two groups were compared (P > 0.05); thus, spiritual care was not yet considered meaningful to the patients' EXs and RSs. However, the differences in the relationship with others (RO), relationship with something greater (RSG), and overall spiritual health scores were statistically significant (P < 0.05 for all; Table 4).

Anxiety and depression

When the anxiety levels from the two groups before and after the spiritual care intervention were compared, the difference in anxiety levels before the intervention was not statistically significant (P > 0.05), indicating the anxiety levels of the two groups were comparable. After the intervention, the difference in anxiety levels when the groups were compared was statistically significant (P < 0.05; Table 5).

The comparison of the two groups' depression before and after the spiritual care intervention showed that there was no statistically significant difference in depression between the groups before the intervention (P > 0.05), indicating the depression levels of the two groups were comparable. The difference in the levels of depression after the intervention when the groups were compared was statistically significant (P < 0.05; Table 6).

Quality of life

The Chinese version of the EORTC QLQ-C15-PAL was used to evaluate the quality of life of the two groups before the intervention. The differences in the results were not statistically significant (P > 0.05), and the data from the two groups were comparable (Table 7).

After the spiritual care intervention, there was no statistically significant difference in the quality of life when the patient groups were compared in terms of physical function, pain, dyspnea, insomnia, and constipation (P > 0.05). Thus, spiritual care was not yet considered meaningful with regard to these parameters. The differences between the groups in terms of symptoms such as emotional function, fatigue, nausea and vomiting, loss of appetite, and overall quality of life were statistically significant (P < 0.05; Table 8).

DISCUSSION

Construction of an intervention plan for the spiritual healthcare of patients with advanced cancer

In this study, the first draft of the spiritual care plan for patients with advanced cancer was formulated through literature analysis. Some items of the plan were deleted, revised, or adjusted through expert meetings. When the experts were selected, their representativeness was fully considered. The literature analysis combined with the expert meeting made the spiritual care plan practical and scientific.

General characteristics and the baseline level of the participants

Studies have demonstrated that the general demographic characteristics and clinical data of patients with advanced cancer (such as age, gender, race, tumor type, cancer

Table 1 General information characteristics, *n* (%)

Characteristics	Control group (*n* = 41)	Experimental group (*n* = 44)	χ^2	*P* value
Gender			0.286	0.593
Male	10 (24.4)	13 (29.5)		
Female	31 (75.6)	31 (70.5)		
Ethnicity			4.027	0.259
Han	34 (82.9)	42 (95.5)		
Manchu	5 (12.2)	2 (4.5)		
Hui	1 (2.4)	0 (0.0)		
Mongolian	1 (2.4)	0 (0.0)		
Marital status			1.777	0.777
Single	2 (4.9)	3 (6.8)		
Married	36 (87.8)	35 (79.5)		
Cohabitation	0 (0.0)	1 (2.3)		
Divorced	1 (2.4)	1 (2.3)		
Widowed	2 (4.9)	4 (9.1)		
Religious beliefs			1.623	0.805
Nil	32 (78.0)	34 (77.3)		
Christian	2 (4.9)	4 (9.1)		
Buddhist	5 (12.2)	5 (11.4)		
Taoist	1 (2.4)	0 (0.0)		
Muslim	1 (2.4)	1 (2.3)		
Cultural beliefs			7.459	0.059
Nil	21 (51.2)	23 (52.3)		
Chinese traditional culture	13 (31.7)	5 (11.4)		
Marxist-Leninist, Maoist, Deng, and the "Three Represents"	7 (17.1)	15 (34.1)		
Others	0 (0.0)	1 (2.3)		
Highest education			3.734	0.443
Primary school	9 (22.0)	6 (13.6)		
Junior high school	10 (24.4)	18 (40.9)		
High school	13 (31.7)	9 (20.5)		
University	8 (19.5)	10 (22.7)		
Postgraduate and above	1 (2.4)	1 (2.3)		
Working status			4.635	0.327
Retirement	20 (48.8)	24 (54.5)		
Unemployed	10 (24.4)	4 (9.1)		
Part time	0 (0.0)	1 (2.3)		
Full time	3 (7.3)	3 (6.8)		
On sick leave	8 (19.5)	12 (27.3)		
Profession			3.994	0.262
Worker	14 (34.1)	12 (27.3)		
Farmer	9 (22.0)	6 (13.6)		
Staff	6 (14.6)	4 (9.1)		

Other	12 (29.3)	22 (50.0)		
Monthly household income (in CNY)			–0.436[1]	0.663
≤ 1000	10 (24.4)	10 (22.7)		
1000–2999	17 (41.5)	15 (34.1)		
3000–4999	8 (19.5)	13 (29.5)		
5000–6999	1 (2.4)	4 (9.1)		
≥ 7000	5 (12.2)	2 (4.5)		
Payment method for medical expenses			5.857	0.320
Social medical insurance	28 (68.3)	37 (84.1)		
Rural cooperative medical service	9 (22.0)	4 (9.1)		
Free medical care	2 (4.9)	0 (0.0)		
Commercial medical insurance	1 (2.4)	1 (2.3)		
Self-paid medical care	1 (2.4)	1 (2.3)		
Others	1 (2.4)	1 (2.3)		
Primary caregivers			7.971	0.240
Unattended	1 (2.4)	4 (9.1)		
Parents	3 (7.3)	6 (13.6)		
Child	11 (26.8)	11 (25.0)		
Spouse	24 (58.5)	16 (36.4)		
Relative	2 (4.9)	4 (9.1)		
Nurses/nannies	0 (0.0)	2 (4.5)		
Others	0 (0.0)	1 (2.3)		

[1]The Mann-Whitney *U* test.

location, employment status, religious beliefs, *etc.*) have an impact on their spiritual health[14-16]. The older the patient, the better their spiritual health. This holds particularly true for those older than 60 years, who have been shown to have significantly better spiritual health[9,17]. Women demonstrate better spiritual health than men; however, the aspects of spiritual health (belief, peace, meaning, overall spiritual health) are not balanced. The level of spiritual health also differs among patients with advanced cancer belonging to different races. However, some studies have demonstrated that spiritual health has nothing to do with general characteristics such as age, gender, race, cancer grade, metastasis, medical insurance, marital status, religious beliefs, *etc.*[18]. The inconsistency of conclusions may be related to different sample size or data collection methods. The general demographic data of the two groups in our study were consistent, except for their living conditions. Consistency was also demonstrated between the two groups in all aspects of the clinical data. Thus, the baseline levels of the two groups were guaranteed before the intervention.

Spiritual care improving spiritual health of patients with advanced cancer

In our study, we found that the provision of spiritual care to patients with advanced cancer could significantly improve their overall spiritual health. The overall spiritual score of the experimental group was higher than that of the control group (4.68 ± 1.36 *vs* 3.63 ± 1.71), and the difference between the two groups was statistically significant ($P = 0.002$). This finding was consistent with the results from other studies that found that spiritual care could promote the spiritual health of patients with advanced cancer [19-22]. In our study, after spiritual intervention, there were inconsistencies in the findings regarding the four dimensions of spiritual health when the two groups were compared. The RO and RSG scores for the experimental group were higher than those for the control group (3.07 ± 0.57 *vs* 2.81 ± 0.58 and 2.65 ± 0.40 *vs* 2.18 ± 0.42, respectively). The differences between the RO and RSG scores before and after the intervention were statistically significant ($P < 0.05$). However, the findings regarding

Table 2 Patients' clinical data, *n* (%)

	Control group	Experimental group	χ^2/Z score	*P* value
Cancer diagnosis			4.693	0.584
Breast cancer	6 (14.60)	4 (9.10)		
Lung cancer	7 (17.10)	6 (13.60)		
Gastrointestinal cancer	7 (17.10)	12 (27.30)		
Nasopharyngeal cancer	2 (4.90)	4 (9.10)		
Gynecological cancer	14 (34.10)	16 (36.40)		
Pancreatic cancer	2 (4.90)	0 (0.00)		
Others	3 (7.30)	2 (4.50)		
Metastasis			0.848	0.357
Yes	16 (39.00)	13 (29.50)		
No	25 (61.00)	31 (70.50)		
Clinical manifestation status			-0.028[1]	0.978
Grade 0	16 (40.00)	9 (20.50)		
Grade 1	7 (17.50)	23 (52.30)		
Grade 2	9 (22.50)	7 (15.90)		
Grade 3	4 (10.00)	5 (11.40)		
Grade 4	4 (10.00)	0 (0.00)		
Stratification			5.320	0.150
Asymptomatic, stable, anti-cancer	6 (15.40)	5 (11.40)		
Asymptomatic, stable, not anti-cancer	2 (5.10)	1 (2.30)		
Symptomatic, anti-cancer remission	24 (61.50)	36 (81.80)		
Symptomatic, symptom control	7 (17.90)	2 (4.50)		
Treatment			16.467	0.110
Palliative care	7 (17.10)	0 (0.00)		
Radiotherapy	0 (0.00)	5 (11.40)		
Chemotherapy	28 (68.30)	31 (70.50)		
Hormone Therapy	0 (0.00)	2 (4.50)		
Chemoradiotherapy	6 (14.60)	4 (9.10)		
Others	0 (0.00)	2 (4.60)		

[1]The Mann-Whitney *U* test.

the EX and RS scores were not statistically significant. This may have been related to the characteristics of the different dimensions of spiritual health. The purpose of spiritual care is to help patients seek the meaning of life, self-realization, hope and creation, faith and trust, peace and comfort, prayer, love and forgiveness, *etc.*, while suffering from illness and pain[23]. Therefore, as core components of quality oncology, spiritual health and spiritual care both promote and influence each other[24].

Spiritual care reducing the levels of anxiety and depression in advanced cancer patients

In our study, after the spiritual care intervention, the number of advanced cancer patients that did not feel anxious and depressed increased significantly, and the differences in these values were statistically significant ($P < 0.001$). This was consistent with the results from a study by Chida *et al*[25], as well as those from other studies, which demonstrated that in advanced cancer patients, effective spiritual care can

Table 3 Spiritual health scores before spiritual care intervention

Dimension	Control group (*n* = 41)	Experimental group (*n* = 44)	*t*/*Z* score	*P* value
EX	2.59 ± 0.69	2.75 ± 0.74	0.986	0.324
RS	2.37 ± 0.59	2.24 ± 0.58	0.983	0.328
RO	2.86 ± 0.59	2.78 ± 0.62	0.593	0.554
RSG	2.55 ± 0.32	2.57 ± 0.43	0.208	0.836
Overall spirituality	2.59 ± 0.69	2.75 ± 0.74	-1.439[1]	0.150

[1]The Mann-Whitney *U* test. EX: Existence; RS: Relationship with self; RO: Relationship with others; RSG: Relationship with something greater.

Table 4 Spiritual health scores after spiritual care intervention

Dimension	Control group (*n* = 41)	Experimental group (*n* = 44)	*t*/*Z* score	*P* value
EX	2.51 ± 0.68	2.79 ± 0.75	–1.811	0.074
RS	2.39 ± 0.59	2.40 ± 0.53	–0.043	0.966
RO	2.81 ± 0.58	3.07 ± 0.57	–2.075	0.041[a]
RSG	2.18 ± 0.42	2.65 ± 0.40	–4.634[1]	*P* < 0.001
Overall spirituality	3.63 ± 1.71	4.68 ± 1.36	-3.077[1]	0.002[a]

[a]*P* < 0.05. EX: Existence; RS: Relationship with self; RO: Relationship with others; RSG: Relationship with something greater.
[1]The Mann-Whitney *U* test.

Table 5 Anxiety status before and after spiritual care intervention, *n* (%)

	Control group	Experimental group	*Z* score	*P* value
Before intervention			-0.558	0.577
No anxiety	22 (53.66)	25 (56.82)		
Critical anxiety	10 (24.39)	13 (29.55)		
Obviously anxious	9 (21.95)	6 (13.64)		
After intervention			-7.834	*P* < 0.001
No anxiety	25 (60.98)	42 (95.45)		
Critical anxiety	8 (19.51)	2 (4.55)		
Obviously anxious	8 (19.51)	0 (0.00)		

reduce negative emotions such as anxiety and depression, reduce suicide risk, and improve their mental health[25,26]. The higher the level of spiritual health, the higher the quality of life; thus, the happier the patient is, the less depressed, anxious, and fatigued they feel, and the less pain they experience[18]. Spiritual health is a valuable coping mechanism. It has unique advantages in its ability to protect cancer survivors from depressive symptoms[27]. As a part of overall health, spiritual health plays an important role in coping with disease-related psychological symptoms and influencing medical decisions before death[28]. Spiritual care interventions can quickly, accurately, and reliably identify the spiritual health of patients with advanced cancer and help them understand their own life, feelings, hope, peace, and other mental states. In our study, following the spiritual care intervention, we found that the emotional function score of the experimental group was lower than that of the control group (2.98 ± 1.34 *vs* 3.73 ± 1.72). This was consistent with the results from the patients' anxiety and depression investigations that were performed after the spiritual intervention.

Table 6 Depression before and after spiritual care intervention, *n* (%)

	Control group	Experimental group	Z score	*P* value
Before intervention				
No depression	22 (53.66)	26 (59.09)	–0.714	0.475
Critical depression	9 (21.95)	11 (25.00)		
Obvious depression	10 (24.39)	6 (13.64)		
After intervention				
No depression	35 (85.37)	43 (97.73)	–2.068	0.039[a]
Critical depression	5 (12.20)	1 (2.27)		
Obvious depression	1 (2.44)	0 (0.00)		
No depression	22 (53.66)	26 (59.09)	–0.714	0.475

[a]$P < 0.05$.

Table 7 Quality of life before spiritual care intervention

Dimension	Control group (*n* = 41)	Experimental group (*n* = 44)	Z score	*P* value
Function				
Physical function	5.90 ± 2.58	5.52 ± 1.72	–0.040	0.968
Emotional function	4.10 ± 1.79	3.80 ± 1.77	–0.915	0.360
Symptom				
Fatigue	4.63 ± 1.95	4.61 ± 1.77	–0.018	0.986
Nausea and vomiting	2.05 ± 1.02	1.80 ± 0.98	–1.187	0.235
Pain	3.56 ± 1.63	3.55 ± 1.73	–0.155	0.877
Dyspnea	1.27 ± 0.55	1.41 ± 0.69	–0.895	0.371
Insomnia	1.90 ± 1.09	2.02 ± 0.90	–0.958	0.338
Poor appetite	2.10 ± 0.97	1.84 ± 0.94	–1.306	0.191
Constipation	1.88 ± 0.98	1.82 ± 1.02	–0.450	0.653
Overall quality of life	4.24 ± 1.50	4.55 ± 1.50	-0.822	0.411

Spiritual care improving the quality of life of patients with advanced cancer

In our study, after the spiritual intervention, we found that the overall quality of life score of the experimental group was higher than that of the control group (5.36 ± 1.16 *vs* 4.39 ± 1.36), and that the difference between the two groups was statistically significant ($P = 0.002$). This was consistent with the results from several studies[29-31]. Spiritual health, as a potential or direct influencing factor, can effectively improve the quality of life of patients with advanced cancer. It can also improve the efficacy of palliative care and is an important indicator for evaluating the quality of life of patients with advanced cancer[32]. In terms of fatigue, the fatigue score of the experimental group was lower than that of the control group (3.41 ± 1.26 *vs* 4.39 ± 1.64), and this difference was statistically significant ($P = 0.005$). We found that spiritual care can alleviate the fatigue experienced by cancer patients, which was consistent with the results from studies by Rabow *et al*[18] and Heidari *et al*[33]. All cancer patients experience fatigue, and higher fatigue scores are observed in patients with stage IV tumors. There is a significant negative correlation between fatigue scores and spiritual health. The more obvious the symptoms of fatigue and the more severe the fatigue that the cancer patient is experiencing, the worse their spiritual health is. Therefore, we propose that fatigue can be used as the primary negative predictor of the spiritual health in patients with advanced cancer[13].

Table 8 Quality of life after spiritual care intervention

Dimension	Control group (*n* = 41)	Experimental group (*n* = 44)	*Z* score	*P* value
Function				
Physical function	5.68 ± 2.61	4.70 ± 1.65	–1.590	0.112
Emotional function	3.73 ± 1.72	2.98 ± 1.34	–2.103	0.035[a]
Symptom				
Fatigue	4.39 ± 1.64	3.41 ± 1.26	–2.829	0.005[a]
Nausea and vomiting	2.05 ± 1.00	1.52 ± 0.73	–2.521	0.012[a]
Pain	3.56 ± 1.45	2.95 ± 1.06	–1.857	0.063
Dyspnea	1.51 ± 0.67	1.36 ± 0.65	–1.198	0.231
Insomnia	1.83 ± 1.05	1.66 ± 0.68	–0.196	0.844
Poor appetite	2.07 ± 0.93	1.66 ± 0.78	–2.179	0.029[a]
Constipation	1.83 ± 0.89	1.50 ± 0.73	–1.823	0.068
Overall quality of life	4.39 ± 1.36	5.36 ± 1.16	-3.077	0.002[a]

[a]$P < 0.05$.

In our study, the effect of spiritual care on pain was not obvious, and the difference between the findings from the two groups was not statistically significant ($P = 0.063$). However, this finding was inconsistent with the results from other studies[34]. This may have been related to the short duration of the intervention or the different grades of pain. Many studies have confirmed that patients with advanced cancer experience significant problems with pain, and the severity of the pain has a negative correlation with their spiritual health[35]. The more severe the patient's pain, the worse their spiritual health is. Our study also found that after the spiritual care intervention, the nausea and vomiting and loss of appetite scores for the experimental group were lower than those for the control group (1.52 ± 0.73 *vs* 2.05 ± 1.00 and 1.66 ± 0.78 *vs* 2.07 ± 0.93, respectively) and these differences were statistically significant. This may have been due to the patients' calmness after undergoing spiritual care. Their psychological disposition had an impact on their physiological function, thus reducing their gastrointestinal reaction and increasing their appetite.

CONCLUSION

Although spiritual care in China began relatively late, many studies have verified that when it was applied to the clinical care of patients with advanced cancer, it could effectively guide clinical nurses or palliative care teams towards providing nursing services to patients with advanced cancer in a systematic, scientific, and targeted manner. We included specific spiritual care content for cancer patients based on psychological cancer care, providing specific help and guidance strategies for the spiritual care of patients with advanced cancer, and complementing psychological care to promote the quality of life of this patient population. We made the palliative care team and its supporters more aware of the spiritual confusion that patients with advanced cancer experience, guided the team to conduct comprehensive patient assessments, implemented spiritual care for the spiritual problems that patients with advanced cancer encountered, and evaluated the effects of this intervention both before and after its implementation. In addition, this intervention can draw the attention of medical staff to the spiritual health of patients with advanced cancer and strengthen their attention to spiritual care. Although it cannot extend the length of the patient's lifespan, it can allow the patient to complete their last journey of life quietly, peacefully, and without regrets.

ARTICLE HIGHLIGHTS

Research background

The quality of life of patients with advanced cancer is generally low, including psychological, physical, social, family, and other aspects. Spiritual care is thought to improve the quality of life for people with advanced cancer. While developed countries have developed mature care models, there is currently a lack of systematic spiritual care programs for patients with advanced cancer in developing countries. This study referred to the mature spiritual care programs in developed countries, and combined the national conditions of China to construct spiritual care programs suitable for Chinese culture and evaluated its effects.

