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EDITORIAL

Suicidal behavior-advances in clinical and neurobiological research and improvement of prevention strategies

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Abstract

Suicide is the 14th leading cause of death worldwide. It is responsible for 1%-5% of all mortality. This article highlights the latest developments in universal, selective, and indicated prevention strategies. Concerning universal suicide prevention, current research has shown that strategies such as restricting access to lethal means (*e.g.*, control of analgesics and hot-spots for suicide by jumping) and school-based awareness programs are most efficacious. Regarding selective prevention, substantial progress can be expected in psychological screening methods for suicidal behavior. The measurement of implicit cognition proved to be more valid in predicting future suicide attempts than classic clinical assessment. Latest developments are smartphone-based interventions and real-time monitoring of suicidal behavior. Great effort has been made to establish valid neurobiological screening methods (*e.g.*, genetic and epigenetic risk factors for suicide, hypothalamic-pituitary-adrenal axis) without yielding a major breakthrough. Potentially, multiple biomarkers rather than a single one are necessary to identify individuals at risk. With regard to indicated prevention in form of psychopharmacological treatment, recent pharmacoepidemiological studies and meta-analyses have supported a protective role of antidepressants, lithium, and clozapine. However, the data concerning a specific anti-suicidal effect of these drugs are currently not consistent. Promising results exist for ketamine in reducing suicidal ideation, independently of its antidepressant effect. Concerning psychotherapy, recent findings suggest that psychotherapeutic interventions

specifically designed to prevent suicide re-attempts are most efficacious. Specifically, cognitive behavioral therapy and psychodynamic therapy approaches proved to decrease the number of suicide re-attempts significantly.

Key Words: Antidepressants; Biomarkers; Cognitive behavioral therapy; Ketamine; Prevention; Suicide

Core Tip: This Editorial highlights recent developments concerning suicide prevention. According to current research, measures such as restricting access to lethal means and school-based awareness programs are the most efficacious universal prevention strategies. Novel psychological screening methods for suicidal behavior (implicit cognition, smartphone-based interventions, and real-time monitoring) have improved suicide risk assessment. Pharmacoepidemiological studies and meta-analyses support a protective role of antidepressants, lithium, and clozapine. Promising results exist for ketamine in reducing suicidal ideation. However, its suicide-preventive effect is under debate. Specific psychotherapeutic approaches for suicide attempters that focus on suicidal episodes proved to be efficacious for reducing suicide re-attempts.

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INTRODUCTION

Suicide and suicidal behavior are major public health concerns. Around 700000 people commit suicide each year. Suicide was the fourth leading cause of death among 15 to 29 year-old individuals globally in 2019[1]. According to the United Nations, more people die by suicide every year than by both homicide and war[2]. In developed countries, more than 90 percent of all suicide victims suffered from mental illnesses, most frequently from mood disorders[3]. In the developing countries, on the other hand, the reasons for suicidal behavior are likely to be similar but the number of suicides is significantly higher there potentially due to a lack of access to medical and especially psychiatric care[4-7]. Mood disorders are regarded as a proximal factor for developing of an increased suicide risk[8]. The risk of suicide is 17 times higher in people with mood disorders than in the general population[9]. Follow-up studies documented that ten to fifteen percent of the patients with major depressive disorder (MDD) die by suicide during the course of the disease[10]. Despite this remarkably high association, however, it remains unclear why most people with mood disorders do not attempt suicide. This suggests that there may be a predisposition to suicidal behavior that is, to some extent, independent of the psychiatric disorder itself[8,11,12]. Although suicidal behavior often occurs in association with affective disorders, there is evidence from genetic, familial and neurobiological studies that it might represent a separate diagnostic entity[13]. In the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5)[14], "suicidal behavior disorder" is therefore included as a "condition for further study". It is characterized by "attempted suicide within the past two years" and does not include suicidal ideation or non-suicidal self-injurious behavior. A key feature of this definition is the intent to die, which distinguishes suicidal behavior from suicidal ideation and non-suicidal self-injury (NSSI).

There is still too little knowledge about the risk factors that facilitate the transition from suicidal ideation to suicidal action. The majority of people considering suicide do not go as far as attempting suicide. Therefore, the central concern is to understand the differences between suicide ideators and suicide attempters and to identify which ideators are at the greatest risk of suicidal behavior[15]. This information could significantly improve risk assessment and theoretical models of suicide. In the subsequent sections we will highlight some recent developments in clinical and neurobiological research that have the potential to significantly improve future suicide prevention strategies. It is likely that these advances will primarily concern selective and indicated prevention measures (*i.e.*, screening methods and therapy).

At this point, we would like to briefly address the existing controversy regarding the classification of preventive measures for mental disorders. First of all, Caplan (1964) introduced his concept of primary, secondary, and tertiary prevention which had a strong influence on the development of early prevention models[16,17]. In 1983, Gordon[18] developed another three-tiered model, in which a division into universal, selective, and indicated preventive interventions was made, depending on the targeted population group. With the 1994 Institute of Medicine (IOM) Framework [IOM, *i.e.*, Institute of

Medicine; the IOM changed its name to National Academy of Medicine (NAM) in 2015], the Caplan model was abandoned in favor of an adapted Gordon approach. At the same time, prevention measures were strictly separated from therapy and maintenance interventions. The term "prevention" was now reserved for interventions designed to reduce the occurrence of new cases (NAM, 2007)[19]. However, only a few years later the National Advisory Mental Health Council (NAMHC) Workgroup on Mental Disorders Prevention Research stated that the IOM definition was too narrow because it excluded all individuals with full-blown disorders[20]. Other authors have also claimed that benefits could be gained from closer integration of prevention and treatment research without separating both from each other, thus sharing methodological advances in the corresponding field[21].

In the present work, we refer to the classification according to the 1994 IOM Framework. On the other hand, we use a unified approach with the inclusion of therapeutic measures, as it was also applied in the most relevant systematic reviews[22,23].

It has already been implicitly mentioned that we are referring here to suicidal behavior and not to NSSI, which has a different etiological background and requires other prevention strategies.

UNIVERSAL PREVENTION STRATEGIES

Universal prevention refers to strategies designed for an entire population regardless of the presence of individual risk factors. Since the 1960s, several developed countries have implemented national suicide prevention plans. According to the WHO[24], universal prevention programs include, inter alia: (1) Limitation of access to lethal means, (2) school-based awareness programs, (3) initiatives with regard to public education and awareness, (4) responsible media reporting, (5) access to health care, and (6) policies to reduce harmful use of alcohol or other substances (Table 1). As one of the first, Mann *et al*[22] performed an exhaustive review on the effectiveness of suicide prevention strategies. Experts from 15 countries evaluated all eligible studies published between 1966 and 2005. Only articles were included that used completed suicide, suicide attempts or suicidal ideations as outcome criteria. The main results were that restricting access to lethal means and the education of physicians (selective prevention; please see the following section) have the potential to prevent suicide. Other measures like public education and media education needed more evaluation. More recently, Zalsman *et al*[23] performed a systematic review using a similar methodology to assess the progress in suicide prevention research between 2005 and 2014. The authors assessed several universal prevention measures: public education, media strategies, and restricting access to suicide means. Moreover, they included studies on selective prevention measures like screening procedures, crisis helplines, and education of physicians, as well as on indicated prevention approaches like treatment methods and community support. Eighteen suicide prevention experts from 13 European countries reviewed all relevant articles and rated the strength of evidence. According to the authors, restricted access to lethal means has been further shown to be an effective suicide preventive measure, especially relating to control of analgesics (overall decrease by 43 percent) and to securing hot-spots for suicide by jumping (reduction by 86 percent). School-based awareness programs have proved to have a protective effect on suicide attempts and suicidal ideation. Other approaches that still needed further investigation included gatekeeper training and education of physicians. These results substantiate that several components of prevention programs as many countries realize them prove to be effective. In the quest for effective suicide prevention programs, no single strategy clearly stands above the others. The lacking efficacy proof of some measures might be due to a paucity of randomized controlled trials (RCTs) which is a major limitation in the evaluation of preventive interventions.

Furthermore, despite implementing various prevention approaches, an increasing trend in the number of suicides over the last two decades is detectable in the United States (Centers for Disease Control and Prevention, CDC), Web-Based Injury Statistics Query and Reporting System (WISQARS) Fatal Injury Reports[25]. Thus, further improvement in specific suicide prevention programs will be necessary to enhance our understanding of these complex and heterogeneous behaviors at the individual level in order to develop more personalized preventive strategies.

SELECTIVE PREVENTION STRATEGIES

Selective prevention refers to strategies designed for one or more subgroups of a population being at risk for suicidal behavior, like patients suffering from an affective disorder. Typical selective prevention strategies are the education of physicians, gatekeeper training, as well as psychological and neurobiological screening methods (Table 1).

Long-established risk factors for suicidal behavior

In suicidology, an important individual-level approach is characterized by searching for valid screening methods or markers of suicidal behavior. Broadly accepted clinical risk factors are, for instance, prior

Table 1 Allocation of single preventive measures to the overarching strategies of universal, selective, and indicated prevention

Type of prevention strategy	Prevention measures
Universal prevention strategies	Limitation of access to lethal means (*e.g.*, control of analgesics and hot-spots for suicide by jumping)
	School-based awareness programs
	Initiatives with regard to public education and awareness
	Media education
	Access to health care
	Policies to reduce harmful use of alcohol or other substances
Selective prevention strategies	Education of physicians
	Gatekeeper training
	Psychological screening methods (*e.g.*, measurement of implicit cognition by the IAT, smartphone-based interventions, real-time monitoring of suicidal thoughts and behaviors)
	ZS model
	Neurobiological screening methods; crisis helplines
Indicated prevention strategies	Assessment and management of suicidal behavior
	Psychopharmacologic treatment approaches (antidepressants [caveat], ketamine, lithium, clozapine)
	Psychotherapeutic treatment approaches (recent methods, specifically focusing on suicidal behavior)
	Assessment and management of substance abuse and other mental disorders
	Community support

IAT: Implicit Association Test; ZS: Zero Suicide.

suicide attempts[26], mental disorders (particularly depression and other mood disorders)[9], abuse of alcohol[27] and other drugs[28], access to lethal means[22], social isolation, gender, and age[13]. However, a careful examination of the suicide literature reveals a considerable gap in knowledge. In particular, commonly known risk factors for suicidal behaviors are, in fact, more likely risk factors for suicidal ideas, and not for the transition from ideas to attempts[15].

For example, hopelessness has long been deemed to be a central risk factor for suicidal behavior[29]. However, several studies have indicated that, while elevated among suicide ideators relative to non-suicidal controls, hopelessness fails to discriminate between suicide ideators and attempters[15]. For example, a study investigating 102 psychiatric patients with bipolar disorder demonstrated that the level of hopelessness was higher among both suicide ideators and attempters compared to healthy controls, but comparable between ideators and attempters[30]. A similar finding that hopelessness is not different between attempters and ideators has been observed in psychiatric patients with Major Depression[31] and adolescents undergoing psychiatric treatment[32]. The same pattern can be seen even when comparing hopelessness between "severe attempters" and suicide ideators[33].

Interestingly, the same also applies for the role of impulsivity, which has been considered as a significant risk factor for suicidal behavior. Furthermore, it has been postulated that this is a key factor in the transition from suicidal ideas to suicide attempts[15]. For example, individuals with high impulsivity scores have been described as being "more likely to act on suicidal feelings"[34]. Similarly, impulsivity has been suggested as "a more significant indicator of suicide attempt than the presence of a specific suicide plan"[15]. An implication of these theoretical perspectives is that impulsivity should be higher in suicide attempters than in ideators. Remarkably, empirical findings do not support the theory that impulsivity is higher in attempters than in ideators. In a large military sample, impulsivity was higher among attempters and ideators compared with non-suicidal individuals, but equivalent between attempters and ideators[15].

The differences between ideators and attempters obviously need further evaluation. Regardless of this, it is important to note that suicide attempters themselves seem to represent a heterogeneous group regarding demographic features, histories of suicide attempts, and the assumed clinical factors, *e.g.*, hopelessness or impulsivity. The authors recently conducted a study on this issue and compared single and multiple suicide attempters for this purpose[35]. A sample of patients with a recent suicide attempt (n = 252) was recruited. Statistical analyses revealed that the re-attempters had more severe psychopathology with significantly higher levels of suicidal ideation and hopelessness. Furthermore, re-attempters had more often first-degree relatives with suicidal behavior and emotional abuse during

childhood. They also exhibited a higher degree of specific personality traits, *i.e.*, higher excitability and higher self-aggressiveness[35]. Multivariate discriminant analysis discriminated the re-attempters from single attempters by higher levels of self-aggressiveness[35]. Although suicidal behavior is a complex and multifaceted phenomenon, in the future individual factors such as self-aggressiveness could be suitable as an indicator in order to identify patients who are particularly at risk and to provide them with suitable therapeutic measures.

Psychological screening methods for suicidal behavior

Another major challenge to scientific and clinical research in this area is that most assessment methods rely on the patients' self-report about suicidal thoughts and intent. This makes the evaluation of suicidal behavior especially difficult because patients often are motivated to deny suicidal thoughts for fear of undesired measures (*e.g.*, involuntary hospitalization)[36]. Moreover, suicidal thoughts are transient in nature and may not be present upon assessment but can return shortly thereafter and some people may lack conscious awareness of their current level of risk[37]. Indeed, nearly 80% of people who die by suicide in hospital wards explicitly deny suicidal thoughts or intent in their last communication before dying[38]. Recently, Woodford *et al*[26] explicitly investigated in a meta-analysis the accuracy of unassisted clinician predictions of future suicidal behavior. Based on 22.499 predictions, this meta-analysis revealed a pooled sensitivity of 0.31 (95%CI: 0.18-0.50), indicating that nearly 70% of patients with repeated suicidal behavior were considered being at low risk. The reported pooled negative predictive value (NPV) of 0.89 (0.86-0.92) shows that nearly 10% of patients classified as low-risk cases will show future suicidal behavior.

Thus, there is an enormous need for standardized methods of assessing suicide risk that do not rely on explicit self-report and unassisted clinicians' decisions. In the last decades, psychological methods were developed to assess people's implicit cognition (*i.e.*, unconscious mental processes that can influence behavior) which could have a significant influence on suicide prediction. For instance, the Suicide Implicit Association Test (IAT) is a brief psychological test that measures reaction times of patients when viewing suicide-related and other stimuli. Previous studies demonstrated that it significantly predicted future suicidal behavior better than other factors like the presence of a mental disorder or a clinicians' prediction of a future suicide attempt[36]. Glenn *et al*[39] replicated these results in a large sample of participants (n=7.015) demonstrating that implicit associations related to suicidal behavior were stronger among individuals with a history of suicide attempt. The results also showed that these implicit associations were robust and sensitive to recency and severity of a given history of suicidal behavior. Associations turned out to be stronger for more recent and more lethal prior suicide attempts[39].