Research motivation

This study constructed a spiritual care plan suitable for Chinese culture and provided a basis for clinicians to take intervention measures to improve the spiritual health of patients with advanced cancer.

Research objectives

This study aimed to build a spiritual care program for advanced cancer patients suitable for China's national conditions and evaluated its application effect in the Chinese population. Future research could explore the extensibility of this program in different cancer populations.

Research methods

This research adopted the Delphi method to construct the spiritual care plan and the method to study the randomly assigned experimental group and control group. The experimental group used the spiritual care plan, while the control group used conventional care plan. The two groups of patients' were evaluated for spiritual health score, anxiety score, depression score and quality of life score to evaluate the effect of spiritual care plan.

Research results

The results showed that the spiritual-care group had higher overall spiritual health scores, lower prevalence of anxiety and depression, and higher overall quality of life scores than the control group, indicating that the spiritual care plan was an effective solution for Chinese patients with advanced cancer.

Research conclusions

The spiritual care program for patients with advanced cancer developed in this study could improve the spiritual health and quality of life of patients with advanced cancer and reduce negative emotions such as anxiety and depression. Spiritual care for patients with advanced cancer is recommended in oncology and hospice units.

Research perspectives

Future studies may evaluate the generalizability of the plan in a broader population of cancer patients.

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SYSTEMATIC REVIEWS

Therapeutic use of melatonin in schizophrenia: A systematic review

Cathy Duan, Zoe M Jenkins, David Castle

ORCID number: Cathy Duan 0000-0001-5809-2436; Zoe M Jenkins 0000-0002-8551-0792; David Castle 0000-0002-3075-1580.

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Cathy Duan, Zoe M Jenkins, David Castle, Department of Psychiatry, University of Melbourne, Parkville 3010, VIC, Australia

Zoe M Jenkins, David Castle, Mental Health Service, St. Vincent's Hospital, Melbourne 3065, VIC, Australia

David Castle, Centre for Complex Interventions, Centre for Addictions and Mental Health, Toronto ON M6J 1H4, Canada

David Castle, Department of Psychiatry, University of Toronto, Toronto ON M5S, Canada

Corresponding author: Zoe M Jenkins, BSc, Research Fellow, Mental Health Service, St. Vincent's Hospital, 46 Nicholson Street, Fitzroy, Melbourne 3065, VIC, Australia.
zoe.jenkins@svha.org.au

Abstract

BACKGROUND

Sleep dysfunction is a common problem in people with schizophrenia, and side effects of treatment often exacerbate metabolic and cardiovascular risk and may induce extrapyramidal side effects. Melatonin (N-acetyl-5-methoxytryptamine) is an endogenously produced hormone which has demonstrated direct and indirect antioxidant and neuroprotective effects. Previous studies have explored the use of exogenous melatonin in improving sleep outcomes in the general population, yet indications for use in schizophrenia are unclear.

AIM

To synthesize the evidence from clinical trials investigating prescribed melatonin as an adjunctive therapy in patients with schizophrenia.

METHODS

A systematic literature review of MEDLINE (Ovid), Embase, PsychINFO, and PubMed on the 27/08/20; and CINAHL and Cochrane Library databases, was conducted. Inclusion criteria were: a peer-reviewed clinical trial published in English; included a group of patients with schizophrenia; used melatonin as an adjunctive therapy; and reported any outcome of any duration. Exclusion criteria were: neurodegenerative diseases, primary sleep disorders, co-morbid substance use or animal studies.

RESULTS

Fifteen studies were included in the current review with the following primary outcomes: sleep (n = 6), metabolic profile (n = 3), tardive dyskinesia (n = 3), cognitive function (n = 2) and benzodiazepine discontinuation (n = 1).

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CONCLUSION
Adjunctive melatonin therapy has some positive outcomes for sleep, metabolic profile and tardive dyskinesia in patients with schizophrenia. No beneficial effect of melatonin was observed on outcomes of cognition or benzodiazepine discontinuation. Future studies utilizing larger samples and investigations specifically comparing the effect of melatonin as adjunctive therapy with different antipsychotics in patients with schizophrenia are required.

Key Words: Schizophrenia; Melatonin; Clinical trials; Sleep; Metabolic syndrome; Tardive dyskinesia

Core Tip: This systematic review synthesized the results of clinical trials that have investigated the effect of exogenous melatonin as adjunctive therapy for patients with schizophrenia. Some positive outcomes were demonstrated for sleep improvement and attenuating antipsychotic-induced metabolic side effects. Future investigations are required to determine differential effects of melatonin when used in conjunction with a range of antipsychotic medications.

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INTRODUCTION

Schizophrenia is a chronic psychiatric disorder characterized by a combination of positive (hallucinations and delusions) and negative symptoms affecting thought, perception, cognition and behaviour through complex mechanisms, often resulting in significant deterioration of function[1]. Along with the cardinal features of psychosis, associated side effects of medications and sleep dysfunction can cause lifelong impact on patients' quality of life[2].

Second-generation antipsychotics (SGAs) are the current standard for treating schizophrenia and related illnesses due to the comparatively lower rates of extrapyramidal side effects (EPS), as compared with first generation antipsychotics[3]. However, it has been demonstrated that EPS remain a potential side effect of SGAs[4]; tardive dyskinesia (TD) remains a risk even with these newer agents[5], with limited understanding of both the mechanisms and treatment options[6]. Furthermore, significant weight gain and an increased incidence of metabolic syndrome (MetS) and cardiovascular disease risk have also been established in association with certain SGA medications[7].

Sleep dysfunction is also common in people with schizophrenia, as demonstrated by poor sleep efficiency and disrupted circadian rhythms[8,9]. Studies have shown that there is decreased endogenous secretion of melatonin in patients with schizophrenia, and this pattern can persist despite improvement of sleep quantity and quality with antipsychotic agents[10]. Benzodiazepines (BZDs) are widely used to ameliorate sleep disruption in schizophrenia. While only recommended for short-term use, many patients remain on BZDs long-term, suffering additional effects including sedation, increased risk of falls, and cognitive impairment[11,12].

In an effort to address sleep dysfunction in individuals with schizophrenia, various studies have explored the use of exogenous melatonin. Melatonin (N-acetyl-5-methoxytryptamine) is an endogenously produced hormone naturally secreted at night from the pineal gland in a circadian rhythm to promote sleep. Adjunctive administration of exogenous melatonin has been recognized to have therapeutic benefit in sleep disorders in the general population[13,14]; however, it remains relatively less explored in people with schizophrenia. Furthermore, melatonin has also demonstrated direct and indirect antioxidant and neuroprotective effects, suggesting various potential clinical uses for treatment in schizophrenia, notably EPS and MetS

[15].

The current review aims to synthesize the evidence from clinical trials investigating the effect of adjunctive use of melatonin on any outcome in individuals with schizophrenia.

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were adhered to throughout the review.

Search strategy

The literature search was conducted online for papers in the English language with no restriction of publication date, using MEDLINE (Ovid), Embase, PsychINFO, and PubMed on 27/08/20; and CINAHL and the Cochrane Library on 28/08/20. Syntax was translated using Polyglot to search the databases appropriately. Search terms included the keywords of "schizophrenia", "melatonin" and with the following trade names — circadin, regulin, benedorm, melaxen or melovine, and "clinical trials" (of any type). Boolean operators OR was used to combine synonyms of the keywords, and AND was used to combine search terms. MeSH headings were specifically used for "schizophrenia", "melatonin" and "clinical trials" as well as searching for these terms in the title and abstract. Additional studies were identified from a manual search of the reference lists of included articles and registered clinical trials.

Inclusion criteria

The inclusion criteria for papers in this systematic review were: (1) A peer-reviewed research article published in English; (2) Included a group of participants with a diagnosis of schizophrenia (including its subtypes), paraphrenia, delusional psychoses, paranoid psychosis, psychosis not otherwise specified, schizophreniform disorder, schizotypal disorder or schizoaffective disorder; (3) A clinical trial using melatonin as adjunctive therapy; (4) Collected an outcome measure of any duration; and (5) Included original data in the paper. Exclusion criteria included review papers, meta-analyses, case reports, animal studies or studies with patient populations that included neurodegenerative diseases, organic causes of disease, and primary sleep disorders.

Study selection

Search results were exported to Endnote bibliographic management software, duplicates removed, and the remainder uploaded to Covidence systematic review software (www.covidence.org) by Duan C Two authors (Duan C, Castle D) independently screened records on title and abstract and then full text against the exclusion criteria and disagreements were resolved by discussion.

Data extraction and assessment of risk of bias

Two reviewers (Jenkins ZM and Duan C) independently extracted data and consensus was confirmed by a third reviewer (Castle D). Extracted data included information on study characteristics, objectives and outcomes. A meta-analysis was not performed as there were too few similarities across studies in terms of study methods and outcome measures. The risk of bias among included studies was assessed independently by two authors (Duan C and Jenkins ZM) using the Cochrane risk-of-bias tool for randomised trials[16] and consensus was confirmed by a third reviewer (Castle D). Studies were classified into three classes of quality, viz.: low, moderate or high risk of bias. The risk of bias was not used as an exclusion criterion in the selection of studies, to provide a complete overview of available data.

RESULTS

A total of 163 papers were identified from the search and an additional two papers were found from the reference list of the identified papers. Sixty eight duplicate records were excluded and the titles and abstracts of the remaining 97 papers were screened independently by two authors (Duan C and Castle D). After title and abstract screening, 25 papers were read in full and assessed for eligibility. A further 10 papers were excluded, leaving 15 papers included for qualitative synthesis (see Figure 1 for an

Figure Legends

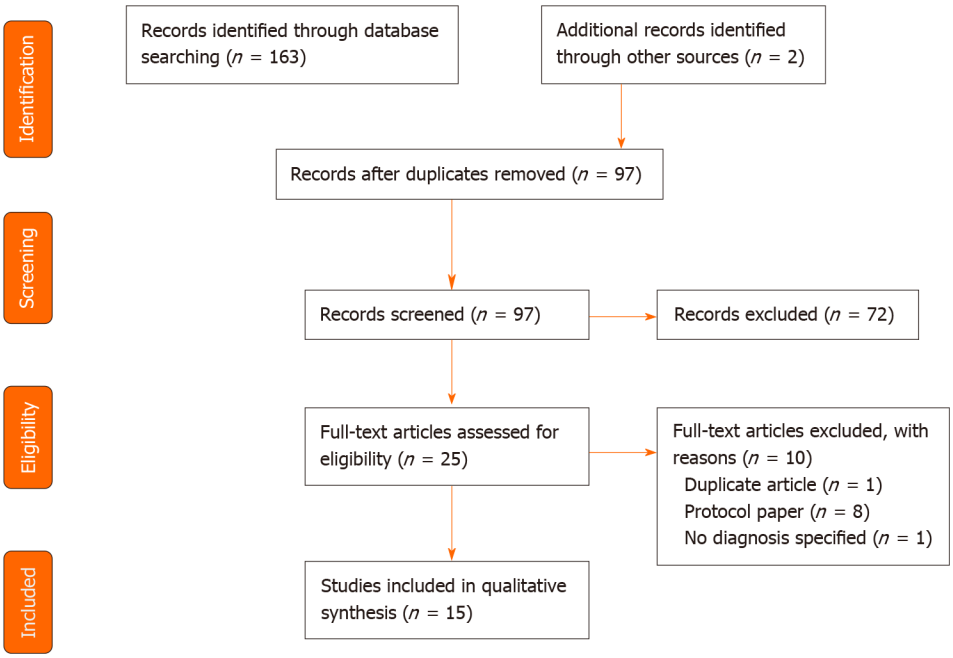

Figure 1 PRISMA flowchart.

overview of the study selection process).

Study characteristics

Characteristics of the 15 included studies for qualitative synthesis are shown in Tables 1-5. Four trials had a crossover design, two were open-label and nine utilized a randomized double-blind parallel design. The 15 trials included a total of 626 participants (351 male, 252 female, 23 not specified) with sample sizes ranging from 10-120. Diagnoses in the studies included 269 participants with schizophrenia, 268 with paranoid schizophrenia, 7 with disorganized schizophrenia, 27 with schizoaffective disorder and 55 with bipolar disorder (the bipolar disorder patients were part of a cohort including people with schizophrenia, hence their inclusion).

Risk of bias

One study was classified as at low risk of bias, nine were classified as having a moderate risk of bias and six were classified as being at high risk of bias (see outcome Tables for overall classification).

Outcome measures

Studies were grouped according to the following primary outcome measures: sleep (n = 6; see Table 1), metabolic profile (n = 3; see Table 2), TD (n = 3; see Table 3), cognitive function (n = 2; see Table 4) and BZD tapering (n = 1; see Table 5).

Sleep outcomes

Six studies primarily assessed the impact of melatonin therapy on sleep parameters in individuals with schizophrenia[17-22], see Table 1.

Two studies assessed the effect of controlled release melatonin formulation on sleep parameters over a three week period[17,18]; one demonstrated a significant improvement in sleep efficiency over three weeks of melatonin treatment, as compared to placebo[17] while the other reported worsened sleep efficiency, prolonged REM sleep latency and increased duration of wakefulness on the first night, as compared to the second night in participants who received melatonin[18]. Another investigation employed a patient-determined dosage of melatonin over a 15 d period; those who received melatonin had a decreased number of awakenings, increased sleep duration and superior self-report sleep parameters than controls[19].

The impact of melatonin on circadian rhythms was assessed by Mishra *et al*[20] according to change in serum and urinary melatonin levels, which increased over the trial period in participants who received melatonin therapy, compared with controls.

Table 1 Sleep outcomes

Ref.	Sample size (sex) melatonin; control	Age (yr) melatonin; control	Dose, duration	Diagnosis	Inclusion criteria	Study design	Outcomes	Significant findings related to melatonin	Risk of bias
Shamir *et al* [18], 2000	14 (11 M, 3 F), 14 (11 M, 3 F)	Overall: 42.3 ± 13.1	2 mg CR melatonin or placebo/day for 3 wk	SZA (*n* = 2); Paranoid SCZ (*n* = 10); Disorganised SCZ (*n* = 2)	Diagnosis of chronic SCZ (as per DSM-IV criteria); poor sleep quality	Randomized, double-blind, crossover trial (1 wk washout)	Sleep latency (min), REM sleep (%), REM sleep latency (min), total sleep time (min), sleep efficiency (%), duration of wakefulness (min), stage 1 sleep (%), slow wave sleep (%)	REM Sleep latency (min): Melatonin: 1st night > 2nd night Sleep efficiency (%): Melatonin: 1st night < 2nd night Duration of wakefulness (min): Melatonin: 1st night > 2nd night Stage 1 sleep (%): Placebo: 1st night < 2nd night	High
Shamir *et al* [17], 2000	19 (12 M, 7 F); 19 (12 M, 7 F)	Overall: 42 ± 5	2 mg CR melatonin or placebo/day for 3 wk	SZA (*n* = 5); Paranoid SCZ (*n* = 9); Disorganised SCZ (*n* = 5)	Diagnosis of chronic SCZ (as per DSM-IV criteria); poor sleep quality	Randomized, double-blind, crossover trial (1 wk washout)	Urinary 6-SMT excretion, sleep efficiency (%), sleep latency (min), total sleep time (min), wake after sleep onset duration (min), fragmentation index (%), number of awakenings (N)	Sleep efficiency (%): Melatonin > Placebo	Some concerns
Suresh Kumar *et al* [19], 2007	20 (13 M, 7 F); 20 (14 M, 6 F)	38.4 ± 14.4; 36.0 ± 13.4	Patient determined dosage of melatonin or placebo for 15 d	Paranoid SCZ (*n* = 40)	Diagnosis of paranoid SCZ (as per DSM-IV criteria); illness duration < 1 yr; clinically stable; receiving same dose of haloperidol for the past month, insomnia present for past 2 wk	Double-blind, placebo-controlled study	Time taken to fall asleep (min), number of awakenings (n), duration of sleep (min), self-report sleep questionnaire	Number of awakenings (N): Melatonin < Placebo Duration of sleep (min): Melatonin > Placebo Self-report sleep questionnaire: Time to fall asleep, quality of sleep, depth of sleep, freshness on awakening, morning headache, morning mental dullness, mood, overall functioning were superior in Melatonin group *vs* Placebo	High
Mishra *et al* [20], 2020	PPS: 30 (15 M, 15 F); 30 (21 M, 9 F). PNS: 30 (21 M, 9 F); 30 (14 M, 16 F)	PPS: 38.6 ± 10.68; 34.0 ± 8.38. PNS: 34.97 ± 12.35; 37.87 ± 3.84	8 mg/d Ramelteon + monotherapy *vs* monotherapy alone for 4 wk	SCZ (*n* = 120). Patients were categorized into PPS (*n* = 60) and PNS (*n* = 60) groups based on PANSS scoring	Diagnosis of SCZ (as per DSM-5 criteria); aged between 18-65 yr; treatment naïve or had not taken treatment for 4 wk	Randomized, open-label, rater-blinded, parallel design clinical trial	Quality of sleep (PSQI), melatonin excretion (urinary melatonin 6aMTs), serum AANAT, symptom severity (PANSS)	Change in serum melatonin at 14:00 h: PPS and PNS: Melatonin > Control Change in serum melatonin 2 h after add on therapy: PPS and PNS: Melatonin > Control Change in urinary melatonin: PPS and PNS: Melatonin > Control Change in serum AANAT: PPS and PNS: Melatonin > Control	High

								PSQI: PPS and PNS: Melatonin > Control Change in PANSS total score: PPS and PNS: Total score improved Melatonin > Control; PPS: Decreased positive symptoms in Melatonin > Control; PNS: Decrease negative symptoms in Melatonin > Control	
Baandrup *et al*[22], 2016	20 (11 M, 9 F); 28 (18 M, 10 F)	47.7 ± 8.2; 45.9 ± 10.3	2 mg/d PR melatonin or placebo for 24 wk	Paranoid SCZ (n = 38), Non-paranoid SCZ (n = 2), SZA (n = 2), BP (n = 6)	Diagnosis of SCZ, SZA or BP (as per ICD-10 criteria); treated with 1 antipsychotic and 1 BZD for 3 m	Randomized, double-blind clinical trial	Actigraphy (sleep and 24 h rhythm activity variables)	-	Some concerns
Baandrup *et al*[21], 2016	28 (14 M, 14 F); 27 (15 M, 12 F)	48.8 ± 7.1; 49.1 ± 12.2	2 mg/d PR melatonin or placebo for 24 wk	Paranoid SCZ (n = 42), non-paranoid SCZ (n = 2), SZA (n = 3), BP (n = 8)	Diagnosis of SCZ, SZA or BP (as per ICD-10 criteria); treated with 1 antipsychotic and 1 BZD for 3 mo	Randomized, double-blind clinical trial	PSQI, polysomnography (n = 23; total sleep time, sleep latency, REM latency, time awake after sleep onset, number of awakenings, sleep architecture)	PSQI sleep quality: Melatonin > Placebo	Some concerns

AANAT: Aryl-alkylamine-N-acetyl-transferase; BP: Bipolar disorder; BZD: Benzodiazepine; CR: Controlled-release; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition; F: Female; ICD-10: International Classification of Diseases, Tenth Revision; M: Male; PANSS: Positive and Negative Syndrome Scale; PNS: Predominant negative symptom group; PPS: Predominant positive symptom group; PR: Prolonged-release; PSQI: Pittsburgh sleep quality index; REM: Rapid eye movement; SCZ: Schizophrenia; SZA: Schizoaffective disorder.

Moreover, significant improvements in sleep (as measured by the PSQI) and symptoms of schizophrenia (as measured by the PANSS) were demonstrated by patients who received ramelteon as an add-on to antipsychotic therapy, compared to antipsychotic therapy alone[20].

Two publications reported different sleep outcomes from the same study whose primary aim was to observe the effect of melatonin on BZD discontinuation/reduction in patients with a diagnosis of schizophrenia or bipolar disorder. One reported no difference between add-on melatonin therapy on circadian rest-activity rhythms[22], compared to placebo. However, the other publication highlighted that participants who received melatonin reported superior subjective sleep quality than the placebo group[21].

Metabolic profile outcomes

Three studies assessed whether melatonin attenuates antipsychotic-induced metabolic side effects[23-25], see Table 2.

Modabbernia *et al*[24] investigated the impact of melatonin on patients with first episode schizophrenia. They reported significantly less increase in weight gain, body mass index (BMI) and total cholesterol over an eight week trial as well as significantly greater reductions in psychiatric symptoms (as assessed by the PANSS) in patients who received melatonin when initiating olanzapine, compared to placebo. Another

Table 2 Metabolic outcomes

Ref.	Sample size (sex) melatonin; control	Age (yr) melatonin; control	Dose, duration	Diagnosis	Inclusion criteria	Study design	Outcomes	Significant findings related to melatonin	Risk of bias
Borba *et al* [23], 2011	14 (8 M, 6 F); 6 (5 M, 1 F)	49 ± 7; 56 ± 9	8 mg/d Ramelton or placebo for 8 wk	SCZ (*n* = 11), SZA (*n* = 9)	Diagnosis of SCZ (as per DSM-IV criteria); aged between 18-65 yr; BMI > 27 kg/m^2, insulin resistance or any component of metabolic syndrome or a BMI of > 30 kg/m^2	Double-blind, placebo-controlled pilot trial	Waist circumference (cm), abdominal fat as measured by DEXA, glucose metabolism, C-reactive protin, lipids, psychopathology (PANSS; HDRS, HCQoL), sleep quality (SSS, FSI, MOSSS), adverse effects (SATEE)	Total cholesterol; cholesterol-to-HDL ratio; LDL particle number: Melatonin < Placebo Adverse effects: Melatonin *vs* control group: drowsiness (57% *vs* 33%), heart burn (21% *vs* 0%), cough (21% vs 0%), akathisia (21% *vs* 0%), increased urinary frequency (14% *vs* 0%), problems with memory or concentration (21% *vs* 0%) Arthralgia/myalgia and anxiety: Placebo > Melatonin	High
Modabbernia *et al*[24], 2014	18 (13 M, 5 F); 18 (12 M, 6 F)	32.7 ± 7.3; 32.8 ± 8.2	3 mg/d melatonin + Olanzapine or placebo + Olanzapine for 8 wk	SCZ (*n* = 36)	Diagnosis of SCZ (as per DSM-IV criteria); aged between 18-65 yr; in their first-episode eligible for starting olanzapine	Randomized, double-blind, placebo-controlled, and parallel-group study	Anthropometric measures, BP, FBS, fasting plasma insulin, Psychopathology (PANSS)	Weight, BMI and Waist circumference: Melatonin < Placebo PANSS total score: Melatonin < Placebo	Some concerns
Romo-Nava *et al*[25], 2014	20 (10 M, 10 F); 24 (12 M, 12F)	Overall: 29.5 ± 8.3	5 mg/d CR melatonin or placebo for 8 wk	SCZ (*n* = 24); BP (*n* = 20)	Diagnosis of SCZ or BP type I (as per DSM-IV criteria); aged between 18-45 yr, initiated treatment with SGAs < 3 mo	Double-blind, placebo-controlled study	Anthropometric measures, body composition, BP, Lipids, Glucose, PANSS, CGI-S. BPD only: HDRS, YMRS. Schizophrenia only: CDS	Weight gain, waist circumference, DBP, fat mass, triglycerides: Melatonin (BP only) < Placebo	Some concerns

BMI: Body mass index; BP: Bipolar disorder; BP: Blood pressure; CDS: Calgary depression scale; CGI-S: Clinical Global Impression-Severity of Illness; CR: Controlled-release; DEXA: Dual-energy x-ray absorptiometry; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition; F: Female; FBS: Fasting blood sugar; FSI: Fatigue scale inventory; HCQoL: Heinrichs-Carpenter Quality of Life Scale; HDL: High-density lipoprotein; HDRS: Hamilton Depression Rating Scale; LDL: Low-density lipoprotein; M: Male; MOSSS: Medical outcomes study sleep scale; PANSS: Positive and Negative Syndrome Scale; SATEE: Systematic assessment for treatment emergent events; SCZ: Schizophrenia; SGA: Second generation antipsychotics; SSS: Stanford sleepiness scale; SZA: Schizoaffective disorder; YMRS: Young mania rating scale.

investigation assessed the impact of melatonin on patients with schizophrenia or bipolar disorder taking SGAs[25]. For the group as a whole, melatonin attenuated weight gain, waist circumference increase and was associated with decreased diastolic blood pressure. However, subgroup analysis of participants with schizophrenia alone demonstrated no significant changes as a result of melatonin therapy[25].

Borba *et al*[23] investigated whether melatonin could attenuate the metabolic side-effects of antipsychotics in patients with a pre-existing BMI of above 27 kg/m^2 and at least one component of MetS. They demonstrated no change in anthropometric outcomes but did observe decreased total cholesterol, cholesterol-to-high-density lipoprotein ratio and low-density lipoprotein (LDL) particle number in those who received melatonin, compared to placebo[23]. Moreover, they reported significantly

Table 3 Tardive dyskinesia

Ref.	Sample size (sex) melatonin; control	Age (yr) melatonin; control	Dose, duration	Diagnosis	Inclusion criteria	Study design	Outcomes	Significant findings related to melatonin	Risk of bias
Shamir *et al* [26], 2000	19 (8 M, 11 F); 19 (8 M, 11 F)	Overall: 74.0 ± 9.5	2 mg/d CR melatonin or placebo for 4 wk	SCZ (n = 19)	Diagnosis of SCZ of > 20 yr (as per DSM-IV criteria), TD > 5 yr, antipsychotic treatment > 10 yr	Double-blind, placebo-controlled, crossover trial (2 wk washout)	AIMS	-	Some concerns
Shamir *et al* [27], 2001	22 (11 F, 11 M); 22 (11 F, 11 M)	Overall: 64.2 ± 14.3	10 mg/d CR melatonin or placebo for 6 wk	SCZ (n = 22)	Diagnosis of SCZ and anti-psychotic-induced TD (as per DSM-IV criteria)	Double-blind, placebo-controlled, crossover trial (4 wk washout)	AIMS	AIMS: Melatonin < Placebo	Some concerns
Castro *et al* [28], 2011	7; 6 (sex NR)	Overall: 59.9 ± 2.7	20 mg/d melatonin or placebo for 12 wk	SCZ (n = 11); BP (n = 2)	Diagnosis of neuroleptic-induced TD (as per DSM-IV criteria)	Randomized, double blind, placebo-controlled pilot study	AIMS; BPRS	-	High

AIMS: Abnormal Involuntary Movement Scale; BP: Bipolar disorder; BPRS: Brief psychiatric rating scale; CR: Controlled-release; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition; F: Female; M: Male; NR: Not reported; SCZ: Schizophrenia; TD: Tardive dyskinesia.

Table 4 Cognitive function

Ref.	Sample size (sex) melatonin; control	Age (yr) melatonin; control	Dose, duration	Diagnosis	Inclusion criteria	Study design	Outcomes	Significant findings related to melatonin	Risk of bias
Shirayama *et al*[29], 2014	10 (NR); -	42.5 ± 7.3	8 mg/d melatonin for 6 mo	SCZ (n = 10)	Diagnosis of SCZ (as per DSM-IV criteria); symptoms stable for 3 mo	Open-label study	TMT (A and B), WCST, VFT, Stroop Test, DSPDT, IGT, RAVLT	RAVLT (total, delayed recall and recognition): Improved at 6-mo compared to baseline	High
Baandrup *et al*[30], 2017	40 (21 M, 19 F); 40 (24 M, 16 F)	47.4 ± 8.6; 49.0 ± 12.1	2 mg/d CR melatonin or placebo for 24 wk	Paranoid SCZ (n = 62), non-paranoid SCZ (n = 6), SZA (n = 3), BP (n = 9)	Diagnosis of SCZ, SZA or BP (as per ICD-10 criteria); treated with 1 antipsychotic and 1 BZD for 3 mo	Randomized, double-blind clinical trial	BACS (domains: verbal memory, working memory, motor speed, verbal fluency, letter fluency, attention and processing speed, executive function), WHO-Five WBI, SWN, PSP, UKU, PANSS	-	Low

BACS: Brief assessment of cognition in schizophrenia; BP: Bipolar disorder; BZD: Benzodiazepine; CR: Controlled-release; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition; DSPDT: Digit span distraction test; F: Female; ICD-10: International Classification of Diseases, Tenth Revision; IGT: Iowa gambling task; M: Male; NR: Not reported; PANSS: Positive and negative syndrome scale; PSP: Personal and social performance scale; RAVLT: Rey auditory verbal learning test; SCZ: Schizophrenia; SWN: Subjective wellbeing under neuroleptic treatment scale; SZA: Schizoaffective disorder; TMT: Trail-making test; part A and part B; UKU: Udvalget for Kliniske Undersoegelser side effect rating scale; VFT: Verbal fluency test; WCST: Wisconsin card sorting test; WHO-Five WBI: WHO-five wellbeing index.

lower levels of arthralgia/myalgia and anxiety, yet significantly more side effects of drowsiness (57% *vs* 33%), heart burn (21% *vs* 0%), cough (21% *vs* 0%), akathisia (21% *vs* 0%), increased urinary frequency (14% *vs* 0%), and problems with memory or concentration (21% *vs* 0%) in those who received melatonin in comparison with those on placebo[23].

Table 5 Benzodiazepine discontinuation

Ref.	Sample size (sex) melatonin; control	Age (yr) melatonin; control	Dose, duration	Diagnosis	Inclusion criteria	Study design	Outcomes	Significant findings	Risk of bias
Baandrup *et al*[12], 2016	42 (23 M, 19 F); 44 (25 M, 19 F)	47.9 ± 8.7; 49.4 ± 12.3	2 mg/d PR melatonin or placebo for 24 wk	Paranoid SCZ (n = 67), Non-paranoid SCZ (n = 6), SZA (n = 3), BP (n = 10)	Diagnosis of SCZ, SZA or BP (as per ICD-10 criteria); treated with 1 antipsychotic drug and 1 BZD drug for 3 mo; able to understand Danish	Randomized, double-blind clinical trial	Mean daily dosage of BZD, pattern of BZD dosage, BZD cessation proportion, BWSQ-2	-	Some concerns

BP: Bipolar disorder; BWSQ-2: Benzodiazepine Withdrawal Symptom Questionnaire; BZD: Benzodiazepine; ICD-10: International Classification of Diseases, Tenth Revision; PR: Prolonged release; SCZ: Schizophrenia; SZA: Schizoaffective disorder.

TD

Three studies investigated the impact of melatonin therapy on symptoms of TD[26-28], see Table 3.

The use of 2 mg/d adjunctive melatonin therapy over a four week period did not affect severity of TD in an initial study by Shamir *et al* [26]. However, a follow-on study from the same investigators found that 10 mg/d of melatonin over a six week period was associated with a significant decrease in TD severity (as measured by the Abnormal Involuntary Movement Scale; AIMS) in patients with chronic schizophrenia, as compared to placebo[27]. In a more recent study, however, Castro *et al*[28] used 20 mg/d of melatonin over a 12 wk period, yet did not observe any difference from placebo in terms of TD symptoms.

Cognitive function

Two studies investigated the impact of melatonin on cognitive function in people with schizophrenia, over a period of 24 wk[29,30], see Table 4.

The only significant change in cognitive function associated with melatonin treatment was improved memory on a verbal learning task post-treatment (8 mg/d for six months), as compared to baseline levels in one of these studies[29]. In contrast, Baandrup *et al*[30] did not report any change in any domain of cognitive functioning — as assessed by the Brief Assessment of Cognition in Schizophrenia (BACS) cognitive battery — in patients receiving 2 mg/d prolonged-release melatonin for 24 wk.

Benzodiazapine discontinuation

Baandrup *et al*[21,22,30] investigated the impact of melatonin during discontinuation or reduction of BZDs and reported various outcomes in four papers, three of which are reported above. Overall, they found that add-on melatonin did not impact average BZD dosage, dosage pattern, cessation proportions or BZD withdrawal symptoms over their 24-wk trial, see Table 5[12].

DISCUSSION

The current review provides a synthesis of investigations using melatonin for individuals with schizophrenia, across a diverse range of outcomes. The various outcomes identified are discussed below.

Sleep

The impact of melatonin on sleep function was the most commonly reported outcome in the current review, with some positive outcomes. Two studies assessed the efficacy of melatonin in improving sleep efficiency (defined as proportion of time asleep over total time in bed). One demonstrated improved efficiency[17] while one reported worsened sleep efficiency[18]. However, the worsened sleep efficiency (and accompanying prolonged REM sleep latency and increased duration of wakefulness) was a comparison between sleep parameters on the first night to the second night of the study. The study objective was to investigate the impact of melatonin on 'the first

night effect (FNE)', whereby individuals have a tendency to experience poorer sleep quality on the first night of a sleep evaluation study[18]. Therefore, while this study demonstrated that melatonin does not ameliorate the FNE, conclusions cannot be drawn about extended sleep efficiency.

The only study in the current review that permitted a patient-determined dosage of melatonin revealed a significantly lower number of night-time awakenings, a longer duration of sleep and improved subjective sleep quality in patients with schizophrenia and comorbid insomnia, as compared to placebo[19]. While the modal dose of melatonin over the trial was 3 mg/d, the authors conceded that conclusions could not be made regarding the optimal dose of melatonin for improved sleep outcomes. Moreover, they did not employ an objective measure of sleep, such as polysomnographic or actigraphic assessments, recommending that further investigation is required[19].

The impact of melatonin on circadian rhythm was assessed in two studies; increased objective measures of serum and urinary melatonin were observed in patients who received melatonin[20], yet actigraphic observations of circadian rhythm revealed no change with melatonin treatment[22]. However, the actigraphic assessments were taken in patients who were concurrently discontinuing BZD medication, limiting generalisation. The same investigation reported improved subjective sleep quality in patients tapering off BZDs[21], suggestive of some beneficial impacts of melatonin.

Overall, melatonin's main indication has been to treat disorders of sleep based on its physiological regulatory effects. In mental health populations, there has been increasing use in treatment of disorders that have a sleep dysfunction component[31]. In patients with schizophrenia, exogenous melatonin induced secretion of endogenous melatonin in a single study and improved sleep efficiency in another. Future replications utilizing a controlled melatonin dosage, free from the impact of BZD discontinuation, are required in order to clarify the indications for melatonin on sleep in people with schizophrenia.

Metabolic profile outcomes

The efficacy of melatonin in ameliorating metabolic side effects of antipsychotics among patients with schizophrenia was explored in three studies; two of which reported some benefits[23,24].

Adjunctive treatment of melatonin was effective in attenuating weight gain in first episode schizophrenia patients who were initiating treatment with olanzapine[24]. However, no significant benefit of melatonin on body weight were observed in two separate studies of patients with an established history of antipsychotic treatment[23,25]. A tentative interpretation of these findings is that the use of melatonin in conjunction with the initiation of antipsychotic treatment may assist in the initial weight gain associated with first episode psychosis and initiation of antipsychotics[32,33], but further studies are required.

The only other beneficial metabolic outcome was an improvement in total cholesterol and LDL-particle number in participants who received ramelteon in a pilot study[23]. However, the inclusion criteria for that study specified patients with a pre-existing BMI of above 27 and a component of the MetS, therefore it may be that melatonin is more effective for those with poorer initial metabolic health. There is also the possibility of the finding simply reflecting regression to the mean. While no significant beneficial impact on lipid profile was seen in the larger studies included in this review, there was a trend towards improvement in triglyceride levels in first episode patients[24]; further studies are required.

Given that some metabolic outcomes were improved in patients with schizophrenia [23,24] and bipolar disorder[25] taking antipsychotic medication, and a recent animal study demonstrated efficacy of melatonin in attenuating antipsychotic-induced weight gain[34], there are positive indications for the adjunctive use of melatonin. It was also suggested that the variation in efficacy may be partly explained by the relative metabolic risk associated with different antipsychotics[25]. Melatonin reduced weight gain in patients receiving medium risk antipsychotics (quetiapine and risperidone), an effect that was not seen in patients receiving high risk antipsychotics (clozapine and olanzapine)[25]. Therefore, future studies should also investigate the differential impact of adjunctive melatonin therapy on individual antipsychotic medications.

TD

Three studies in the current review assessed the impact of melatonin on TD severity using the AIMS, with one group suggesting that both duration and dosage of melatonin therapy are pertinent to alleviating symptoms of TD. Shamir *et al*[27] initially found no beneficial impact of a low dose of melatonin on TD, yet their later

investigation using a higher dose of melatonin for a prolonged period suggested clinical efficacy for symptoms of TD[27]. However, these results were not replicated in a further study[28]. While melatonin has demonstrated efficacy in attenuating symptoms of TD in animal models, it has been suggested that this may be due to anti-dopaminergic activity masking the movements, as opposed to treating TD *per se*[35].

Cognitive function

It is well established that schizophrenia is associated with impairments across a wide range of cognitive domains[36]. The current review identified only one study whose primary objective was to observe the effect of add-on melatonin on cognitive function in patients with schizophrenia[29]. While a test of memory function (RAVLT) improved over six months in patients with schizophrenia, this improvement was in comparison to baseline assessments rather than controls[29]. Moreover, given the study design was open-label and conducted in a small sample size, this result requires further replication. Cognitive outcomes were assessed as a secondary outcome in a separate study whose primary objective was to observe the efficacy of melatonin as facilitator of reduction or discontinuation of chronic use of BZDs[30]. No cognitive improvements were observed in the cognitive battery (BACS), consistent with the literature suggesting that pharmacological adjuncts are yet to prove effectiveness in significantly enhancing cognition in patients with schizophrenia[37].

BZD discontinuation

One study in the current review investigated the effects of melatonin in facilitating reduction or discontinuation of chronic use of BZDs in patients with schizophrenia [12], concluding that adjunctive melatonin had no significant effect on BZD dosage or cessation over 24 wk. Moreover, any interpretation of secondary outcomes from this investigation would need to be considered within the context of BZD withdrawal.

Limitations

The interpretations from the current review are limited by the small sample sizes of included studies. Melatonin formulations and dosages differed across studies. Moreover, risk of bias assessment indicated that only one study was deemed at low risk of bias, with the remainder carrying moderate or high risk of bias. Furthermore, some samples included patients with diagnoses of schizophrenia and bipolar disorder, making it difficult to delineate the effect of melatonin for schizophrenia alone. It remains an open question whether efficacy of melatonin for sleep in people with schizophrenia endures over the longer term: future studies should address this important topic.