Recent studies have shown that even brief, smartphone-based interventions that aimed to increase aversion to self-harm, can significantly reduce such behavior[40]. Another promising approach is the real-time monitoring of suicidal thoughts and behaviors. Real-time monitoring has provided important information about several essential characteristics of suicidal thinking. Some of these studies have revealed that the severity of suicidal ideation varies significantly over a short period of time[41]. Two studies have shown that the occurrence of suicidal ideas varies from hour to hour almost as much as from person to person[42,43]. Moreover, episodes of suicidal ideation have a quick onset with nearly one third of all observations in one study differing by a standard deviation or more from the prior rating just a few hours earlier[42]. In the same sense, episodes of suicidal ideation tend to be brief, with participants reporting that most episodes are shorter than an hour[37]. Furthermore, suicidal ideation can be differentiated from thoughts of NSSI using real-time assessment. Thus, it turned out that thoughts of suicide co-occur less than half the time with thoughts of NSSI[37].

Prior suicide prevention studies have failed to provide sufficient evidence for the benefits of screening individuals in primary care and of establishing internet and helpline support[24]. Hopefully, this is going to change due to the development of improved screening methods as well as the use of multiple screening and assessment tools.

In this regard, the Zero Suicide (ZS) model also represents a remarkable advance. In this prevention approach all persons receiving care for a mental disorder are screened for suicidal thoughts and behaviors at intake. Whenever a patient screens positive for suicide risk, a full risk formulation is completed for the client[44]. The core features of this prevention strategy are the targeted detection and support of people at risk by trained specialist staff, but also by gatekeepers and family members, as well as the development and implementation of specific interventions[44]. Layman *et al*[45] were able to demonstrate in a current study that less suicidal behavior occurred in clinics that had introduced and used ZS organizational best practices.

Neurobiological screening methods for suicidal behavior

Previous biological studies on suicidal behavior have consistently revealed that biological factors underpin this condition in terms of a predisposing diathesis[46]. This diathesis rests on the known genetic risk factors for suicide[47], but also on epigenetic mechanisms, which represent changes in gene expression and activity due to environmental factors[48]. One such factor discussed for suicidal behavior and producing pronounced effect on the epigenome, is early life adversity (ELA), *e.g.*, physical or sexual abuse during childhood[46,49]. A significant number of subjects with suicidal behavior have a

history of early life adversities, which is therefore considered as a risk factor for future suicide attempts [50]. In our recent work (see above) we were able to show that especially patients with multiple suicide attempts had higher levels of early life adversities compared to single attempters[35].

Animal studies[51] have shown that epigenetic alterations following early life adversities may affect the regulation of the hypothalamic-pituitary-adrenal (HPA) axis, a key system for cortisol release and stress response. A dysregulated HPA axis has also been often reported in subjects with suicidal behavior. For example, a lack of decrease in cortisol levels in the dexamethasone suppression test (DST) was associated with an increased risk of a future suicide death[52]. Postmortem studies in suicide victims indicated that early life adversities may lead to increased methylation of the promoter region of the glucocorticoid receptor and decreased expression of its mRNA in the hippocampus[53]. Recently, Jokinen *et al*[54] showed reduced methylation of several HPA-related genes in individuals at high-risk of suicide. Thus, dysregulation of this major stress system is an important component of diathesis to suicide.

Moreover, markers of neuroinflammation influencing the stress response by modulation of the HPA axis, have been recently investigated in suicide. Altered levels of cytokines, such as IL-1, IL-6, and tumor necrosis factor alpha (TNF-α) have been detected in the frontopolar cortex of suicide victims[55]. Additionally, microgliosis was observed in prefrontal, anterior cingulate, and thalamic regions in suicide victims[56]. Due to the putative role of cytokines in neuroplasticity and neurotoxicity, the authors related the detected microglial activation to pre-suicidal stress.

Recently, growing attention was paid to the polyamine system, also important for stress-response, and its relation to suicide risk[57]. Studies investigating postmortem suicide brains show that expression levels of gene products associated with the polyamine stress response system are dysregulated[46,58]. Expression of the enzyme spermine N1-acetyltransferase (SAT1) was found to be altered in the brain of suicide victims, which has been therefore recognized as a potential biomarker for suicide[59].

Thus, all these studies suggest a complex stress-diathesis interaction between genetic, epigenetic factors, and early traumatic experiences, which alter the response of stress systems to proximal stressors and accompanied response of the immune system, thus increasing the risk for suicidal acts.

Furthermore, the serotonergic system was extensively studied in subjects with suicidal behavior. Low levels of the main metabolite of serotonin (5-hydroxyindoleacetic acid, 5-HIAA) were detected in suicide attempters[60] and predicted future suicide deaths[52]. Postmortem studies additionally showed alterations in serotonin (5-HT) markers[61]. Blunted prolactin response to fenfluramine challenge was found in high *vs* low lethality suicide attempters. High lethality suicide attempters had significantly lower prolactin response than low lethality suicide attempters[62]. Recently, PET studies showed greater raphe 5-HT1A receptor binding potential in high compared to low lethality suicide attempters [63]. Variants in several 5-HT genes have also been associated with the risk of suicide[64,65]. While persisting 5-HT deficits are robustly associated with suicide, the causal mechanisms remain to be clarified.

Finally, based on recent clinical studies suggesting an "anti-suicidal effect" of ketamine[66], the role of the glutamatergic system in suicidal behavior received growing attention. However, previous findings on glutamatergic alterations in suicidal behavior are inconsistent and need further examinations. For example, N-methyl-D-aspartate (NMDA) binding in the prefrontal cortex in suicide has been shown to be decreased[67] or unaffected[68].

To sum up, a number of biological alterations in different systems have been detected in subjects with suicidal behavior. However, currently, there are no biomarkers with a positive predictive value for suicide. A deeper understanding of the biological foundation of suicidal behavior and thus identification of stable and clinically useful biomarkers for suicide would equip clinicians with additional valuable information to properly address suicidal behavior in those most at risk. In light of the number of biological findings in suicidal behavior, Oquendo *et al*[69] state in their review on biomarkers for suicide that potentially multiple biomarkers, rather than a single one, are necessary to identify individuals at risk.

INDICATED PREVENTION STRATEGIES

Indicated prevention strategies target individuals showing suicidal ideations and/or having past suicidal behavior. Psychopharmacological and psychotherapeutic treatment approaches are used for this (Table 1).

Psychopharmacological treatment approaches

Regarding psychopharmacological treatment approaches, the role of antidepressants has been discussed controversially. Indeed, meta-analyses indicate a slightly increased risk for suicidal behavior in pediatric patients and young adults[70,71]. In contrast, there seems to be a protective effect in older adults[71]. Pharmacoepidemiological studies, however, show a protective effect across the whole life span[72]. In the same sense, Simon *et al*[73] reported in a population-based study that the rate of suicide attempts subsequently to the initiation of an antidepressant was much lower than the rate before the initiation.

From a methodological point of view, the question arises as to why the results of RCTs and pharmacoepidemiological studies differ so remarkably. From our point of view, three decisive factors are involved in this discrepancy: (1) Suicidal patients are not usually included in RCTs and the design of RCTs is therefore poorly suited for assessing the influence of antidepressants on suicidal behavior; (2) the duration of the majority of RCTs is too short to detect the possible beneficial long-term effects of antidepressants on suicidal behavior; on the contrary, during the earlier stages of treatment antidepressants may act as an additional stress factor for the patients, due to adverse drug reactions, unfulfilled expectations or dissociated states during partial remission (*e.g.*, willpower improved, mood still depressed); and (3) additionally, the sample size of pharmacoepidemiological studies is much larger, and the time frame much longer compared with RCTs. Thus, although pharmacoepidemiological studies still have some challenges regarding standards in conducting and reporting, they have the strengths to have sufficient statistical power to measure differences in the actual frequency of rare events like suicides (instead of "suicidal events" as is usual in RCTs)[72].