CONCLUSION

The current review synthesized the results of clinical trials investigating the effect of adjunctive melatonin therapy on any outcome in patients with schizophrenia. To date, investigated outcomes include sleep function, metabolic benefits, TD attenuation, cognitive function and as an adjunct to BZD discontinuation. Positive outcomes were demonstrated for the use of melatonin in improving sleep efficiency and circadian rhythm as well as certain metabolic outcomes, specifically in first-episode patients initiating antipsychotic treatment. One study reported benefit for the use of melatonin in attenuating TD, but this was not found in other studies. There was no observed benefit for the use of melatonin in improving cognitive function or facilitating BZD discontinuation in individuals with schizophrenia. Given that the pharmacokinetics of melatonin and interactions with other drugs are unclear, future studies investigating these in relation to specific antipsychotic medications are required. Moreover, the range of melatonin dosage used and the duration of the studies in the current review highlights that there is currently no standardized melatonin recommendation and the effects of contamination and different formulations are unknown.

ARTICLE HIGHLIGHTS

Research background

Schizophrenia is a chronic psychiatric condition consisting of positive and negative

symptoms causing significant impacts on life. Current treatment includes second-generation antipsychotics (SGAs), the use of which is associated with side effects including: increased metabolic risk, sleep dysfunction and extrapyramidal side effects (EPS). Exogenous melatonin has been demonstrated to attenuate sleep dysfunction in the general population, however its indication in schizophrenia has been relatively unexplored. The proven antioxidant and neuroprotective effects of melatonin suggest potential for therapeutic benefit in adjunctive treatment of schizophrenia, especially in attenuating side effects associated with SGAs.

Research motivation

Current therapeutic treatment for schizophrenia often causes side effects including increased cardiovascular and metabolic risk, sleep dysfunction and EPS. Adjunctive use of melatonin has been suggested to benefit sleep disturbances, however its indication in schizophrenia has remained unclear. Therefore, we synthesized the current evidence for the effect of adjunctive use of melatonin on any outcome in individuals with schizophrenia.

Research objectives

To synthesize clinical trials conducted to date that have investigated the use of melatonin as an adjunctive therapy for individuals with schizophrenia in improving any therapeutic outcome.

Research methods

A systematic literature search was conducted on MEDLINE (Ovid), Embase, PsychINFO, PubMed, CINAHL and Cochrane Library for clinical trials using melatonin as an adjunctive therapy that included a group of patients with schizophrenia. PRISMA guidelines were adhered to and the Cochrane risk-of-bias tool for randomized controlled trials was used by two authors to assess the trials independently, with consensus confirmed by a third reviewer.

Research results

A total of 15 trials were included for qualitative synthesis after assessing for eligibility and removing duplicates. The trials assessed the following primary outcomes: sleep (n = 6), metabolic profile (n = 3), tardive dyskinesia (n = 3), cognitive function (n = 2) and benzodiazepine discontinuation (n = 1).

Research conclusions

Positive outcomes were demonstrated for the use of melatonin in improving sleep efficiency and certain metabolic outcomes, specifically in first-episode patients initiating antipsychotic treatment. Currently, there is limited therapeutic indication for the use of melatonin in treatment of tardive dyskinesia, cognitive function or facilitating benzodiazepine discontinuation. Limitations included small sample sizes and no standardization of the duration and/or dosage of adjunctive melatonin used.

Research perspectives

Future studies are required to confirm these improvements, determine the pharmacokinetic interactions of melatonin with specific antipsychotic medications and develop a standardized duration and dosage of adjunctive melatonin treatment. Moreover, a long-term safety and efficacy profile remains to be determined.

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META-ANALYSIS

Hypomanic/manic switch after transcranial magnetic stimulation in mood disorders: A systematic review and meta-analysis

Andrea Miuli, Gianna Sepede, Gianfranco Stigliano, Alessio Mosca, Francesco Di Carlo, Giacomo d'Andrea, Aliseo Lalli, Maria Chiara Spano, Mauro Pettorruso, Giovanni Martinotti, Massimo di Giannantonio

ORCID number: Andrea Miuli 0000-0003-2431-0460; Gianna Sepede 0000-0003-3697-5574; Gianfranco Stigliano 0000-0001-9078-3851; Alessio Mosca 0000-0003-3832-1339; Francesco Di Carlo 0000-0001-8058-3426; Giacomo d'Andrea 0000-0002-6808-3960; Aliseo Lalli 0000-0003-0900-5724; Maria Chiara Spano 0000-0003-4986-6289; Mauro Pettorruso 0000-0002-4164-3040; Giovanni Martinotti 0000-0002-7292-2341; Massimo di Giannantonio 0000-0001-9681-8058.

Author contributions: Miuli A, Sepede G, Pettorruso M, Martinotti G and di Giannantonio M designed the research study; Miuli A, Stigliano G, Mosca A, Di Carlo F, d'Andrea G, Lalli A and Spano MC performed the research; Miuli A and Sepede G analyzed the data and wrote the manuscript; All authors have read and approve the final manuscript.

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Andrea Miuli, Gianna Sepede, Gianfranco Stigliano, Alessio Mosca, Francesco Di Carlo, Giacomo d'Andrea, Aliseo Lalli, Mauro Pettorruso, Giovanni Martinotti, Massimo di Giannantonio, Department of Neuroscience, Imaging and Clinical Sciences, "G. d'Annunzio" University of Chieti, Chieti 66100, Italy

Maria Chiara Spano, Department of Psychiatry Affective Neuropsychiatry, Sahlgrenska University Hospital, Göteborg 40530, Sweden

Giovanni Martinotti, Department of Pharmacy, Clinical Science, University of Hertfordshire, Herts AL10 9AB, Italy

Corresponding author: Francesco Di Carlo, MD, Doctor, Department of Neuroscience, Imaging and Clinical Sciences, "G. d'Annunzio" University of Chieti, ITAB-Via dei Vestini 33, Chieti 66100, Italy. francesco.dic@hotmail.it

Abstract

BACKGROUND

Nowadays there is an increasing use of transcranial magnetic stimulation (TMS) both in neurological and psychiatric fields. After Food and Drug Administration approval of TMS for the therapy of treatment-resistant depression, TMS has been widely used in the context of mood disorders (MD). However, growing reports regarding the possibility of developing hypomanic/manic switch (HMS) have generated concern regarding its use in MDs.

AIM

To investigate the actual risk of developing HMS due to TMS in the treatment of MD.

METHODS

We led our research on PubMed, Scopus and Web of Science on March 22, 2020, in accordance to the PRISMA guidelines for systematic review. Only double blind/single blind studies, written in English and focused on the TMS treatment of MD, were included. A meta-analysis of repetitive TMS protocol studies including HMS was conducted using RevMan 5.4 software. The assessment of Risk of Bias was done using Cochrane risk of bias tool. This protocol was registered on PROSPERO with the CRD42020175811 code.

RESULTS

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Grade B (Very good): 0
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Twenty-five studies were included in our meta-analysis: Twenty-one double blind randomized controlled trials (RCT) and four single blind-RCT (no. of subjects involved in active stimulation = 576; no. of subjects involved in sham protocol = 487). The most frequently treated pathology was major depressive episode/major depressive disorder, followed by resistant depression, bipolar depression and other MD. The majority of the studies used a repetitive TMS protocol, and the left dorsolateral prefrontal cortex was the main target area. Side effects were reported in eight studies and HMS (described as greater energy, insomnia, irritability, anxiety, suicidal attempt) in four studies. When comparing active TMS *vs* sham treatment, the risk of developing HMS was not significantly different between conditions.

CONCLUSION

Applying the most usual protocols and the appropriate precautionary measures, TMS seems not to be related to HMS development.

Key Words: Hypomanic/manic switch; Transcranial magnetic stimulation; Active *vs* sham comparison; Mood disorders; Adverse event; Safety

Core Tip: Transcranial magnetic stimulation (TMS) has been widely used in the context of mood disorders. The purpose of this review/meta-analysis was to examine the risk of developing a hypomanic/manic switch (HMS) during active TMS treatment of mood disorders. Twenty-five double blind/single blind studies were included in the quantitative synthesis. When comparing active TMS *vs* sham treatment, we did not find any significant difference in the risk of developing HMS between conditions. So, we can conclude that, applying the appropriate precautionary measures, TMS seems not to be related to HMS development.

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INTRODUCTION

Non-invasive brain stimulation is a complex of neuromodulation techniques that have a therapeutic effect by stimulating the nervous system[1]. Transcranial magnetic stimulation (TMS) uses the principle of magnetic induction to modulate the neural circuitry[2]. Some electrical currents pass through a coil to induce repetitive magnetic field pulses that, if applied on the scalp, can stimulate target brain regions depolarizing the underlying neurons[3]. Depending on the stimulation frequency, cortical activity can be inhibited [low frequencies (LF) ≤ 1 Hz] or improved [high frequencies (HF) ≥ 5 Hz][4].

There are different protocols based on the number of pulses administrated (single pulses or paired pulses TMS)[5] or specific intervals between trains [like intermittent theta burst stimulation (TBS)[6], but one of the most used protocol is repetitive TMS (rTMS) where the pulses are applied as repetitive stimulation trains set at a specific frequency[4].

The use of rTMS has found an application in the field of substance[7] and non-substance addiction[8] but also in major psychiatric disorders such as post-traumatic stress disorder, schizophrenia and obsessive–compulsive disorder and in suicide[9-12]. It has also been used in the treatment of bipolar disorder, with good results in the treatment of depressive states and controversial results in mania[13]. In particular, TMS was approved by Food and Drug Administration in 2007 as a therapy for the treatment resistant depression (TRD)[14]. The standard protocol used in the treatment

of depression provides 75 trains *per* session for a total of 3000 pulses over about 35 min generated at 120% of resting motor threshold at 10 Hz, train duration of 4 s[14,15].

The role of the left dorsolateral prefrontal cortex (LDLPFC) in the pathophysiology of depression has been widely demonstrated with numerous evidences from functional imaging[16]. TMS, stimulating the DLPFC, is able to increase the neuronal excitability and to induce growth of the new connections having an antidepressant effect[17], both as a single treatment and as an add-on to antidepressants[18]. Some evidence, in fact, suggests that it may increase or decrease the neural excitability producing lasting changes in the efficiency of the synaptic transmission known as long-term potentiation and long-term depression[3,19].

When provided within recommended guidelines[20], rTMS is a very safe and well-tolerated technique both in the elderly[21] and in children[22] and has shown a favorable profile compared to antidepressant medications[23,24].

The most common side effects of TMS are headache, neck pain and local pain during the treatment at the site of stimulation[25]. The serious side effects are typically uncommon: Those reported were seizures, noted in less than 1% of healthy subjects and in patients with neurological morbidities and/or epilepsy[20,26], and hearing impairment, preventable with adequate protection[27]. Another potential side effect of TMS is the development of hypomanic/manic switch (HMS)[24,28].

HMS is one of the most critical events in bipolar disorder, affecting the severity of illness and being associated with an increased risk of suicide[29]. It can be linked to antidepressant treatments, and therefore antidepressants should be associated with mood stabilizers in bipolar patients[30]. Following the Diagnostic and Statistical Manual of Mental Disorders-5 criteria, hypomanic symptoms subsiding after stopping the antidepressants are called "antidepressant-induced hypomania", otherwise the episode can be defined as a true HMS[31,32].

During TMS treatment, cases of HMS were described in some reports[33,34], but to date the risk of TMS-induced HMS has not been yet extensively reported.

The purpose of this study was therefore to examine the actual risk of developing HMS due to TMS in the treatment of mood disorders, providing both qualitative and quantitative synthesis.

MATERIALS AND METHODS

The statistical methods of this study were reviewed by Gianna Sepede (GSe), who has qualified experience in Biomedical Statistics, Systematic Reviews and Meta-analysis.

Our systematic review was conducted to study the risk of developing HMS in a population of patients with mood disorders. We led our research on PubMed, Scopus and Web of Science (WoS) on March 22, 2020 using the following search strategy: (1) PubMed: (TMS OR Transcranial Magnetic Stimulation) AND (side effect OR adverse event) AND (depression OR manic OR bipolar OR hypomanic OR switch) NOT review NOT (animal OR rat OR mouse); (2) Scopus: [TITLE-ABS-KEY (tms) OR TITLE-ABS-KEY (transcranial AND magnetic AND stimulation) AND TITLE-ABS-KEY (side AND effect) OR TITLE-ABS-KEY (adverse AND event) AND TITLE-ABS-KEY (depression) OR TITLE-ABS-KEY (manic) OR TITLE-ABS-KEY (bipolar) OR TITLE-ABS-KEY (hypomanic) OR TITLE-ABS-KEY (switch) AND NOT TITLE-ABS-KEY (review) AND NOT TITLE-ABS-KEY (animal) OR TITLE-ABS-KEY (rat) OR TITLE-ABS-KEY (mouse)]; and (3) WoS: [(TMS OR Transcranial Magnetic Stimulation) AND (side effect OR adverse event) AND (depression OR manic OR bipolar OR hypomanic OR switch) NOT review NOT (animal OR rat OR mouse)]

All the procedures are in accordance with the PRISMA guidelines for systematic review[35]. Exclusion criteria, both for the first and the second phase of the screening, were: (1) Non-original research (*e.g.*, review, commentary, editorial, book chapter); (2) Non full-text article (*e.g.*, meeting abstract); (3) Language other than English; (4) Animal/*in vitro* studies; (5) Non double blind randomized controlled trial (DB-RCT) or single blind-RCT (SB-RCT) design; (6) Use of other neuromodulation techniques (*e.g.*, tDCS, MST); (7) Treatment of other conditions unrelated to mood disorders and (8) Data not reported.

We found 702 articles (PubMed = 80; Scopus = 338; WoS = 284). After removing the duplicates (No = 239), we screened 463 records and, of all these, 80 were non-original articles (review, meta-analysis, commentary, letter to the editor without data available), 267 were not related to the focus of the review (animal/*in vitro* studies, no DB-RCT or SB-RCT design, open label study, no sham comparison, no mood disorder treated, no TMS treatment), and 23 were not written in English. Out of 93 articles

assessed for eligibility, 46 were case report/series, 19 were not relevant to the subject (no DB-RCT or SB-RCT design, open label study, no sham comparison, no mood disorder treated, no TMS treatment) and three articles were not available. Twenty-five articles, finally, were taken into consideration for qualitative synthesis.

The process was conducted individually by AM, GS and Amo, creating an Excel database. For doubtful cases, the eligibility was discussed with GM, MP or MdG. These research methods were approved by PROSPERO (CRD42020175811 identification code). The method is summarized in Figure 1.

Risk of bias

The assessment of risk of bias was measured independently by AM, GS and AMo using the Cochrane risk of bias tool (Figure 2)[36]. This result was discussed with GSe and evaluated by MP, GM and MdG.

Quantitative analysis

The main outcome was to calculate the risk of developing HMS with TMS therapy in a population with mood disorders, so an active *vs* sham treatment comparison was conducted. The meta-analysis was performed using Review Manager Software v 5.4 [37]. Provided that HMS is an uncommon side effect and in order to include the studies with an event frequency of zero, a risk difference (RD) and not a risk ratio was applied[38,39].

The RD of the HSM for each individual article was calculated and, therefore, computed together obtaining a Fixed Effect with 95% confidence interval (CI). Statistical significance was set for values of $P < 0.05$.

We used I^2 to calculate the heterogeneity of the studies: $I^2 < 30\%$ low heterogeneity; $30\% < I^2 < 60\%$ moderate heterogeneity; $60\% < I^2 < 75\%$ substantial heterogeneity; $I^2 > 75\%$ high heterogeneity[40].

In case of heterogeneous results, a meta-analysis *per* categorical variable level was performed to evaluate the influence of categorical moderators on study outcomes. The final result is shown in the Forest Plot.

In order to assess potential publication bias, a funnel plot of study effect sizes was visually inspected for asymmetry (Figure 3).

RESULTS

All the characteristics of the included articles are described in Table 1.

We obtained a total of 25 studies for our systematic review. Following our inclusion and exclusion criteria all of them were DB-RCTs except for four SB-RCTs[41-44].

Among the included studies, the most frequently treated pathology was major depressive episode (No = 10)[42,44-52] followed by resistant depression (No = 5)[43,44,53-55], bipolar depression (No = 4)[41,43,44,56], major depressive disorder (No = 3)[57-59] and other mood disorders (No = 6)[60-65].

We found four studies allowing the use of antidepressants: Fluoxetine[49], paroxetine[46], amitriptyline[48] and not specified molecules (tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors) [45].

The majority of the studies had LDLPFC as the main target area (No = 19)[41,42,44-53,56-60,62,64], although other areas have been stimulated, in particular: Right DLPFC (RDLPFC; No = 4)[44,53,55,65], bilateral (LDLPFC and RDLPFC; No = 4)[43,54,55,63] and other area (No = 1)[42], specifically the anterior cingulate.

The most used coil was the figure eight coil (No = 16)[41-49,51,53-56,59-63,65]. Other coils used were the double cone coil (No = 1)[42] and the H1 coil (No = 3)[52,58,64]. The number of studies where the type of coil was not specified were two[50,57].

The duration of the treatment also differed greatly in our sample: Most of our sample received 2 wk of acute treatment (No = 10)[41,43-47,49,51,59,61]. Other durations of acute treatment were 3 wk (No = 3)[42,54,56], 4 wk (No = 4)[48,52,58,65], 5 wk (No = 2)[50,63], 6 wk (No = 3)[53,55,64], only 1 wk (No = 2)[57,60] and less than 1 wk in just one study[62].