The important role of effective pharmacological treatment of depression for suicide prevention was also emphasized in an influential systematic review by Zalsman *et al*[23] In addition, the authors were in favor of suicide-protective effects of lithium and clozapine. Several RCTs have supported the assumption that lithium reduces the risk of suicide in patients with mood disorders[74-77]. A specific anti-suicidal effect of lithium was suggested in a controlled treatment study on suicide attempters, although the number of suicides was very small (three suicides in the control group *vs* no suicides on lithium)[77]. Clozapine is the only drug that has been approved by the United States Food and Drug Administration (FDA) for reduction of the suicide risk in psychosis. A meta-analysis of the effects of clozapine in comparison with other dopamine and serotonin-receptor antagonists (*e.g.*, olanzapine and risperidone) supports its anti-suicidal effects in schizophrenia[78]. Nevertheless, a recent review has called into question, whether certain drugs that improve the underlying disease also have an independent anti-suicidal effect[79].

Other promising drugs for the treatment of suicidal behavior are ketamine and esketamine. Ketamine (a racemic mixture of S- and R-ketamine) is a drug with dissociative properties. It was approved by the FDA in 1970 for anesthetic use[66]. The mechanism of action of ketamine has not yet been fully elucidated, but it is known that ketamine antagonizes glutamatergic NMDA receptors in the central nervous system[80]. Moreover, several studies have implied a role for opioid neurotransmission, as ketamine also appears to activate the mu, kappa, and delta-opioid receptors[81-84]. In recent years, it became a target of research for its antidepressant effects, which occur within hours at subanesthetic doses[80]. Grunebaum *et al*[66] reported the acute effect of intravenous ketamine on suicidal ideation in patients with MDD. Ketamine therapy resulted in a clinically significant reduction of suicidal ideation in depressed patients within 24 h. Adverse drug reactions (ADRs) were transitory, and clinical improvement was maintained for several weeks. Abbar *et al*[85] investigated the anti-suicidal efficacy of intravenous infusions of ketamine in a placebo-controlled RCT. The primary outcome was that at day 3 of the study more participants in the ketamine group reached full remission of suicidal ideas than in the placebo arm (63.0% *vs* 31.6%)[85]. This effect persisted at follow-up after 6 wk[85].

To avoid the distress of intravenous ketamine therapy, alternative formulations and routes of application were sought[86]. Esketamine has four times higher affinity for the NMDA receptor than ketamine and thus allows for a lower dosage with a corresponding decrease in dissociative symptoms [87]. Moreover, esketamine is available through an intranasal delivery system[88]. Ultimately, esketamine was approved by FDA in 2019 as a nasal spray for treatment-resistant depression in adults and in conjunction with an oral antidepressant for treatment of depressive symptoms in adults with MDD with acute suicidal ideation or behavior. Because of the potential risks associated with this drug, including sedation, dissociation, and abuse or misuse, its label contains boxed warnings, and esketamine is subject to strict safety controls on administration under a safety program called Risk Evaluation and Mitigation Strategy (REMS)[89]. In 2019, esketamine was also approved by the European Medicines Agency (EMA) for the same indication. Because of the risk of abuse, the approval applies only to inpatient treatment[90].

Unfortunately, recent studies on ketamine and esketamine have been less conclusive with regard to their anti-suicidal effects[91-93]. In their current review, Witt *et al*[92] came to the conclusion that the reduction of suicidal ideations might be stronger after intravenous ketamine than after esketamine administration. However, there was still no evidence of a long-lasting effect beyond 3 d[92]. Siegel *et al* [93] performed a review of trials on patients with high level of baseline suicidal ideations. In this work, esketamine was not superior to placebo regarding the effect on suicidal ideations. Intravenous ketamine appeared to immediately and significantly ameliorate suicidal ideation, but was not superior to placebo regarding long-lasting effects[93]. Finally, it should be noted that esketamine seems to be inferior to intravenous ketamine in the treatment of depression as Bahji *et al*[91] reported in their meta-analysis.

In previous sections we pointed out that suicidal ideation represents only a comparatively unspecific parameter that only provides limited information about imminent suicide attempts. Therefore, the validity of studies that only refer to suicidal ideation as an outcome criterion is limited. To date there are no prospective RCTs, which investigated the effect of ketamine/esketamine treatment on future suicidal behavior and suicides as outcome parameter. Thus, the evidence for the efficacy of ketamine/esketamine therapy as a suicide preventive treatment measure has yet to be determined.

Psychotherapeutic treatment approaches

Regarding psychotherapeutic treatment, it has to be noted that results differ considerably and even the adequate targets of suicide interventions are still a matter of debate. For instance, Franklin *et al*[94] point out that the majority of applied intervention targets are derived from untested theoretical assertions, moderate correlates, or weak risk factors of suicidal thoughts and behaviors. None of these forms of evidence would allow somebody to draw conclusions regarding causal inferences. For cutting this Gordian knot, we first of all recommend to make a strict distinction between suicidal ideation and suicidal behavior[95]. Suicidal ideation refers to any thoughts, imaginations, beliefs, or other cognitions associated with ending one's life. Previous studies demonstrated a consistent reduction in suicidal ideations during psychotherapeutic or antidepressant treatment of affective disorders, very likely resulting from the general effect on depression[96,97]. Furthermore, the predictive value of suicidal ideation for suicidal behavior has been shown to be low[29]. There is also some evidence for the notion that the genetic transmission of suicidal ideation may follow a different pathway than suicidal behavior [95]. Suicidal behavior, on the other hand, is a strong predictor for suicide re-attempts[98]. This fact underscores the need for development of specific psychotherapeutic approaches for individuals with suicidal behavior to reduce the risk of suicide re-attempts. In a most recent meta-analysis on psychotherapeutic interventions only RCTs were included that referred directly to suicide attempts and used the number of re-attempts as an outcome variable[99]. By this procedure, 18 studies were identified. Statistical comparison of all studies showed that psychotherapeutic interventions in general reduced the risk of future suicidal behavior nearly by a third[99]. Separate analyses revealed that cognitive behavioral therapy (CBT) as well as two different psychodynamic therapy approaches were significantly more efficacious than control conditions. Dialectical behavior therapy (DBT) and elementary problem solving therapy (PST) were not superior to control conditions in reducing the number of suicide re-attempts[99]. Based on the results of this meta-analysis, it appears as a key recommendation for future psychotherapeutic approaches to focus the intervention directly on the episodes of suicidal behavior.

CONCLUSION

In this work we have pointed out significant advances in the field of scientific suicidology. We would like to add that, from our point of view, it already represents a progress that suicidal behavior disorder was included in the DSM-5 as a disorder for further consideration. This decision has sharpened the focus on suicidal behavior and both, screening methods and therapeutic approaches can be developed in a more targeted manner. As an example, we would like to point out the advances in screening methods, *e.g.*, using implicit cognition, smartphone-based interventions, and real-time monitoring. These methods should be further developed and much more involved in the patient care. The same applies to the development of a valid biomarker set. On the other hand, existing psychotherapy approaches should be further developed. In our view, the greatest opportunities arise for procedures that are aimed directly at suicidal behavior. Concerning pharmacotherapy, a specific anti-suicidal effect of antidepressants, lithium, and clozapine is likely but not yet proven. Ketamine is a promising new drug with promising results for reducing suicidal ideation. However, more evidence is needed to demonstrate sustained and specific anti-suicidal efficacy. The advances such as highlighted in this editorial make us optimistic. Since each of the methods shown has its strengths and weaknesses, we believe that far-reaching future progress can only be achieved with a multifaceted approach using appropriate universal, selective and indicated prevention strategies.