About the TMS technique used, most have used a rTMS protocol (No = 23)[41-55,57,59-63,65]. Other protocols were TBS at 50 Hz (No = 2)[56,59] and deep TMS (dTMS) at 18 Hz (No = 2)[58,64].

rTMS protocols

Based on the Hz set, the sample can be divided between those who have used LF

Table 1 Characteristics of the studies included in the systematic review

Ref.	Population (No total, No male, No subgroups, age ± SD of the subgroups)	Type of treatment	Protocol (type, Hz, No pulses/session, RMT, coil type, target area, treatment duration)	Mood Disorder Sub-type	Reported adverse events (yes, no, NS)	HMS (No tot)	Drop out due to HMS
Trevizol *et al* [53], 2019-A	Active TMS, No = 20, age = 66.8 ± 5.8 (M = 13). Sham = 12, age = 64.1 ± 3.7 (M = 3)	Only TMS	rTMS, 1 Hz, 465 impulse/session, 120% RMT, B-65 figure-8 coil, RDLPFC, 15 session AND rTMS, 10 Hz, 750 impulse/session, 120% RMT, B-65figure-8 coil, LDLPFC, 15 session	Late-life TRD	No (light and not worth mentioning)	0	no
Trevizol *et al* [53], 2019-B	Active TMS, No = 11, age = 66.1 ± 8.5 (M = 4). Sham = 12, age = 64.1 ± 3.7 (M = 3)	Only TMS	rTMS, 10 Hz, 1450 impulse/session, 120% RMT, B-65 figure-8 coil, LDLPFC, 15 session	Late-life TRD	Yes (TMS, No = 2; SHAM, No = 0)	1	no
Rao *et al*[65], 2019	Active TMS, No = 13, age = 39.8 ± 14.2 (M = 5). Sham = 17, age = 40.2 ± 14.6 (M = 11)	Only TMS	rTMS, 1 Hz, 12000 impulse/session, 110% RMT, B-65 figure-8 coil, RDLPFC, 20 session	MDE after traumatic Brain Injury	No (light and not worth mentioning)	0	no
Matsuda *et al* [64], 2020	Active TMS, No = 20, age = 43.4 ± 5.5 (M = 18). Sham = 20, age = 45.2 ± 7 (M = 19)	Only TMS	dTMS, 18 Hz, 1980 impulse/session, 120% RMT, H1 coil, LDLPFC, 30 session	Depression NS	No (light and not worth mentioning)	0	no
Li *et al*[59], 2020-A	Active TMS, No = 35, age = 47.1 ± 13.8 (M = 11). Sham = 35, age = 47.1 ± 12.4 (M = 11)	Only TMS	rTMS, 10 Hz, 1600 impulse/session, 100% RMT, figure-8 coil, LDLPFC, 10 session	Recurrent major depression	Yes (TMS, No = 12; SHAM, No = 8)	0	no
Li *et al*[59], 2020-B	Active TMS, No = 35, age = 47.1 ± 14.2 (M = 12). Sham = 35, age = 47.1 ± 12.4 (M = 11)	Only TMS	piTMS, 50 Hz, 1800 impulse/session, 80% RMT, figure-8 coil, LDLPFC, 10 session	Recurrent major depression	Yes (TMS, No = 9; SHAM, No = 8)	0	no
Bulteau *et al* [56], 2019	Active TMS, No = 12, age = 52.7 (M = 5). Sham = 14, age = 53.1 (M = 10)	Only TMS	iTBS, 50 Hz, 990 impulse/session, 80% RMT, figure-8 coil, LDLPFC, 15 session	BD	No	0	no
Siddiqi *et al* [63], 2019	Active TMS, No = 9, age = 43 ± 13 (M = 7). Sham = 6, age = 50 ± 18 (M = 4)	Only TMS	Bilateral rTMS, 10 Hz, 4000 impulse/session, 120% RMT, B-65 figure-8 coil., LDLPFC, 25 session AND Bilateral rTMS, 1 Hz, 1000 impulse/session, 120% RMT, B-65figure-8 coil, RDLPFC, 25 session	MDE after traumatic Brain Injury	Yes (TMS, No = 9; SHAM, No = 0)	0	no
Kaster *et al* [52], 2018	Active TMS, No = 25, age = 65.0 ± 5.5 (M = 17). Sham=27, age = 65.4 ± 5.5 (M = 15)	Only TMS	rTMS, 18 Hz, 6012 impulse/session, 120% RMT, H1 coil, LDLPFC, 20 session	Late-life MDE	No (light and not worth mentioning)	1	no
Xie *et al*[57], 2015	Active TMS, No = 35, age=65.3 ± 5.1 (M = 12). Sham = 26, age = 64.7 ± 4.2 (M = 8)	rTMS + shuganjieyu	rTMS, 10 Hz, NS impulse/session, 30% RMT, B-65NS coil, LDLPFC, 5 session	MDD	Yes (TMS, No = 14; SHAM, No = 13)	0	no
Levkovitz *et al* [58], 2015	Active TMS, No = 101, age = 45.1 ± 11.7 (M = 53). Sham = 111, age = 47.6 ± 11.6 (M = 58)	Only TMS	dTMS, 18 Hz, 1980 impulse/session, 120% RMT, H1 coil, LDLPFC, 20 session	MDD	No (light and not worth mentioning)	0	no
Kreuzer *et al* [42], 2015-A	Active TMS, No = 13, age = 43.5 ± 10.3 (M = 8). Sham = 12, age = 43.8 ± 10.5 (M = 4)	Only TMS	rTMS, 10 Hz, 2000 impulse/session, 110% RMT, B-65 double cone coil, Anterior Cingulate, 15 session	MDE	Yes (TMS, No = 7; SHAM, No = 8)	0	no
Kreuzer *et al* [42], 2015-B	Active TMS, No = 15, age = 46.1 ± 9.5 (M = 7). Sham = 12, age = 43.8 ± 10.5 (M = 4)	Only TMS	rTMS, 10 Hz, 2000 impulse/session, 110% RMT, B-65 figure-8 coil., LDLPFC, 15 session	MDE	Yes (TMS, No = 4; SHAM, No = 8)	0	no
George *et al* [62], 2014	Active TMS, No = 20, age=38.7 ± 15 (M = 18). Sham = 21, age = 46.1 ± 15.9 (M = 17)	Only TMS	rTMS, 10 Hz, 6000 impulse/session, 120% RMT, B-65 figure-8 coil., LDLPFC, 9 session	MDE	Yes (TMS, No = 7; SHAM, No = 6)	0	no

Lingeswaran [51], 2011	Active TMS, No = 9, age = 34 ± 10.5 (M = 3). Sham = 14, age = 37.26 ± 11.8 NS (M = 6)	Only TMS	rTMS, 10 Hz, 500 impulse/session, 100% RMT, B-65 figure-8 coil, LDLPFC, 10 session	MDE	No	0	no
Pallanti *et al* [54], 2010-A	Active TMS, No = 20, age=47.6 ± 12.33, (M = 9). Sham = 20, age = 47.85 ± 9.12 (M = 8)	Only TMS	Bilateral rTMS, 1 Hz, 420 impulse/session, 110% RMT, B-65 figure-8 coil., RDLPFC, 15 session AND rTMS, 10 Hz, 1000 impulse/session, 100% RMT, B-65 figure-8 coil., LDLPFC, 15 session	TRD	No (light and not worth mentioning)	0	no
Pallanti *et al* [54], 2010-B	Active TMS, No = 20, age = 51.2 ± 12.33, (M = 8). Sham = 20, age = 47.85 ± 9.12 (M = 8)	TMS + placebo	rTMS, 1 Hz, 420 impulse/session, 110% RMT, B-65 figure-8 coil., RDLPFC, 15 session	TRD	No (light and not worth mentioning)	0	no
Fitzgerald[55], 2008	Active TMS, No = 30, age = 45.7 ± 10.8 (M = 10). Sham = 28, age = 44.8 ± 11.4 (M = 15)	Only TMS	LF rTMS, 1 Hz, 900 impulse/session, 110% RMT, B-65 figure-8 coil., rDLPFC, 10 session	Depression NS	No (light and not worth mentioning)	0	no
Fitzgerald *et al* [44], 2007	Active TMS, No = 25, age = 46.8 ± 10.7 (M = 10). Sham = 25, age = 43.7 ± 10.2 (M = 9)	Only TMS	Bilateral rTMS, 10 Hz, 750 impulse/session, 100% RMT, B-65 figure-8 coil., LDLPFC, 30 session AND Bilateral rTMS, 1 Hz, 420 impulse/session, 110% RMT, B-65 figure-8 coil., RDLPFC, 30 session	TRD	No (light and not worth mentioning)	0	no
O'Reardon *et al*[50], 2007	Active TMS, No = 155, age = 47.9 ± 11 (M = 69). Sham = 146, age = 48.7 ± 10.6 (M = 72)	Only TMS	rTMS, 10 Hz, 3000 impulse/session, 120% NS coil, LDLPFC, 25 session	MDE	No (light and not worth mentioning)	0	no
Fitzgerald *et al* [43], 2006	Active TMS, No = 25, age = 46.8 ± 10.7 (M = 10). Sham = 25, age = 43.7 ± 10.2 (M = 9)	Only TMS	Bilateral rTMS, 10 Hz, 750 impulse/session, 100% RMT, B-65 figure-8 coil., LDLPFC, 30 session AND Bilateral rTMS, 1 Hz, 420 impulse/session, 110% RMT, B-65figure-8 coil., RDLPFC, 30 session	TRD	No (light and not worth mentioning)	0	no
Rumi *et al*[48], 2005	Active TMS, No = 22, age = 39.3 ± 12.8 (M = 3). Sham = 24, age = 38.9 ± 8.8 (M = 4)	TMS + Amitriptyline	rTMS, 5 Hz, 1250 impulse/session, 120% RMT, B-65 figure-8 coil, LDLPFC, 20 session	MDE	No (light and not worth mentioning)	0	no
Boggio *et al* [49], 2005	Active TMS, No = NS, age = NS (M = NS). Sham = NS, age = NS, (M = NS)	TMS + fluoxetine+ placebo	rTMS, 15 Hz, 3000 impulse/session, 110% RMT, B-65figure-8 coil, LDLPFC, 10 session	MDE in Parkinson's disease	No	0	0
Poulet *et al* [46], 2004	Active TMS, No = NS, age=NS (M = NS). Sham = NS, age = NS (M = NS)	TMS + paroxetine	rTMS, 10 Hz, 400 impulse/session, 80% RMT, B-65 figure-8 coil, LDLPFC, 10 session	MDE	No	0	no
Mosimann *et al* [47], 2004	Active TMS, No = 15, age = 60 ± 13.4 (M = 10). Sham = 9, age = 64.4 ± 13 (M = 5)	Only TMS	rTMS, 20 Hz, 1600 impulse/session, 100% RMT, B-65 figure-8 coil, LDLPFC, 10 session	MDE	Yes (TMS, No = 7; SHAM, No = 5)	1	no
Hansen *et al* [45], 2004	Active TMS, No = 6, age = 42.5 (M = 4). Sham = 7, age = 46, (M = 5)	TMS + antidepressant	rTMS, 10 Hz, 2000 impulse/session, 90% RMT, B-65 figure-8 coil, LDLPFC, 10 session	MDE	No	0	no
Nahas *et al* [41], 2003	Active TMS, No = 11, age = 42.4 ± 7.3 (M = 4). Sham = 12, age = 43.4 ± 9.3 (M = 5)	Only TMS	rTMS, 5 Hz, 1600 impulse/session, 110% RMT, B-65 figure-8 coil, LDLPFC, 10 session	BD	No (light and not worth mentioning)		no
Fitzgerald *et al* [66], 2003-A	Active TMS, No = 20, age = 42.4 ± 9.8 (M = 12). Sham = 20, age = 49C.15 ± 14.243 (M = 9)	Only TMS	rTMS, 1 Hz, 300 impulse/session, 100% RMT, B-65 figure-8 coil, RDLPFC, 10 session	BD,MDE, TRD	No (light and not worth mentioning)	0	no
Fitzgerald *et al* [66], 2003-B	Active TMS, No = 20, age = 45.55 ± 11.49 (M = 13). Sham = 20, age = 49.15 ± 14.243 (M = 9)	Only TMS	rTMS, 10 Hz, 1000 impulse/session, 100% RMT, B-65 figure-8 coil., LDLPFC, 10 session	BD,MDE, TRD	No (light and not worth mentioning)	1	no

Pascual-Leone *et al*[60], 1996	Active TMS, No = 17, age = 48.6 ± NS (M = 6). Sham = 17, age = 48.6 ± NS (M = 6)	Only TMS	rTMS, 10 Hz, 2000 impulse/session, 90% RMT, B-65 figure-8 coil, LDLPFC, 5 session	Psychotic depression	Yes (TMS, No = 7; SHAM, No = 7)	0	no

SD: Standard deviation; RMT: Resting motor thresholds; HMS: Hypomanic/manic switch; TMS: Transcranial magnetic stimulation; rTMS: Repetitive TMS; RDLPFC: Right dorsolateral prefrontal cortex; LDLPFC: Left dorsolateral prefrontal cortex; TRD: Treatment resistant depression; MDE: Major depressive episode; dTMS: Deep TMS; piTBS: Prolonged intermittent theta burst stimulation; iTBS: Intermittent theta-burst stimulation; BD: Bipolar depression; MDD: Major depressive disorder.

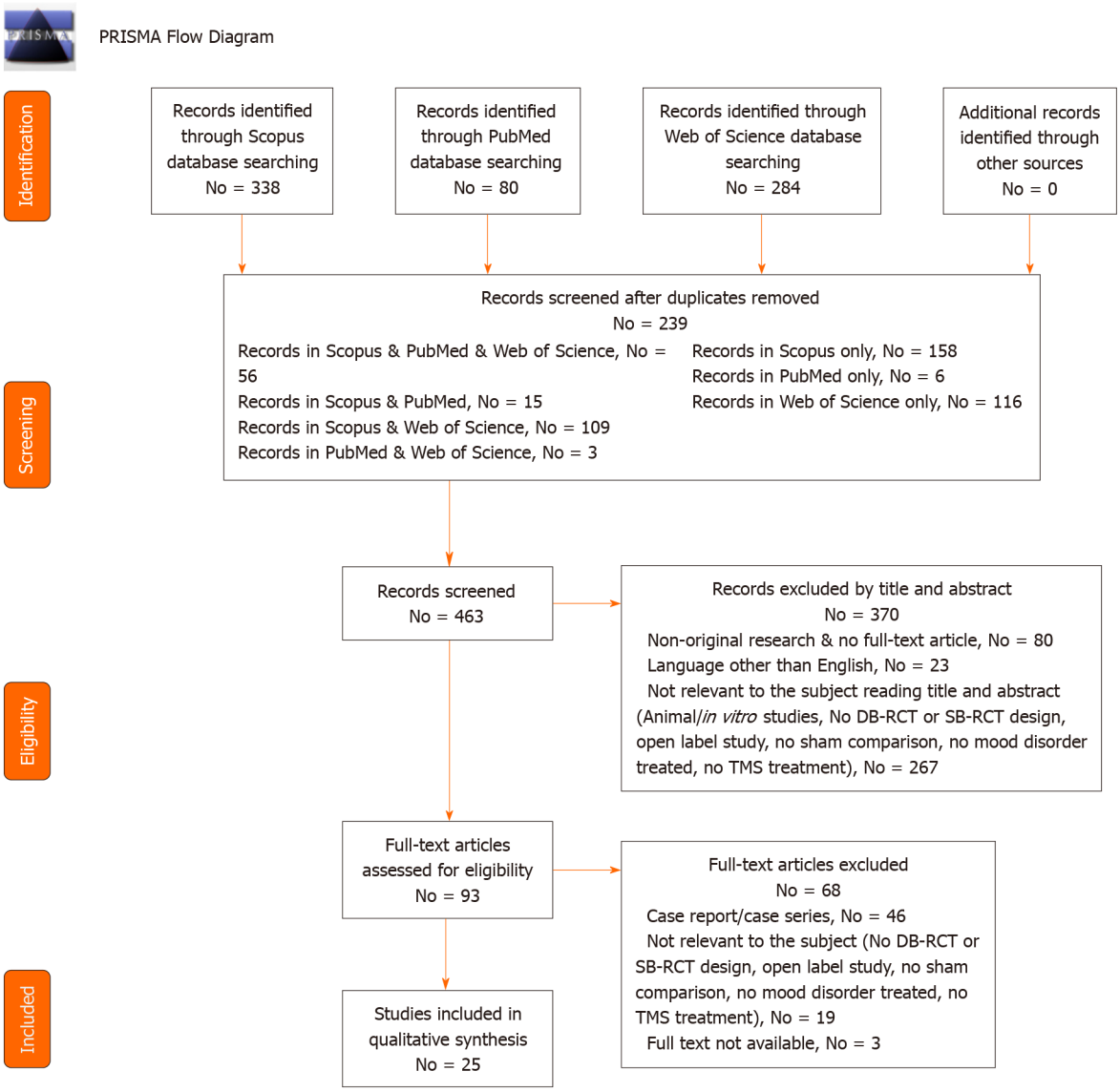

Figure 1 PRISMA flow diagram: Studies included in qualitative and quantitative synthesis. DB-RCT: Double blind randomized controlled trials; SB-RCT: Single blind randomized controlled trials.

treatment at 1 Hz (No = 7)[44,53-55,61,63,65] and those who have used a HF treatment (No = 21) divided in 5 Hz (No = 2)[41,48], 10 Hz (No = 15)[42-46,50,51,53-55,57,59,60,62,63], 15 Hz (No = 1)[49] and 20 Hz (No = 1)[47].

The number of pulses/session was very heterogeneous, more frequently 2000 pulses/session (No = 3)[42,45,60] and 3000 pulses/session (No = 2)[49,50].

Side effects

Only eight studies reported at least one side effect[42,47,53,59,60,62,63]. HMSs (described as greater energy, insomnia, irritability, anxiety and suicidal attempt in bipolar patients), were present in four studies[44,47,52,53] and, in particular, once in the sham group and three times in the active group. Only one episode of HMS was

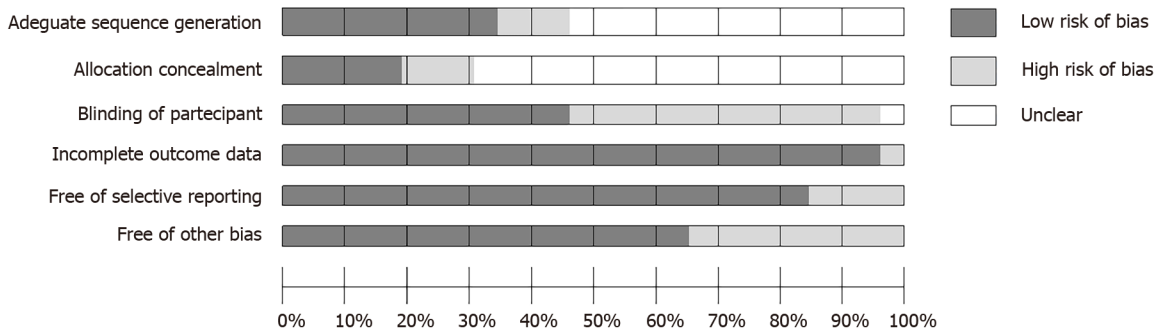

Figure 2 Risk of bias assessment.

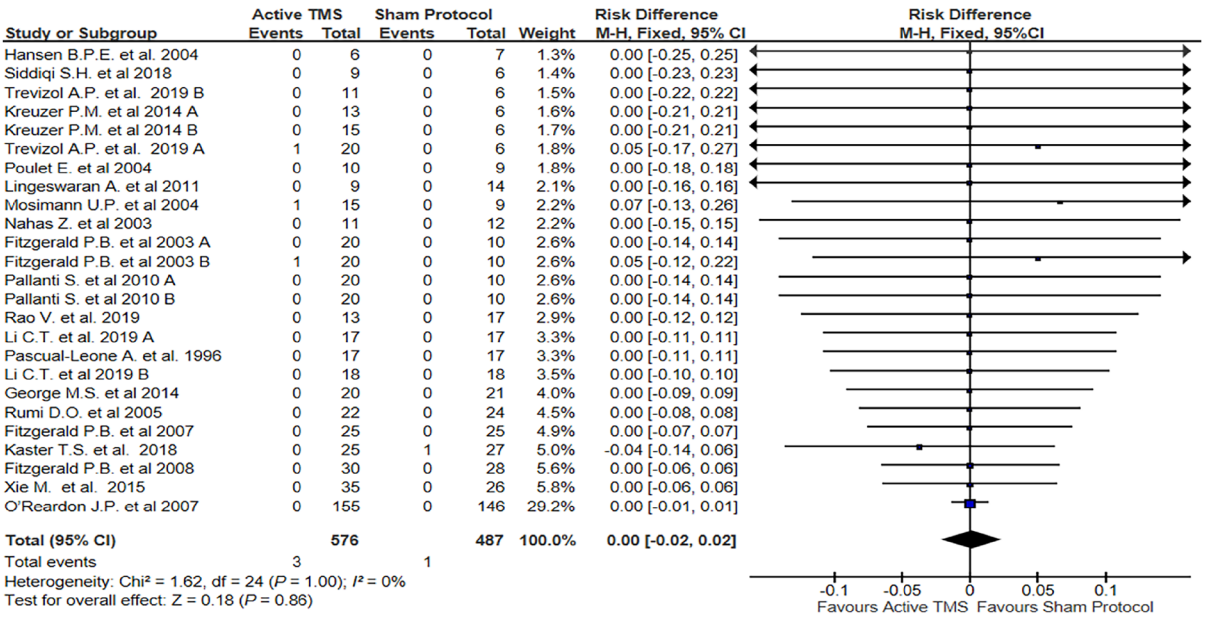

Figure 3 Forest plot: Risk to develop a hypomanic/manic switch after a transcranial magnetic stimulation protocol. TMS: Transcranial magnetic stimulation.

specifically reported[66], after stopping taking a mood stabilizer and after the end of the rTMS treatment. No drop-outs due to HMSs were reported. None of the studies that used antidepressants in addition to TMS treatment reported the onset of HMS[45,46,48,49].