FOOTNOTES

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OPINION REVIEW

Emerging role of psychosis in Parkinson's disease: From clinical relevance to molecular mechanisms

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disease. Psychosis is one of the common psychiatric presentations in the natural course of PD. PD psychosis is an important non-motor symptom, which is strongly correlated with a poor prognosis. Increasing attention is being given to PD psychosis. In this opinion review, we summarized and analyzed the identification, screening, epidemiology, mechanisms, risk factors, and therapeutic approaches of PD psychosis based on the current clinical evidence. PD psychosis tends to have a negative effect on patients' quality of life and increases the burden of family caregiving. Screening and identification in the early stage of disease is crucial for establishing tailored therapeutic strategies and predicting the long-term outcome. Development of PD psychosis is believed to involve a combination of exogenous and endogenous mechanisms including imbalance of neurotransmitters, structural and network changes, genetic profiles, cognitive impairment, and antiparkinsonian medications. The therapeutic strategy for PD psychosis includes reducing or ceasing the use of dopaminergic drug, antipsychotics, cholinesterase inhibitors, and non-pharmacological interventions. Ongoing clinical trials are expected to provide new insights for tailoring therapy for PD psychosis. Future research based on novel biomarkers and genetic factors may help inform individualized therapeutic strategies.

Key Words: Psychosis; Parkinson's disease; Hallucinations; Delusions; Antipsychotics

Core Tip: Parkinson's disease (PD) psychosis encompasses a variety of misperception symptoms including illusions, passage hallucinations, presence hallucinations, and delusions as well as formed visual hallucinations. PD psychosis is an independent predictor of mortality. A variety of risk factors for development of PD psychosis have been identified. Side effects of anti-Parkinsonism medications and patient-specific characteristics are both involved in the onset and progression of PD psychosis. Targeting the 5-hydroxytryptamine subtype 2A receptor is a promising pharmacological intervention.

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INTRODUCTION

With progressive aging of the population, Parkinson's disease (PD) has become the second most common neurodegenerative disease after Alzheimer's disease. Studies have shown a global increase in the prevalence and incidence of PD with increasing age, with no predilection for a particular sex[1]. The neuropathological hallmarks of PD are gradual degeneration and loss of dopaminergic neurons in the pars compacta of the substantia nigra, along with the formation of Lewy bodies. Since these dopaminergic neurons project to the striatum, it causes reduction in dopamine levels in striatum, impairing neurotransmitter homeostasis in the central nervous system. PD is traditionally recognized as a movement disorder with prominent motor symptoms including tremor, bradykinesia, rigidity, gait disturbance, and unstable posture[2], which is the main cause of disability in these patients. However, PD is also believed to be associated with a variable spectrum of complex non-motor symptoms, such as cognitive and affective impairment, hyposmia, sleep disturbance, neuropsychiatric complications (depression, psychosis, apathy, dementia), and autonomic disorders. Hyposmia may precede the onset of typical motor symptoms of PD by up to 20 years[3]. These findings highlight that PD not only involves the dysfunction of the dopaminergic system, but also other neurotransmitter systems, such as cholinergic, noradrenergic, and serotonergic systems related to the above clinical entities[4].

Psychosis is one of the common psychiatric presentations in the natural course of PD. Studies have indicated a diverse range of psychotic symptoms in patients with PD; however, there is no standardized classification of these symptoms. The spectrum of PD psychosis encompasses a variety of misperception symptoms including illusions, passage hallucinations, presence hallucinations, delusions, well-structured visual hallucinations, and other perceptual disturbances. In general, visual illusions, passage and presence hallucinations are termed minor hallucinations, which are the most common psychotic phenomena of psychosis in PD[5]. Minor hallucinations are accompanied by other non-motor symptoms (typically rapid eye movement sleep behavior disorder and cognitive impairment) in PD psychosis[6,7].

The onset of some psychotic manifestations may occur even earlier than motor symptoms of PD[6]. The presence of severe psychotic symptoms is an independent risk factor of impaired health-related quality of life in PD[8].

PD psychosis has a negative influence on patients' quality of life and increases the burden of caregiver and family. A study including 80 patients with PD who were followed up for approximately four and a half years, found that visual hallucinations and visual illusions in PD patients heralded a higher risk in development of dementia[9]. A large-scale longitudinal study with approximately 10-year follow-up including 12077 PD patients revealed an increased risk of falls and fractures in PD patients with psychosis[10]. A small case-control study involving 21 PD patients with mild cognitive impairment suggested that patients with visual hallucinations may have a higher rate of dementia progression (50% *vs* 25% in patients without visual hallucinations)[11]. A long-term follow-up study showed that PD psychosis is an independent factor for predicting mortality[12] and likewise, increased occurrence of hallucinations contributed markedly to mortality in PD patients[13].

Furthermore, it is currently considered that minor hallucinations are important events during the natural history of PD; this is because patients with PD psychosis not only require increasing levels of assistance and care from their caregivers but also have increased likelihood of moving to a nursing home and being at potential risk of mortality[14,15].

EPIDEMIOLOGY

Almost all PD patients develop at least one of the neuropsychiatric manifestations in the late stage of the disease[16]. Nevertheless, the reported frequency of PD psychosis is slightly discrepant among studies due to the different assessment and screening methods used in epidemiological studies. In a

community-based cross-sectional study of 250 PD patients, the prevalence of any psychotic symptom was 26%; 47.7% of PD patients with psychosis had mild phenomena and 52.3% had hallucinations and/or delusions[17]. Similarly, Kulick *et al*[18] reported a 29% prevalence of any psychotic symptom in a cohort of 199 PD outpatients[18]. Longitudinal studies have suggested that the prevalence of psychosis in PD patients tends to increase over time. The incidence of PD psychosis gradually increases with the progression of PD[19]. Data from Parkinson's Progression Markers Initiative showed that the incidence of PD psychosis at baseline, 1st year, and 2nd year was 3%, 5.3%, and 10%, respectively, increasing with duration of PD[20]. Yoritaka *et al*[21] conducted a retrospective study of 1,453 PD outpatients, and found that 53.9% of patients with late-onset PD and 22.1% of patients with early-onset PD finally developed psychosis by the 12th year[21]. In a recent cross-sectional study, 38% of PD patients were found to suffer minor hallucinations based on questionnaire analysis[22]. Moreover, it is noted that minor phenomena such as presence, passage hallucinations presented as a pre-motor symptom in approximately one-third of drug-naive PD patients; moreover, the minor phenomena preceded the onset of the first representative motor symptoms of PD by 7 mo to 8 years[6]. The variable rates of psychotic symptoms in PD patients may be attributable to different diagnostic criteria and study settings. However, more than 50% PD patients are expected to develop at least one psychotic symptom during the course of the disease[19].

IDENTIFICATION AND SCREENING

Diagnostic criteria

According to the consensus from working groups of National Institute of Neurology and Stroke (NINDS), and the National Institute of Mental Health (NIMH), the diagnostic criteria for psychosis spectrum related to PD is mainly defined as follows: (1) Hallucinations (passage and presence hallucinations, visual formed hallucinations), illusions, delusions, and a false perception of things or people that do not actually exist around them with preservation of insight. The psychotic and misperception symptoms appear periodically or continuously for more than 1 mo in the setting of a clear sensorium; (2) Diagnosis of PD is based on United Kingdom brain bank criteria and onset of characteristic phenomena follows the diagnosis of PD; and (3) Exclusion of other disorders characterized by similar psychotic symptoms such as dementia with Lewy bodies (DLB) (with accompanying visual hallucinations), primary psychiatric disorders, delirium, and extrapyramidal symptoms induced by drugs[23].