Risk of bias

The results of the risk of bias assessment reveal a good quality of the reported data, as evidenced by the items "*Incomplete Outcome Data*" and "*Free of Selective Report*". However, only a few of the included studies accurately indicated the blinding method and the allocation concealment (Figure 2).

Meta-analysis of rTMS protocols

The meta-analysis of the 25 studies included (No. of subjects involved in active stimulation = 576; No. of subjects involved in sham protocol = 487), showed no significant results about the risk of developing HMS after TMS stimulation (RD = 0.00; 95%CI = -0.02-0.02; P = 1.00; I^2 = 0%) for a fixed effect.

The inspection of the funnel plot of the RD of the included studies (Fixed Effect) suggested a symmetry of the studies, showing the same concentration of studies on the left and on the right of the mean RD (Figure 4).

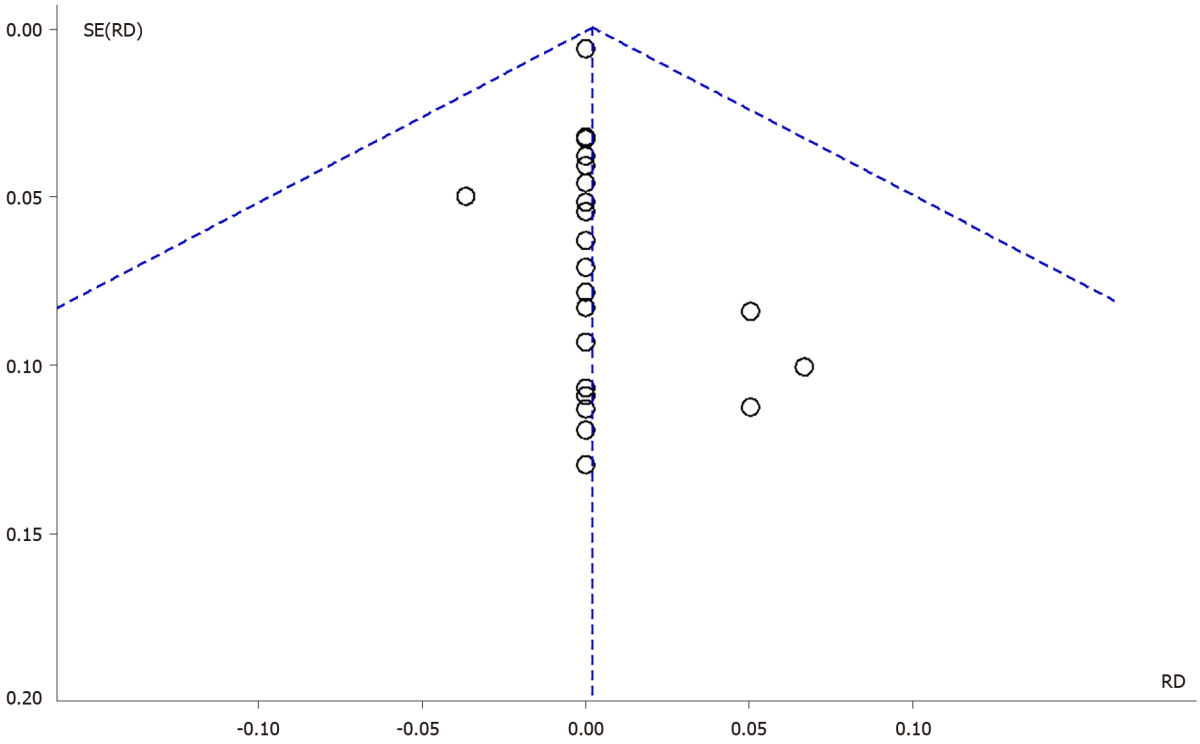

Figure 4 Funnel plot for publication bias. RD: Risk difference.

DISCUSSION

The mechanisms underlying HMSs in mood disorders are complex and still unknown, even if a main role of increased levels of dopamine and/or norepinephrine and of seasonal changes of neural activity were suggested[67]. Antidepressant treatments are well known triggers for HMSs, especially in bipolar disorders[68]. Due to its increasing use in the treatment of mood disorders, the same concern has been voiced about the safety of TMS. In particular, in a previous meta-analysis on the topic, it was hypothesized that HMS was induced by a too intensive treatment with TMS and an incorrect diagnosis of unipolar depression[69]. However, the most recent scientific literature regarding the use of TMS in mood disorders seems to deny the hypomanic effect of TMS. Nowadays, in fact, several TMS treatments (rTMS and TBS in particular) [6,70] are increasingly used not only for the therapy of TRD but also for the treatment of mood disorders in general, including bipolar disorders[71]. However, a critical role on the onset of HMS is probably played by the concomitant use of high-dosage antidepressant treatments[72,73], pointing out the importance of a deep and accurate anamnesis.

In our systematic review focused on RCTs using TMS to treat mood disorders, we found that only 4/25 studies reported a HMS as an adverse event, and the difference between sham and active treatment was not significant.

The most used protocol was rTMS, set at 10 Hz (16/25 studies), 120% RTM (9/25 studies) with a variable number of pulses (the most common included the 2,000 pulses/session present in 3/26 studies). The most investigated brain area was the DLPFC, (24/25 studies); only one study examined the AC with a deep-brain stimulation technique. However, in the context of the DLPFC, lateralization to the right seems preferred in the context of a LF stimulation (all eight studies in question stimulate the RDLPFC) while the left one in the context of a HF (all of the remaining 17 studies stimulate the LDLPFC). The application of the most widely used research protocols could therefore be a useful method to avoid the genesis of HMSs.

Another aspect highlighted by our results is the absence of drop-outs due to HMS. Considering the severity of HMS symptomatology, the absence of drop-outs is a further indication of the TMS safety in the treatment of MD.

CONCLUSION

Considering the still not understood and complex mechanisms underlying the development of HMS, from the results of our systematic review of the literature and from our meta-analysis (although in the context of a statistical non-significance), it seems clear that by applying the most usual protocols of rTMS and TBS and applying, where necessary, the appropriate precautionary measures (for example going on with mood stabilizers) TMS can be considered a safe technique also in the context of mood disorders.

ARTICLE HIGHLIGHTS

Research background

One of the most innovative and most investigated non-invasive brain stimulation techniques is Transcranial Magnetic Stimulation (TMS). This device has received Food and Drug Administration approval for the treatment of various neurological (headache) and psychiatric (treatment resistant depression) disorders. Several studies have been conducted to find new applications of TMS in conditions that do not respond or partially respond to standard psychopharmacological therapies.

Research motivation

TMS is an increasingly used technique in the neurological and psychiatric fields. One of the greatest concerns about its use is the possibility of developing severe side effects such as hypomanic/manic switches (HMS).

Research objectives

The aim of this meta-analysis is to quantify the risk of developing HMS after treatment with TMS in mood disorders and to evaluate the drop-out rate due to that adverse event.

Research methods

The search was conducted using PubMed, Scopus and Web of Science databases on March 22, 2020. All procedures were registered on PROSPERO and performed according to the PRISMA guidelines. Only double blind/single blind articles, written in English were included. RevMan 5.4 Software for Windows was used to perform the meta-analysis.

Research results

Of the 25 eligible studies, only four HMSs were described. No dropouts were reported due to symptoms severity.

Research conclusions

Our data confirm that, by applying appropriate psychopharmacological and anamnestic precautions, TMS is a safe technique for treating mood disorders.

Research perspectives

Greater uniformity of protocols, their online registration and the timely reporting of side effects on scientific papers could guarantee a more accurate analysis of the health risks induced by TMS in future meta-analyses.

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SCIENTOMETRICS

Knowledge domain and emerging trends in visual hallucination research: A scientometric analysis

Min Zhong, Zhuang Wu, Xu Jiang, Bo Shen, Jun Zhu, Li Zhang

ORCID number: Min Zhong 0000-0002-3987-662X; Zhuang Wu 0000-0002-0491-2416; Xu Jiang 0000-0002-3278-6883; Bo Shen 0000-0001-7763-3496; Jun Zhu 0000-0002-9034-2324; Li Zhang 0000-0003-1092-7531.

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Min Zhong, Zhuang Wu, Xu Jiang, Bo Shen, Jun Zhu, Li Zhang, Department of Geriatric Neurology, Affiliated Brain Hospital of Nanjing Medical University, Nanjing 210029, Jiangsu Province, China

Li Zhang, Institute of Neuropsychiatric Diseases, Affiliated Brain Hospital of Nanjing Medical University, Nanjing 210029, Jiangsu Province, China

Corresponding author: Li Zhang, PhD, Doctor, Professor, Department of Geriatric Neurology, Affiliated Brain Hospital of Nanjing Medical University, No. 264 Guangzhou Road, Nanjing 210029, Jiangsu Province, China. neuro_zhangli@163.com

Abstract

BACKGROUND

Visual hallucination (VH) refers to a spontaneous visual perception without corresponding external stimuli and often occurs in ophthalmological and neuropsychiatric disorders. It is associated with poor quality of life, and increased patient hospitalization and nursing home admission. To date, a scientometric analysis of research on VH is lacking.

AIM

To objectively summarize the features of VH research and gain insights into the emerging trends in research on VH.

METHODS

CiteSpace V was used in this article. Publication outputs, document types, geographic distributions, co-authorship status, research hotspots, and co-citation status were analyzed. A total of 2176 original articles and 465 reviews were included in the database downloaded from the Web of Science Core Collection. We selected the top 50 most cited or occurring articles or items to create a visualized network with a 1-year interval. In the document co-citation analysis stage, we performed clustering analysis on co-cited references, and log likelihood tests were used to name the clusters.

RESULTS

The results showed that most publications can be classified into neurology, sports, and ophthalmology studies. In addition, North America, Europe, Asia and Australia published the most documents. Some well-known authors have always had a leading role in this field; meanwhile, new authors keep emerging. A relatively stable cooperation has been formed among many authors. Furthermore,

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neuropsychiatric symptom and functional connectivity are the top hotspots. Research on VH in dementia with Lewy bodies and Parkinson's disease (PD) have received much attention. Studies on VH in PD are likely to be the new emerging trends in the future, especially the mechanisms of VH.

CONCLUSION
Research on VH has formed a complete system. More large-scale clinical and in-depth basic research are required to better understand the mechanisms underlying VH, which will contribute to our understanding of the patho-physiology and therapeutic options for VH.

Key Words: Visual hallucination; Psychiatry; Parkinson's disease; Dementia with Lewy bodies; CiteSpace; Scientometric

Core Tip: Visual hallucination (VH) is very common and research on VH keeps emerging. In this review, CiteSpace V was used to objectively summarize the features of VH research and gain insights into the emerging trends for research on VH. Publication outputs, document types, geographic distributions, co-authorship status, research hotspots, and co-citation status were analyzed.

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INTRODUCTION

Visual hallucination (VH) is a spontaneous visual perception in the absence of corresponding external stimuli; it has been aptly described by Collerton *et al*[1] as seeing things that are not there. It is a common symptom often associated with eye diseases (*e.g.*, Charles Bonnet syndrome [CBS])[2,3] and neuropsychiatric conditions (*e.g.*, Parkinson's disease [PD][4-6], dementia with Lewy bodies [DLB][7-9], epilepsy[10], schizophrenia[11,12], occipital stroke[13]). In some cases, it can be a side effect of medications, such as anticholinergics, dopamine agonists, and a wide range of medications modulating diverse neurochemical pathways[14]. VH is related to the poisoning and withdrawal of alcohol, cannabis, and cocaine and other physical conditions such as physical illness and stress[15-17]. A small percentage of healthy individuals have reported experienced VH in their life[18,19]. Although VH occurs in a significant proportion of cases, it mostly occurs sporadically in healthy people. The frequent occurrence of VH tends to be a signal of pathology[20].

The prevalence of VH varies widely in different diseases. Almost 40% of people with eye or visual pathway disease, typically macular degeneration, develop VH known as CBS[3]. VH is also a core feature for DLB diagnosis and has a 54%-70% prevalence in DLB[21,22]. Furthermore, 22%-78% of patients with PD suffer from VH [23]. Hallucinations have been described as a hallmark of schizophrenia, showing a prevalence of 36.5%[24]. The lifetime prevalence of VH in healthy subjects is 3.4%[25]. Progressive and recurrent VH is often associated with a likelihood of poor life quality, increased patient hospitalization, and nursing home admission[26,27]. In addition, it is a risk factor for dementia and is associated with the high mortality rate of patients with dementia[28,29].

Extensive research on VH has been widely conducted worldwide, and a large number of papers have been published. However, to the best of our knowledge, VH has not been systematically reviewed by scientometric analysis. The knowledge domain and emerging trends of existing research have not been fully understood. Therefore, objectively summarizing the features of VH and gaining insights into the new emerging trends for research on VH are crucial. This work conducted a systematic

and scientific analysis of the research on VH by using CiteSpace, a powerful tool for data analysis and visualization[30]. The findings elaborate on annual publications, document type, co-country, co-authorship, burst keywords, and document co-citation.

MATERIALS AND METHODS

Data collection

Our data were retrieved from the Web of Science Core Collection (WOSCC), which is the specified article data source for CiteSpace as it contains citation information. An initial topic search for 'visual hallucination' resulted in 3178 records published between 1985 and 2020. We filtered out conference abstracts and proceedings and corrigendum documents, which were less representative[31]. We believe that original research papers can better represent the state of the research field compared with other types of documents. Review papers can attach additional importance to the representative papers selected by domain experts[32]. A total of 2641 publications which consist of 2176 articles and 465 reviews, were selected as a database to be used in subsequent analysis (537 were excluded). Then we downloaded raw data, which included full records and cited references, from WOSCC in the form of plain text files.

Statistical methods

CiteSpace V based on Java was utilized for information visualization analysis, which provides insights into VH research and makes it easy to effectively follow the progress of information[30,32,33]. In this study, we selected the top 50 most cited or occurring articles or items to create a visualized network with a 1-year interval. In the document co-citation analysis stage, we performed clustering analysis on co-cited references, in which similar references were combined to determine related research fields. Moreover, log likelihood tests (LLRs) typically provide the unique and best results that consider all of the contents of a cluster; thus, we extracted noun phrases from the keywords of articles that cited a cluster on the basis of LLR to characterize the nature of the cluster[34]. Office Excel 2019 was also applied to our study.

RESULTS

Characters of publication outputs

To determine the general trend of VH research, we summarized the publications of original articles and reviews over the years. The earliest record we found in WOSCC was published in 1999. The results in Figure 1 show that the publication outputs are mainly in a fluctuating growth trend, with an increase from 61 in 1999 to 182 in 2020.

Analysis of document type

Dual-map overlays in CiteSpace can help reveal the trends of the scientific portfolio under a background of a global map of scientific literature. The background has two base maps, the left part shows a base map of citing journals and the right part shows the cited journals, each containing a network of over 10000 journals. Similar journals form a cluster, which is labeled on the basis of the terms in the journal titles of the cluster. The reference relationships between the left and right parts are connected by colored curves that indicate how a current research obtains inspiration from previous works[33]. The vertical and horizontal axes of the ellipse in the left part respectively indicate the number of articles and authors published in journals. The number of citations determines the size of the ellipse in the right part[34]. Figure 2 shows a dual-map overlay visualization of the citing and cited papers with regard to the topic search on VH. Four threads of citations stand out. They originate from four clusters in the citing base map: the orange threads from the cluster of molecular, biology and immunology, the pink threads from the cluster of neurology sports and ophthalmology, the blue threads from the cluster of psychology, education and health, and the green threads from the cluster of medicine, medical and clinical. These threads generally point to two clusters in the cited base map. One is the cluster of molecular, biology and genetics; the other is the cluster of psychology, education and social. New developments are highlighted in red from the publication point of view. The new progression of VH is in the field of mathematics, systems and mathematical, which is worth further research.

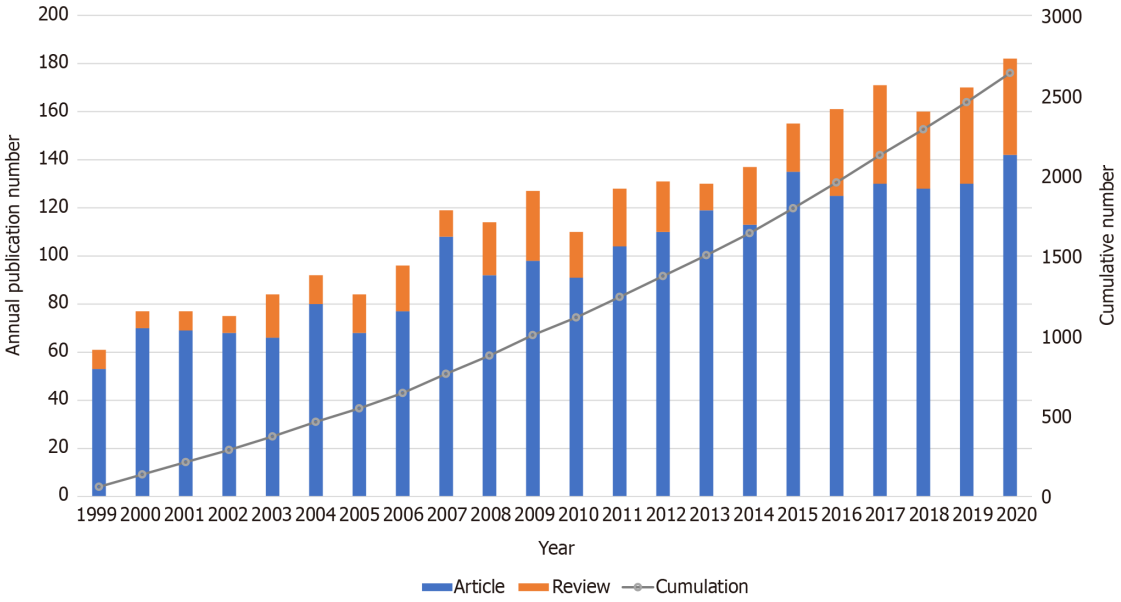


Figure 1 Publication output performance during 1999-2020.

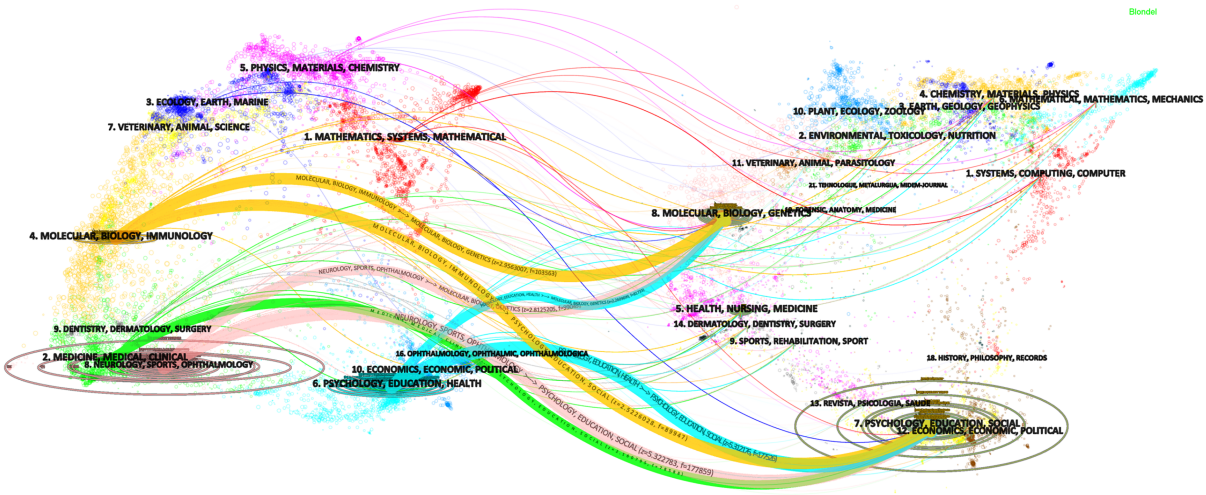


Figure 2 Dual-map overlay for final document storage. The nature of each region is labeled by the journal of the corresponding region. The colored curve represents the reference path from the citing base map on the left to the cited base map on the right. The number of articles and authors published in journals determines the size of the ellipse in the graph.

Geographic distribution of the publications

The total number of publications by country was analyzed to understand their geographic distribution. We checked the names of all countries and merged some regions into corresponding countries. The analysis is presented in Figure 3. The larger the published quantity, the deeper the color. The United States, England, and Japan were the top three countries.

Distribution of authors and co-authorship

Co-authorship was analyzed to detect active authors and their cooperation in the field. For accuracy and objectivity, we reviewed all of the authors' names to reduce misidentification. The result is displayed in Figure 4. The font size of each author's name corresponds to the number of articles by each author, which represents the contribution of the author to this field. The color of the tree ring stands for the year in which the author published his or her articles. The thickness of the tree ring represents the number of his or her articles in a particular year. Collaborative intensity between authors is indicated by the thickness of a connecting line. Chronological order information is included in the color of the lines that appear together between nodes:

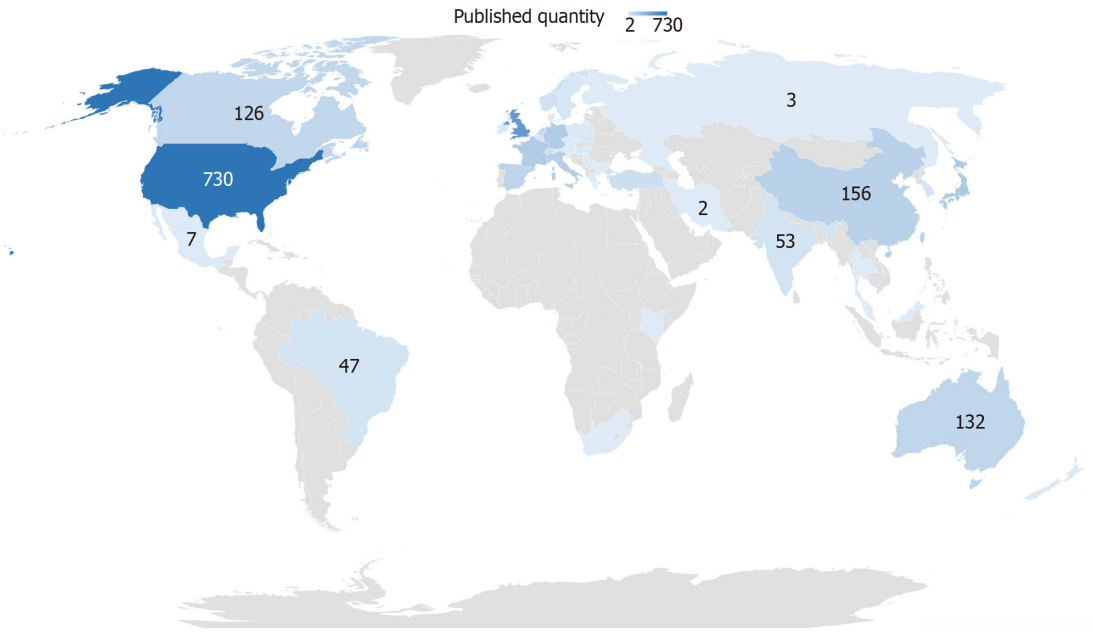


Figure 3 Geographic distribution of the countries. The figures represent the corresponding country's total published quantity on visual hallucination between 1999 and 2020. The larger the published quantity, the deeper the color.

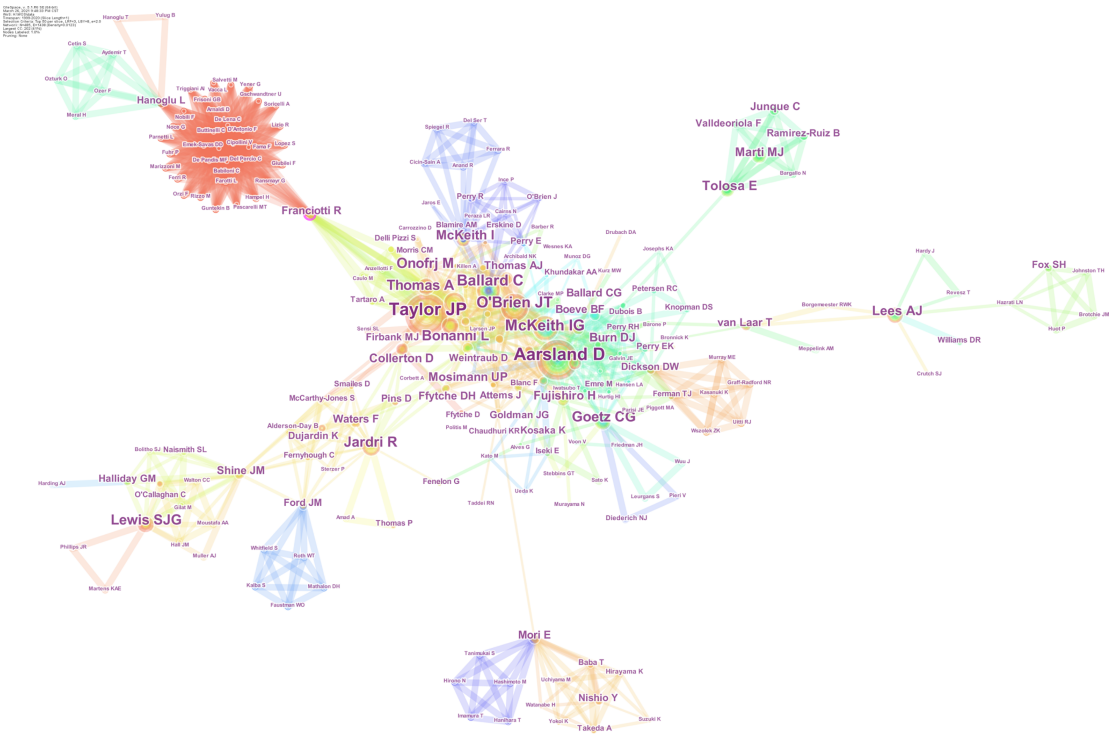


Figure 4 Map of active authors in the visual hallucination field. The font size of each author's name represents the article counts of each author. Different colors inside the circle represent different time intervals. The collaborative intensity between authors can be seen from the thickness of the connecting line.

blue represents the oldest, green the middle, and red the newest. In summary, top-productivity authors have greatly contributed to this field, and a relatively stable cooperation has formed among many authors. More than 485 authors have made contributions to the research on VH. Among these authors, Taylor JP (40 articles) ranked first, followed by Aarsland D (38 articles), O'Brien JT (25 articles) and McKeith IG (24 articles).

Keywords burst detection

The topics involved in VH can be described by the keywords extracted from each

article in the dataset[31]; however, new insights into this field should be determined. The burst patterns of keywords reveal research hotspots in the field of VH because a burst of a keyword is a sharp increase of the keyword that is likely to have a great influence[32]. Among the 340 selected keywords, 104 have the strongest strength of burst during 1999-2020. Figure 5 lists the top 104 keywords with strongest burst. The blue line represents the timeline from 1999 to 2020, and the red line stands for the years when a keyword has burst. Among the top 104 keywords, particular attention was paid to those keywords that remain to have a burst until 2020, such as 'neuropsychiatric symptom' and 'functional connectivity'. Other burst keywords included 'auditory verbal hallucination, diagnostic criteria, functional magnetic resonance imaging (fMRI), meta-analysis, management, impulse control disorder, sleep behavior disorder, and default mode network'.

Analysis of co-cited references

The most outstanding function in CiteSpace is co-citation analysis, which was used to analyze all references of the 2641 documents downloaded from WOSCC, and the top 50 most-cited references each year was select. As a result, 776 nodes of references were generated and automatically linked in the visual interface. Only if two references were cited by the same document could they be connected. If two references were often cited by documents together, they tended to have a close relationship, so they were classified to the same cluster. In our analysis, the smallest clusters were filed out, and 69 clusters were left. The information on all references formed the intellectual base of this field, and 776 highly cited references were classic documents[32]. By mining the most classic references in each cluster, we can understand the general development process and research frontiers of the VH research field. An overview of a co-cited reference network is shown in Figure 6. The overall structure can be divided into three major parts: the upper left part of the nodes and links, which represent the co-citation of the first 7 years from 1999 to 2005, is essentially in blue. The central part of the network is mainly in green and yellow, which indicates that the relationship was probably constructed between 2006 and 2012. The bottom right part is predominantly in red, and connections are formed credibly in the most recent 8 years.

The quantity of the clusters can be measured *via* two indexes: Modularity Q value and Silhouettre value. Modularity Q value is a network modularization index with a value range of 0-1. $Q > 0.3$ indicates that the structure of a certain cluster is significant. Silhouettre value indicates the homogeneity or consistency of the cluster. The closer the S value is to 1, the better the homogeneity of the cluster is. When $S > 0.5$, the clustering result can be considered reasonable; when $S > 0.7$, the clustering result is efficient. The number of references constituting the cluster must be greater than 10 [35]. Table 1 lists the major clusters of co-cited references selected from 69 clusters. In general, the 10 clusters in the table represent 10 research directions in the field.

The earliest formed cluster is Cluster #1 senile dementia, whose average publication year is 1997. It has more than 100 references as its members. A common theme of this cluster is identifying DLB from Alzheimer's disease, which are both belong to senile dementia[36-38]. The 82 members of Cluster #2 are evenly published in 2001, mainly involve PD with hallucination and focus on phenomenology[39]. Cluster #5 Charles bonnet syndrome, #3 incident dementia, and #6 schizophrenia introduce CBS, DLB and schizophrenia, respectively. These diseases all have VH as a hallmark. The research foundation in the three fields was mostly established in 2001, 2005, and 2014. Their high silhouette values indicate a high homogeneity of the clusters. Importantly, Cluster #2 and #3 are very close to each other in Figure 6; this may be partly because both PD and DLB are Lewy bodies (LB) diseases[40], and persistent VH is related to the spread of LBs[29].

The largest cluster is Cluster #0 labeled body disease, which includes 154 complete references. These references' average publication year is 2011. Cluster #4 Parkinson's disease dementia (PDD), which has 70 group members with an average publication year of 2014. These two clusters constitute the main body of VH research in the last decade and are closely connected in Figure 6 because they include research that introduces PD with VH. Cluster #0 focuses on the evidence of changes in brain structure and function in PD with VH[41,42], while Cluster #4 is mainly about the comparison and management of VH in PDD and DLB[43,44].

Other clusters, such as Cluster #7 impulse control disorder and Cluster #9 REM sleep behavior disorder (RBD) are formed more recently. Impulse control disorder and RBD are both included in the non-motor symptoms of PD. The co-cited references in these two clusters demonstrate the relationship between these two symptoms and VH respectively. Cluster #10 5-HT2A involves the investigation of serotonin 2A receptor in PD with psychosis (PDP)[45,46]. It includes publications averagely in 2010.

Table 1 Major clusters of co-cited references

Cluster	Size	Silhouette	Mean (year)	Label (LLR)
0	154	0.727	2011	Body disease
1	110	0.883	1997	Senile dementia
2	82	0.715	2001	Hallucinosis
3	71	0.77	2005	Incident dementia
4	70	0.903	2014	Parkinson's disease dementia
5	57	0.957	2001	Charles bonnet syndrome
6	52	0.968	2014	Schizophrenia
7	47	0.822	2008	Impulse control disorder
9	11	0.975	2006	Rem sleep behavior disorder
10	11	0.99	2010	5 HT2a receptor

Ten major clusters were selected from the total 69 clusters. Each cluster represents a research subfield. The size is the number of cited articles in one cluster. The Silhouettre value indicates the homogeneity or consistency of the cluster. Mean year stands for the mean publication year of the cited articles. The label of cluster is based on log-likelihood ratio.

To detect emerging trends in the field, we further investigated the top high-quality co-cited references. In this part, we used the first author's name plus the publication year as a notion to refer to the articles extracted from 776 co-cited articles. Top three references are shown in Table 2 as ranked by citation counts, centrality, burst and sigma respectively.

DISCUSSION

Research on VH has formed a complete system. A total of 2641 articles were published between 1999 and 2020. Apparently, more original articles than reviews were published every year. In terms of the cumulative number of publications, the cumulation in 2020 (2641) is approximately twice that in 2011 (1244). Following the analysis of the chart, we can predict that this study period will further attract attention and continually grow in the next few years.

On a global scale, many countries conduct numerous studies on VH. This field has attracted wide attention worldwide. However, research imbalance between countries exists. To date, studies on VH have been predominantly conducted in North America (*e.g.*, United States and Canada), Europe (*e.g.*, United Kingdom, France, Germany), Asia (*e.g.*, Japan and China), and Australia. The United States published the largest number of studies between 1999 and 2020. England was the second country that stands out in studies involving VH.

Dr. Taylor JP and Dr. Aarsland D are pioneers in the field. Dr. Taylor JP pushes back the frontiers of DLB[47] and plays an important role in the studies on the visual cortical excitability in the VH of DLB[7,48-50]. Dr. Aarsland D opens doors to reveal the psychiatric symptoms of PD[51-54]; his outstanding contribution to this field is clarifying that the presence of hallucination in PD is an important contributor to institutionalization and caregiver distress[55,56]. In addition, a group of new experts has emerged in this field in 2020, and their cooperation is very close. The team is mainly engaged in the research of electroencephalogram and evoked potentials of VHs, which is a new research breakthrough[57,58].

The most active topics of this field are 'neuropsychiatric symptom' and 'functional connectivity'. For example, the burst period of keywords 'neuropsychiatric symptom' is from 2014 to 2020, and the burst intensity is 11.91. Cross-diseases (mainly psychiatric and neurological diseases) VH research started in 2014[59]. This article sparked a heated discussion on the relationship between VH in psychiatric and neurological diseases. Many scholars tend to believe that VH in different neuropsychiatry disorders have the same mechanism. Some experts have proposed that impairments in attentional network activity can explain all hallucinations in various diseases[60]. Yao *et al*[61] proposed that apart from schizophrenia, aberrant default mode network (DMN) was also found to contribute to the VH in PD. Meanwhile, the dorsal attention

Table 2 Top three references ranked by four values respectively

Values		Ref.	Journal, volume, start page	Cluster #
Counts	124	Mckeith *et al*[69], 2005	*Neurology*, 65, 1863	3
	93	Harding *et al*[70], 2002	*Brain*, 125, 391	3
	91	Mckeith *et al*[36], 1996	*Neurology*, 47, 1113	1
Centrality	0.09	Aarsland *et al*[71], 2002	*J Neurol Neurosur Ps*, 72, 708	1
	0.08	Goetz *et al*[72], 2011	*Movement Disord*, 26, 2196	0
	0.07	Cummings *et al*[46], 2014	*Lancet*, 383, 533	0
Bursts	44.12	Mckeith *et al*[74], 2017	*Neurology*, 89, 88	4
	43.96	Mckeith *et al*[36], 1996	*Neurology*, 47, 1113	1
	43.86	Mckeith *et al*[69], 2005	*Neurology*, 65, 1863	3
Sigma	4.49	Teunisse *et al*[79], 1996,	*Lancet*, 347, 794	5
	4.36	Cummings *et al*[46], 2014	*Lancet*, 383, 533	0
	4.04	Mckeith *et al*[69], 2005	*Neurology*, 65, 1863	3

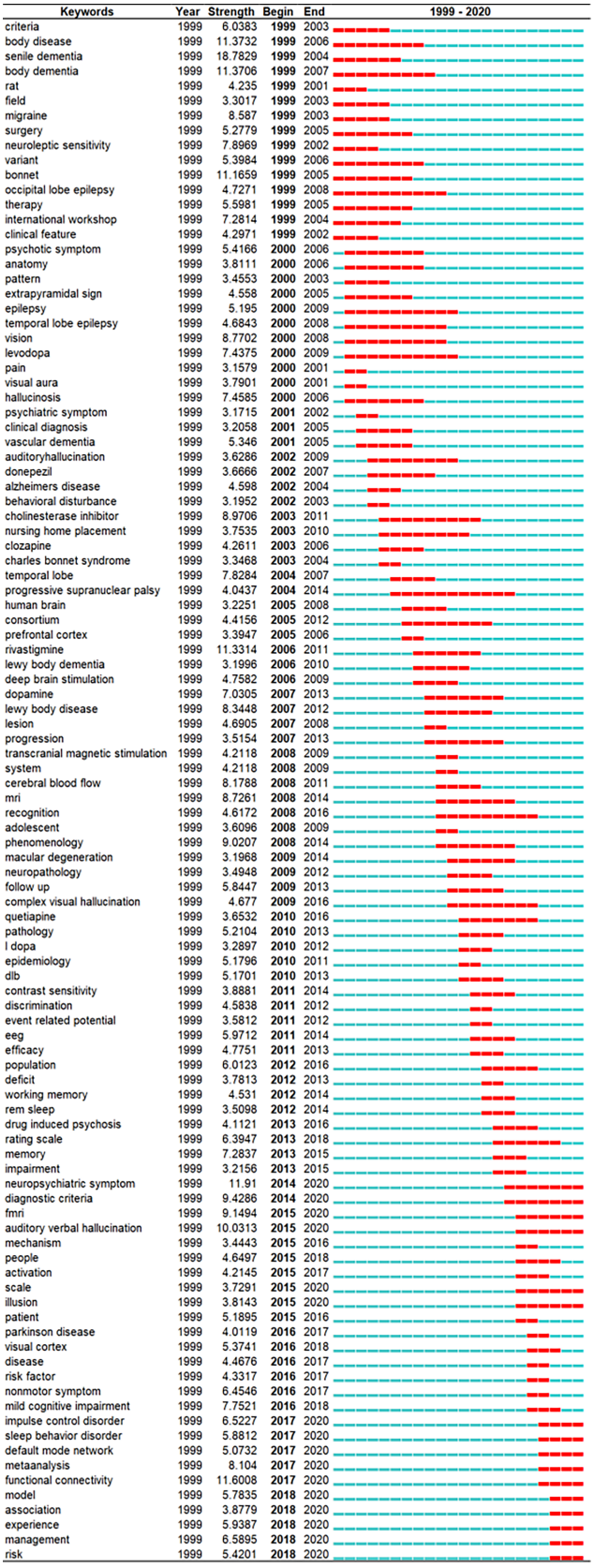
network (DAN) and the ventral attention network (VAN) also play important roles in the occurrence of VH[62]. DMN involves the function of sensory information perception and processing, while VAN engages attention to salient stimuli and DAN generates selective attention. The underactivation of VAN and overactivation of DAN and DMN lead to the recall of previously stored perception information, resulting in VH[63]. In the cohort of patients with VH, thinner retinal nerve fiber layer thickness was found by using spectral domain optical coherence tomography[64], and grey matter atrophy in visual perception region was shown in structural magnetic resonance imaging. These all provide evidence to support the attention deficit network model.