Notably, given the shared symptoms and overlapping crucial neuropathological characteristics, some clinicians considered that DLB and PD dementia are the two extremes or the different stages in the spectrum of a clinical entity[24,25]. Both PD and DLB are categorized as alpha synucleinopathies spectrum which commonly present with hallucination and delusions distress[26]. The relationship between DLB and PD dementia is still under debate; nevertheless, according to some experts, the treatment principles and the pathogenetic mechanisms of psychosis in DLB and PD share a certain commonality[27].

However, the diagnostic criteria formulated by NINDS-NIMH work group for PD psychosis was not completely concordant with the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-V) criteria for "psychosis due to a medical condition," proposed by the American Psychiatric Association, which is generally acknowledged as the diagnostic reference standard for psychosis and psychotic disorders. It was highlighted that patients with PD psychosis who fulfilled the NINDS-NIMH criteria but not the formal DSM-V criteria for psychosis due to PD manifested only mild psychotic symptoms, suggesting that NINDS-NIMH diagnostic criteria would be useful for the surveillance and identification of early symptoms of emerging psychosis[28]. Gordon *et al*[29] proposed a modified score assessment for NINDS-NIMH criteria and showed that the scoring approach can improve the diagnostic performance for PD psychosis[29]. The NINDS-NIMH diagnostic criteria work group, DSM-V criteria, and modified NINDS criteria proposed by Gordon *et al*[29] are summarized in Table 1.

Patients who develop hallucinations can still retain their awareness about misperception in the early stage, a phenomenon previously referred to as "benign hallucinations." However, with advancing disease, patients tend to lose insight into discerning hallucinations, a phenomenon referred to as "malignant hallucinations." Malignant hallucinations are disabling, and are interspersed with paranoid thoughts of suspiciousness, accusations, and being slovenly[5]. In patients with PD psychosis, any form of hallucinations tend to persist intermittently once they occur. Minor hallucinations, such as illusions, are relatively easier to handle than visual hallucinations[30,31].

Screening tools

Explicitly screening for minor hallucinations in the early stage of disease might be crucial for establishing tailored therapeutic strategies and predicting the long-term outcome[30]. The high incidence and prevalence of PD psychosis in different stages and the associated mortality risk underlies the importance of routine screening for psychosis in all patients with PD. Optimal screening and identification of PD psychosis is vital for following treatment and management. Though some neuropsychiatric scales such as the Positive and Negative Syndrome Scale (SAPS), Brief Psychiatry Rating Scale,

Table 1 Diagnostic criteria for Parkinson's disease psychosis according to the National Institute of Neurology and Stroke-National Institute of Mental Health and Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition and Modified National Institute of Neurology and Stroke score

NINDS-NIMH diagnostic criteria		DSM-V criteria	Modified NINDS criteria score proposed by Gordon *et al*[29]
PD diagnosis	(1) United Kingdom Brain Banks criteria; and (2) The onset of PD must be preceded the psychotic symptoms	Prominent hallucinations or delusions	Assigning scores to each psychotic symptoms of NINDS-NIMH diagnostic criteria: (1) Delusions score with 2; (2) Other psychotic symptoms score with 1; and (3) Cut-off sum for PD psychosis equal to or higher than 2
Psychotic symptoms: At least one of the following	(1) Hallucinations; (2) False perceptions; (3) Illusions; and (4) Delusions	There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiological consequence of PD	
The duration of psychotic symptoms	(1) Periodically or continuously; and (2) Last more than 1 mo	The disturbance is not better explained by another mental disorder	
Exclusion of other probable disorders and conditions	(1) Dementia with Lewy bodies; (2) Primary psychiatric disorders; (3) Extrapyramidal symptoms induced by drugs; and (4) Delirium	(1) The disturbance does not occur exclusively during the course of a delirium; and (2) The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning	

DSM-V: Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition; PD: Parkinson's disease; NINDS-NIMH: National Institute of Neurology and Stroke and the National Institute of Mental Health.

Neuropsychiatric Inventory, Clinical Global Impression Scale, Schedule for Assessment of Positive Symptoms are recommended for assessment of psychotic symptoms, none of these scales has been tailor-made for PD psychosis[32]. In clinical practice, some tools need to be combined with other PD assessment scales such as Movement Disorder Society United PD Rating Scale (MDS-UPDRS) and Parkinson's Psychosis Questionnaire. Currently, some abridged and clinically-designed versions such as perception/hallucinations domains of Non-Motor Symptom Assessment Scale for PD[33,34], SAPS for PD (SAPS-PD)[35], and modified version of SAPS-PD[18] with high reliability and sensitivity have been widely applied in clinical trials.

In summary, the NINDS-NIMH diagnostic criteria should be the basis for identifying PD psychosis in suspected patients. Since minor hallucinations may be missed in clinical practice, we recommend the use of scales such as SAPS-PD specifically for screening and assessment of abnormal perceptions in all patients with a diagnosis of PD.

MECHANISMS AND RISK FACTORS

Although insights obtained from studies investigating the mechanisms of PD psychosis have opened new avenues for individualized treatment strategies for PD, the pathophysiology of PD psychosis is not fully elucidated owing to its complexity and multifactorial nature. Current evidence suggests the involvement of a combination of exogenous and endogenous mechanisms[36]. Studies of the endogenous pathophysiological features of PD psychosis will facilitate the development of novel treatment strategies.

Neurotransmitters imbalance

Some neurobiochemical studies have revealed the involvement of impaired homeostasis of some neurotransmitters (especially serotonin, dopamine, acetylcholine, and glutamate) in the endogenous development of PD psychosis. The imbalance between serotonergic and dopaminergic neurotransmission is one of the pivotal factors mediating the occurrence of PD psychosis[37]. Serotonin activators can elicit delirium and psychosis by inducing the release of dopamine from glutaminergic neurons in the ventral tegmental area and nucleus accumbens, while reducing the activity of serotonin can alleviate psychiatric symptoms[38,39]. Additionally, PD patients have been considered to have cholinergic deficiency in the nucleus basalis of Meynert; this phenomenon is more likely to occur in patients with PD who have cognitive impairment and psychotic symptoms[40].

Abnormal activation of the special serotonin (5-hydroxyltryptamine) receptor subtype, 5-hydroxytryptamine subtype 2A (5-HT2A) results in psychotic symptoms[41]. Ballanger *et al*[42] first performed a serotonergic imaging study using the 5-HT2A receptor ligand setoperone-F18 positron emission tomography. They found remarkable enhancement of 5-HT2A receptor binding in PD patients with visual hallucinations. The regions with excessive binding were located in the cortex and were involved

in ventral visual pathway, medial orbitofrontal cortex, and bilateral dorsolateral prefrontal cortex[42]. Additionally, Huot *et al*[43] performed an autoradiographic study using [(3)H]-ketanserin and spiperone binding 5-HT2A receptor, and revealed increased 5-HT2A receptor binding in inferolateral temporal cortex, which is also involved in visual processing[43]. By contrast, another study using a similar imaging technique found no relationship between 5-HT1A receptor-binding and psychosis, though high expression of 5-HT1A binding was universally observed in all patients with PD, regardless of visual hallucination status[44].

Clinical biomarkers

A variety of risk factors related to the underlying mechanisms of the development of PD psychosis have been identified[45]. Studies have focused on clinical presentations and laboratory indices as clinical markers of PD psychosis. In a case-control study including 111 PD patients, elevated level of plasma C-reactive protein was found to be an independent predictor of the occurrence of hallucinations or illusions[46]. A cross-sectional study conducted in Japan showed a significant correlation of minor hallucinations with cognitive impairment and rapid eye movement (REM) sleep behavior disorders[22]. In a study of 423 subjects (mean follow-up: More than 4 years), patients with PD early-onset psychosis had lower cerebrospinal fluid amyloid Aß1-42, decreased olfactory scores, increased depression scores, and increased symptoms of REM sleep behavior disorders compared with those without early-onset psychosis. A pathological study revealed a close association of visual hallucination with amyloid deposition, the density of neurofibrillary tangles, and α-synuclein in the brain of PD patients[47].

Structural and network changes

Recent studies have revealed that PD psychosis may also be triggered by altered brain structural connectivity that disturbs the normal attention and perception, resulting in high-amplitude activity of the default mode network.

In a study by Ffytche *et al*[48], patients with early-onset formed hallucinations showed low-level visual function, thinning of right cortex (frontal, occipital, parieto-temporal, and insular lobes), and reduced volumes of bilateral basal ganglia and bilateral hippocampus at baseline[48]. Firbank *et al*[49] studied 36 patients with PD by magnetic resonance spectroscopy, and found that the ratio of γ-aminobutyric acid/creatine in occipital lobe of PD patients with visual hallucinations was lower than that in PD patients without any psychotic symptom; in addition, there were signs of gray matter loss in V4 region of anterior temporal lobe and visual cortex[49]. Patients with PD with minor hallucinations showed reduced gray matter atrophy in visuoperceptive regions[50,51]. Zarkali *et al*[52] used fixel-based analysis to assess neural network and structure; they found that left inferior fronto-occipital white matter tracts connected with posterior thalamic projections were degenerated and decreased in PD patients with hallucinations[52], suggesting that splenium and posterior thalamus may play a major role in maintaining the network balance and regulating the default mode network.

Genetic profiles

Genetic susceptibility to PD psychosis is a subject of ongoing research. Studies have largely focused on the polymorphism of related genes such as apolipoprotein (Apo) E genes, cholecystokinin system-related genes, dopamine system-related genes, serotonergic system-related genes, and tau protein-related genes. However, with the exception of polymorphisms of cholecystokinin system-related genes, the conclusions pertaining to most of the other studies were inconsistent with respect to predicting the development of any psychotic profile in PD[53]. This suggests that Mendelian genetic inheritance may not play a predominant role in the development of PD psychosis. Additionally, a longitudinal cohort study of 215 PD patients and 126 controls with up to 12 years of follow-up identified mutations in the glucocerebrosidase gene as a susceptibility factor for early-onset PD psychosis[54]. This highlights that standardized long-term follow-up studies may help unravel the predisposing genes of PD psychosis.

Motor and cognitive impairment

Motor symptoms of PD are also inextricably linked with psychosis. In a cross-sectional study of 500 subjects, PD psychosis was related to freezing of gait (as evaluated by UPDRS Part II score), age, and disease duration, rather than genetic polymorphisms of ApoE, α-synuclein promoter, and microtubule-associated protein tau[55]. In a retrospective cohort study of PD patients (n = 331) conducted by Sawada *et al*[56] (duration of follow-up: 2 years), longer duration and high severity of PD (modified Hoehn-Yahr stage ≥ 4) was identified as a risk factor for PD psychosis[56]. Cognitive impairment (Mini-Mental State Examination scores ≤ 24) increases the risk of PD psychosis[56]. In addition, PD clinical subtypes are also believed to be closely related to PD psychosis. A prospective study categorized 206 PD patients into four subgroups based on motor symptoms. Compared with the tremor subtype, patients with rigid-kinetic subtype showed a tendency for development of visual hallucinations[57]. Moreover, the prevalence of visual hallucinations in patients with late-onset PD was found to be higher than that in patients with early-onset PD[58].

However, research on the pathophysiology of PD psychosis is still in the exploratory stage, and there is no robust evidence of the pathophysiology and risk factors for PD psychosis. Neither biomarkers nor

genetic mutations play a dominant role as endogenous factors in the pathophysiology of PD psychosis. Multivariate analysis of data from large-scale clinical trials with long-term follow-up may help characterize the pathogenesis of PD psychosis.

Antiparkinsonian medications

Both environmental susceptibility factors and patient-specific characteristics are involved in the initiation and progression of PD psychosis. The side effects of some antiparkinsonian medications are well recognized as exogenous factors triggering PD psychosis. Currently, the treatment strategy for motor symptoms of PD involves targeting several molecular targets. Based on these targets, there are eight categories of antiparkinsonian drugs in clinical use: Dopamine (DA) precursor (levodopa), dopamine receptor (DR) agonists (ropinirole, pramipexole, rotigotine), DA decarboxylase inhibitors (carbidopa, benserazide), catechol-O-methyltransferase (COMT) inhibitors (entacapone, tolcapone), monoamine oxidase (MAO)-B inhibitors (rasagiline, selegiline, safinamide), N-methyl-D-aspartate receptor antagonists (amantadine), anticholinergics (trihexyphenidyl, benztropine), and adenosine A2A antagonist (istradefylline)[59]. Long-term use of almost all types of antiparkinsonian medications may lead to psychotic symptoms in patients with PD.

A decade earlier, treating with higher levodopa equivalent daily dose at baseline was found to be a predictor of developing PD psychosis in a large-scale prospective study during 12 years of follow-up[60] and in a small retrospective study[22].

Compared with levodopa, the risk of psychosis may be higher with DR agonists. DR agonists are widely prescribed to patients with early-onset PD and PD patients in whom levodopa does not effectively control the motor symptoms. In a prospective multicenter study, patients with early-onset PD receiving DR agonist treatment at baseline were more likely to develop PD psychosis during the 2 years of follow-up[61]. In the PROPARK study, both DR agonists and DA precursors were identified as independent risk factors for hallucinations in patients with PD[62]. Barrett *et al*[63] showed a significant relationship between the occurrence of psychosis and the use of dopamine agonists in PD patients without dementia[63]. Similarly, in a cross-sectional study involving 805 PD patients, use of DR agonists was associated with impulse control disorders (mainly pathological gambling and hypersexuality)[64]. A comprehensive retrospective analysis of serious adverse drug events reported by the United States Food and Drug Administration (FDA) over a 10-year period also revealed an association of DR agonists with impulse control disorders; of these, pramipexole and ropinirole showed the strongest correlation due to their strong affinity for dopamine D3 receptors[65]. Moreover, a cross-sectional study of 805 PD patients also found an association between DR agonists and delusional jealousy[66].

PD psychosis also occurred during long-term treatment with amantadine, especially in elderly patients. A report showed that excessive reduction or sudden withdrawal of amantadine can cause delirium, which may be due to the rapid shortage of functional dopamine in the cerebral cortex and limbic system[67]. In addition, other anti-PD drugs, such as anticholinergics[56] and COMT inhibitors [68] may also increase the risk of PD psychosis.

The underlying mechanism of the relationship between antiparkinsonian medications and PD psychosis has not been fully elucidated, and relevant clinical studies have yielded contradictory results [69]. PD psychosis induced by dopaminergic drugs may be associated with abnormal upregulation of serotonin receptors in the cerebral cortex and the ventral striatum that presumably are the results of shift from dorsal to ventral in midbrain dopaminergic projections and increased thalamic/raphe serotonergic function[70]. Slow and sustained stimulation of DA receptors by dopaminergic drugs in the nigra-striatal pathway can also enhance the sensitivity of dopamine receptor and dysfunction of cerebral limbic system. PD psychosis is also believed to be due to dyshomeostasis of serotonin-dopamine balance [37].