The keyword 'functional connectivity' burst from 2017 to 2020 with a burst intensity of 11.6008. Although current research has produced deep insights into the symptoms and nature of VH, the pathophysiology and etiology of VH remain unclear. Therefore, understanding neural mechanisms has considerable scientific and clinical significance. Evidence from the autopsy can only reveal changes in VH and not explain the cause of VH[65]. Functional neuroimaging studies are beneficial at capturing spontaneous VH in the neuroimaging scanner and the examination is noninvasive[66]. fMRI can investigate changes in specific parts of the brain rather than gross brain abnormalities [67]. It can reveal alterations in brain connectivity even before structural deficits occur. Resting state and task state are two main types of functional neuroimaging in the studies on VH[66]. The most recent research into the neural underpinnings of VH in schizophrenia concluded that the lateral occipital cortex (LOC) of patients showed increased connection with the frontoparietal task-control network and thalamus in the resting state; however, during task switching, LOC has an increase in interaction with the DMN[68].

Emerging trends of VH were identified based on structural and temporal properties derived from the relevant publications.

Landmark articles

Given the groundbreaking contributions, the most cited articles in the research field are often considered the landmarks[31]. Mckeith IG (2005) and Harding AJ (2002) are at the top of the list. Both of them are in Cluster #3. Mckeith IG (1996) is the third most cited article and belongs to Cluster #1. Notably, Mckeith IG is a pioneer in the field of DLB and has published a series of DLB clinical guidelines in Neurology. Mckeith IG (1996) proposed the first consensus guideline for the clinicopathological diagnosis of DLB[36]. In 2005, Mckeith *et al*[69] published the third revised clinical diagnostic and treatment criteria for DLB, which included management in the criteria for the first time. These two guidelines authoritatively summarized the clinicopathological diagnosis of DLB and showed the direction of DLB treatment at that time. The article by Harding *et al*[70] entitled *Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe* advanced the finding that temporal lobe LB is strikingly associated with VH given the distribution of LB in the brain. This result is a



Keywords	Year	Strength	Begin	End	1999 - 2020
criteria	1999	6.0383	1999	2003	
body disease	1999	11.3732	1999	2006	
senile dementia	1999	18.7829	1999	2004	
body dementia	1999	11.3706	1999	2007	
rat	1999	4.235	1999	2001	
field	1999	3.3017	1999	2003	
migraine	1999	8.587	1999	2003	
surgery	1999	5.2779	1999	2005	
neuroleptic sensitivity	1999	7.8969	1999	2002	
variant	1999	5.3984	1999	2006	
bonnet	1999	11.1659	1999	2005	
occipital lobe epilepsy	1999	4.7271	1999	2008	
therapy	1999	5.5981	1999	2005	
international workshop	1999	7.2814	1999	2004	
clinical feature	1999	4.2971	1999	2002	
psychotic symptom	1999	5.4166	2000	2006	
anatomy	1999	3.8111	2000	2006	
pattern	1999	3.4553	2000	2003	
extrapyramidal sign	1999	4.558	2000	2005	
epilepsy	1999	5.195	2000	2009	
temporal lobe epilepsy	1999	4.6843	2000	2008	
vision	1999	8.7702	2000	2008	
levodopa	1999	7.4375	2000	2009	
pain	1999	3.1579	2000	2001	
visual aura	1999	3.7901	2000	2001	
hallucinosis	1999	7.4585	2000	2006	
psychiatric symptom	1999	3.1715	2001	2002	
clinical diagnosis	1999	3.2058	2001	2005	
vascular dementia	1999	5.346	2001	2005	
auditoryhallucination	1999	3.6286	2002	2009	
donepezil	1999	3.6666	2002	2007	
alzheimers disease	1999	4.598	2002	2004	
behavioral disturbance	1999	3.1952	2002	2003	
cholinesterase inhibitor	1999	8.9706	2003	2011	
nursing home placement	1999	3.7535	2003	2010	
clozapine	1999	4.2611	2003	2006	
charles bonnet syndrome	1999	3.3468	2003	2004	
temporal lobe	1999	7.8284	2004	2007	
progressive supranuclear palsy	1999	4.0437	2004	2014	
human brain	1999	3.2251	2005	2008	
consortium	1999	4.4156	2005	2012	
prefrontal cortex	1999	3.3947	2005	2006	
rivastigmine	1999	11.3314	2006	2011	
lewy body dementia	1999	3.1996	2006	2010	
deep brain stimulation	1999	4.7582	2006	2009	
dopamine	1999	7.0305	2007	2013	
lewy body disease	1999	8.3448	2007	2012	
lesion	1999	4.6905	2007	2008	
progression	1999	3.5154	2007	2013	
transcranial magnetic stimulation	1999	4.2118	2008	2009	
system	1999	4.2118	2008	2009	
cerebral blood flow	1999	8.1788	2008	2011	
mri	1999	8.7261	2008	2014	
recognition	1999	4.6172	2008	2016	
adolescent	1999	3.6096	2008	2009	
phenomenology	1999	9.0207	2008	2014	
macular degeneration	1999	3.1968	2009	2014	
neuropathology	1999	3.4948	2009	2012	
follow up	1999	5.8447	2009	2013	
complex visual hallucination	1999	4.677	2009	2016	
quetiapine	1999	3.6532	2010	2016	
pathology	1999	5.2104	2010	2013	
l dopa	1999	3.2897	2010	2012	
epidemiology	1999	5.1796	2010	2011	
dlb	1999	5.1701	2010	2013	
contrast sensitivity	1999	3.8881	2011	2014	
discrimination	1999	4.5838	2011	2012	
event related potential	1999	3.5812	2011	2012	
eeg	1999	5.9712	2011	2014	
efficacy	1999	4.7751	2011	2013	
population	1999	6.0123	2012	2016	
deficit	1999	3.7813	2012	2013	
working memory	1999	4.531	2012	2014	
rem sleep	1999	3.5098	2012	2014	
drug induced psychosis	1999	4.1121	2013	2016	
rating scale	1999	6.3947	2013	2018	
memory	1999	7.2837	2013	2015	
impairment	1999	3.2156	2013	2015	
neuropsychiatric symptom	1999	11.91	2014	2020	
diagnostic criteria	1999	9.4286	2014	2020	
fmri	1999	9.1494	2015	2020	
auditory verbal hallucination	1999	10.0313	2015	2020	
mechanism	1999	3.4443	2015	2016	
people	1999	4.6497	2015	2018	
activation	1999	4.2145	2015	2017	
scale	1999	3.7291	2015	2020	
illusion	1999	3.8143	2015	2020	
patient	1999	5.1895	2015	2016	
parkinson disease	1999	4.0119	2016	2017	
visual cortex	1999	5.3741	2016	2018	
disease	1999	4.4676	2016	2017	
risk factor	1999	4.3317	2016	2017	
nonmotor symptom	1999	6.4546	2016	2017	
mild cognitive impairment	1999	7.7521	2016	2018	
impulse control disorder	1999	6.5227	2017	2020	
sleep behavior disorder	1999	5.8812	2017	2020	
default mode network	1999	5.0732	2017	2020	
metaanalysis	1999	8.104	2017	2020	
functional connectivity	1999	11.6008	2017	2020	
model	1999	5.7835	2018	2020	
association	1999	3.8779	2018	2020	
experience	1999	5.9387	2018	2020	
management	1999	6.5895	2018	2020	
risk	1999	5.4201	2018	2020	

Figure 5 The top 104 burst keywords. The blue line represents the timeline from 1999 to 2020, while the red line stands for the years when a keyword has burst.

remarkable finding that links the clinical and pathological features of DLB together [70].

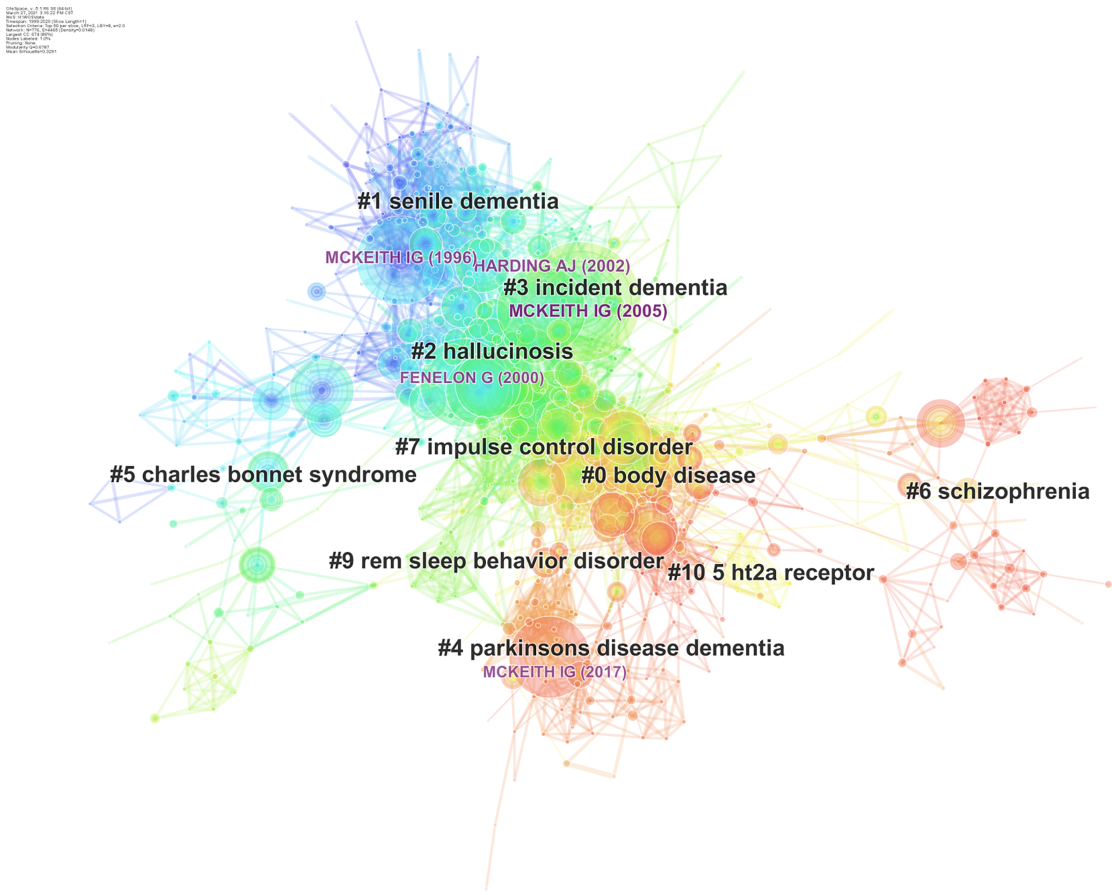


Figure 6 A network of 776 co-cited references representing citation patterns of top 50 articles per year between 1999 and 2020. The overall structure can be divided into three major parts: the upper left part of the network is essentially in blue, which represent the co-citation between 1999 and 2005. The central part of the network is mainly in green and yellow, which indicates the relationship is probably constructed in the middle 7 yr from 2006 to 2012. The bottom right part is predominantly in red and connections were formed credibly in the most recent 8 yr, that is 2013-2020.

Pivot articles

Pivot articles often refer to gateway articles between two densely connected subfields with a unique position. This type of articles can provide insights into emerging trends. The top ranked article by centrality is Aarsland D (2002) in Cluster #1, which has a centrality of 0.09. This double-blind, randomized, placebo-controlled study included 14 PDD patients to study the safety and effectiveness of the cholinesterase inhibitor donepezil in the treatment of PDD. This study lasted for 20 wk and finally they found that donepezil is safe and effective, also it does not worsen motor symptoms of PD [71]. This outstanding discovery has important therapeutic implications for PDD. The second one is Goetz CG (2011) in Cluster #0, with centrality of 0.08. Goetz *et al*[72] followed up 60 patients with PD but without hallucinations at baseline for more than 10 years. VH was found to dominate in early hallucination profile. This discovery revealed the outstanding position of VH in PDP. The third is Cummings J (2014) in Cluster #0, with centrality of 0.07. Cummings *et al*[46] conducted a randomized controlled double-blind trial on patients with PDP and concluded that this population can achieve benefit from Pimavanserin, a selective serotonin 5-HT2A inverse agonist, which is the only U.S. Food and Drug Administration-approved medication for PDP [23]. This study was a phase 3 trial that marks a critical breakthrough in the treatment of PDP, in which VH is a common symptom[73].

Burst articles

The importance of burst cannot be overemphasized. Through burst testing of all cited articles, we easily found that Mckeith IG (2017), Mckeith IG (1996), and Mckeith IG (2005) are on the top of the diagram. They are the milestones in relation to DLB. We discussed the last two articles in front part. The top one was Mckeith IG (2017) in Cluster #4. Mckeith *et al*[74] renewed the consensus report of DLB in 2017. Compared with the 2005 edition, the 2017 edition clearly distinguished clinical features and biological markers. According to different clinical features and biological markers, the

Ref.	Strength	Begin	End	1999-2020
Waters *et al*[59], 2014	19.3898	2015	2020	
Pagonabarraga *et al*[29], 2016	19.2073	2016	2020	
Onofrj *et al*[80], 2013	12.6453	2014	2020	
Mckeith *et al*[74], 2017	44.1227	2018	2020	
Lenka *et al*[81], 2015	13.3785	2016	2020	
Vann Jones al[82], 2014	12.621	2017	2020	
Goldman *et al*[83], 2014	14.5101	2015	2020	
Ffytche *et al*[73], 2017	18.9805	2018	2020	
Cummings *et al*[46], 2014	21.7452	2016	2020	
Archibald *et al*[84], 2011	12.3342	2014	2020	

Figure 7 The top 10 references that retained citation burst until 2020.

diagnosis was divided into probable and possible DLB. Consistency of the diagnostic criteria for DLB will be more conducive to further research on DLB.

It is valuable to examine the citation burst in more recent articles while eliminating the overshadow burst of those landmark articles. The top 10 references that retained citation burst until 2020 are shown in Figure 7, which anticipates emerging trends in the future. In general, a new emerging trend involves PD with VH. Waters F (2014) is a relatively early article comparing VH in different diseases[59]. This article opened up a new dimension in VH research. Although many hypotheses have been proposed to explain the mechanism of VH, and many imaging and electrophysiological studies have partly proved these hypotheses; it is still unclear whether VH in different diseases has the same mechanism, and further research is needed. Pagonabarraga J (2016) is the only article that had citation burst as soon as its publication. PD minor hallucination is not a newly found phenomenon in PD but is underestimated because previous research on PDP focused on the study of well-structured VH. Pagonabarraga *et al*[29] reported that minor hallucination is the most frequent symptom in PDP and may even occur before the onset of parkinsonism. The third paper was Onofrj M (2013). This paper reviews the hypothetical mechanisms of VH in PD and DLB. To date, three predominant mechanistic models have been presented: a disturbance between top-down and bottom-up aspects of visual perception[1,75]; chronic deafferentation causing hyperexcitability to cortical structures involved in vision[3,76]; and the misattribution of internal imagery[59,77,78]. The authors tend to identify with the attention deficit network model as mentioned before.

Structurally and temporally significant articles

Sigma is defined as: $(centrality + 1)^{burstness}$, which can simultaneously measure a cited reference's structural centrality and citation burstness. Teunisse RJ (1996) is at the top of the list, which objectively describes the characteristics of CBS by using a semi-structured interview[79]. The advanced nature of this article lies not only in the formation of the prototype semi-structured interview of VH but also in the occurrence of CBS, which is partly due to sensory deprivation and low arousal. The second was Cummings J (2014) in Cluster #4, Mckeith IG (2005) ranked third in this part and their importance is self-evident.

CONCLUSION

Through systematic analysis of the literature of VH over the past 22 years, we found that with the yearly progress of research on VH, its mystery has been gradually unveiled. Current research mainly focuses on neuropsychiatry. Countless countries,

institutions, and authors have collaborated together and contributed to this field. North America, Europe, Asia and Australia showed outstanding contributions, and Dr. Taylor JP and Dr. Aarsland D are the most active contributors. Several research hotspots in the field of VH were detected in the recent research. The neuropsychiatry symptom and MRI function connectivity have been paid much attention. In the field of VH, neurodegenerative diseases, especially PD and DLB, were found to be widely studied. We believe that research on these two diseases will continue to advance the field of VH.

Although VH is of clinical importance, and its pathophysiology or treatment is mainly focused on single diseases and its mechanisms remain unclear. Additional clinical studies are required to provide higher evidence-based support for the diagnosis and treatment of VH. We investigated the basic literature related to VH and concluded that the small number of such studies is partly caused by difficulty in inducing and testing VH in animal models. Further efforts are required in this direction to obtain profound insights into the mechanisms that underlie VH. This issue will have important pathophysiologic and possible therapeutic implications in the future.

ARTICLE HIGHLIGHTS

Research background

Visual hallucination (VH) refers to a spontaneous visual perception without corresponding external stimuli and often occurs in ophthalmological and neuropsychiatric disorders. It is associated with poor life quality, increased patient hospitalization, and nursing home admission.

Research motivation

To date, there is a lack of scientometric analysis of the research on VH.

Research objectives

To objectively summarize the features of VH research and gain insights into the emerging trends for research on VH.

Research methods

CiteSpace V was used in this article. Publication outputs, document types, geographic distributions, co-authorship status, research hotspots, and co-citation status were analyzed. A total of 2176 original articles and 465 reviews were included in the database downloaded from the Web of Science Core Collection.

Research results

The results showed that most publications can be classified into neurology, sports and ophthalmology studies. In addition, North America, Europe, Asia, and Australia published the most documents. Some well-known authors have always had a leading role in this field; meanwhile, new authors keep emerging. A relatively stable cooperation has been formed among many authors. Furthermore, neuropsychiatric symptom and functional connectivity are the top hotspots. Research on VH in dementia with Lewy bodies and Parkinson's disease (PD) have received much attention.

Research conclusions

Studies on VH in PD are likely to be the new emerging trends in the future, especially the mechanism of VH.

Research perspectives

More large-scale clinical and in-depth basic research studies are required to better understand the mechanisms underlie VH, which will contribute to our understanding of pathophysiology and therapy in VH.

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