It is worth noting that not all PD patients receiving dopamine replacement therapy present psychotic symptoms. A high prevalence of minor symptoms was shown in drug-naïve PD patients[6], and in some prospective studies, L-dopa dose equivalence was not found to increase the risk of psychosis[71]. We believe that psychosis and other neuropsychiatric complications are potential side effects of DA replacement therapy. That is, in the pathophysiology of PD psychosis, antiparkinsonian medications may act as an external factor that triggers the development of psychosis in genetically-predisposed individuals.

TREATMENT AND MANAGEMENT

Development of psychosis in PD patients should prompt careful evaluation of the potential causes by neurologists and psychiatrists. If psychotic symptoms are regarded to be related to antiparkinsonian medications, PD medications should be gradually withdrawn, and discontinued in the following sequence: Firstly, reduce the dosage or discontinue anticholinergic drugs, followed by MAO-B inhibitors, amantadine, DR agonists, COMT inhibitors, and finally DA precursors[72]. If psychotic symptoms persist after withdrawal of antiparkinsonian medications, antipsychotic drugs should be initiated early. Although reducing or even stopping the use of DA precursor and DA agonists may

minimize psychological distress, it may lead to worsening of motor symptoms of PD. Otherwise, if PD psychosis is less relevant with deterioration of motor symptoms, use of antipsychotics should be considered.

Serotonin 5-HT2A receptors antagonists

Antipsychotics can be divided into two categories. First-generation antipsychotics are not recommended for the treatment of PD psychosis due to extrapyramidal side effects (EPS). EPS caused by the use of antipsychotics can cause deterioration of motor function, including acute dystonia, akathisia, parkinsonism, and tardive dyskinesia[73]. Second-generation antipsychotics, also known as atypical antipsychotics (including clozapine, quetiapine, olanzapine, risperidone, and amisulpride) mainly mitigate or antagonize the activity of DA on receptors of DA2 and 5-HT2A. Two network meta-analyses and systematic reviews revealed that most antipsychotic medications may potentially cause EPS in schizophrenia[74] and worsening of motor function in PD psychosis[75]. EPS occurs less frequently during treatment with second-generation antipsychotics compared to the first-generation antipsychotics, which were widely used as the standard treatment for PD psychosis. The development of EPS is believed to be related to the non-specific blocking of DA2 receptors signaling in the nigrostriatal dopaminergic system by antipsychotics. Targeting only the 5-HT2A receptor is an ideal pharmacological intervention which can relieve PD psychosis without worsening PD motor function [38].

Prior to the approval of pimavanserin for the treatment of PD psychosis by the United States FDA, most guidelines for pharmacological treatment relied mainly on clinical evidence pertaining to second-generation antipsychotics. Among the antipsychotics, clozapine and quetiapine were the most commonly prescribed for PD psychosis[76].

Clozapine is a benzodiazepine antipsychotic that can regulate DA receptors (binding affinity DR1 > DR4 > DR2). It also targets multiple types of receptors, and is a potent antagonist at the 5-HT2A receptor. The therapeutic efficacy of clozapine is believed to be mediated through antagonism of the dopamine type 2 and 5-HT2A receptors. In addition, it acts as an antagonist at alpha-adrenergic, histamine H1, cholinergic, and other dopaminergic and serotonergic receptors. Clozapine was the first atypical antipsychotic drug to be proven effective in the treatment of PD psychosis with relatively low impact on PD motor symptoms[75]. Two randomized, controlled, double-blind trials conducted more than 10 years ago demonstrated the effectiveness of low-dose clozapine for the treatment of PD psychosis without significantly worsening the motor symptoms[77,78]; however, poor patient tolerance of the adverse effects of clozapine (granulocytopenia, excessive sedation, orthostatic hypotension, salivation, and metabolic syndrome) limits its clinical utility. A recent network meta-analysis suggested a notable therapeutic performance of clozapine without marked exacerbation of motor symptoms in patients with PD psychosis[79].

Quetiapine, an atypical antipsychotic medication with a similar molecular structure to clozapine, is a selective antagonist of 5-TH2 and DA2 in the limbic system of the midbrain, and it also has a high affinity for histamine and adrenergic α1 receptors in the brain. In a double-blind, placebo-controlled study of quetiapine for treatment of PD psychosis, none of the PD patients withdrew from the clinical trial due to adverse reactions, indicating favorable safety profile of quetiapine in PD patients[80]. In comparative studies for PD psychosis, the efficacy of quetiapine was similar to that of clozapine, but the results were not consistent between quetiapine and placebo[80-83]. A meta-analysis of data from six studies indicated that the efficacy of quetiapine for alleviating psychotic symptoms in PD is not higher than that of clozapine[84]. A recent systematic review of seven controlled trials revealed that the efficacy of quetiapine for treatment of psychosis in patients with PD, PD dementia, and DLB is not superior to that of placebo or clozapine; however, quetiapine showed less adverse reactions, EPS, and greater safety than clozapine[85]. Although the therapeutic benefit of quetiapine does not fully meet the need in the treatment of PD psychosis, quetiapine was one of the predominant first-line antipsychotic drugs due to its high tolerability and safety.

Pimavanserin

Pimavanserin has a unique mechanism of action in the treatment of PD psychosis. It is a highly-selective inverse agonist of the serotonin 5-HT2A receptors (Ki value: 0.087 nmol/L) rather than a DR antagonist. Different with other atypical antipsychotics with 5-HT2A receptor antagonism, pimavanserin is an inverse agonist which not only predominantly mediates 5-HT2A receptor antagonism but also mitigates the intrinsic activity of the receptors. It also has a certain affinity for 5-HT2C (Ki value: 0.44 nmol/L) [86]. In the neocortex of PD patients, with the increase in 5-HT2A receptor affinity in the visual regions, PD patients are more likely to experience visual hallucinations. Pimavanserin regulates 5-HT2A activity by targeting and controlling the excitatory impulses in the central nervous system, reducing the risk of hallucinations and delusions. In addition, pimavanserin has minimal effect on 5-HT2B, dopaminergic, adrenergic, histaminergic and muscarinic receptors, and calcium channels. Therefore, theoretically, unlike other antipsychotics, it is not expected to have adverse effects, such as worsening of motor symptoms, excessive sedation, or orthostatic hypotension[87].

The efficacy and safety of pimavanserin were evaluated in a randomized, double-blind, placebo-controlled multicenter phase III clinical trial. The trial was conducted at 52 medical centers in the United States and Canada and included 199 patients with PD psychosis recruited from August 2010 and August 2012. Compared to placebo, patients receiving pimavanserin showed 37% improvement in SAPS-PD scores without any noteworthy safety concerns or deterioration of PD motor function as assessed by the UPDRS. The results of this trial indicated a clinically significant therapeutic effect of pimavanserin for psychotic symptoms related to PD[88]. In another 6-wk, randomized, double-blind, placebo-controlled phase III clinical trial enrolling 298 PD patients with psychotic symptoms, pimavanserin arm showed a significant improvement in nighttime sleep score without affecting daytime sleepiness[89]. Ballard *et al*[90] reported the largest clinical trial to date evaluating the long-term tolerability and safety of pimavanserin in the treatment of PD psychosis with a median follow-up of approximately 15 mo (mean follow-up: Approximately 2 years; maximum: Approximately 9 years). The phase III open-label extension study was performed in 14 countries spanning three continents and included 459 PD patients with psychotic symptoms who had completed previous randomized, placebo-controlled studies. The results indicated a favorable benefit/risk profile of long-term treatment with 34 mg daily of pimavanserin without increasing caregiver burden or mortality risk related to long-term use of pimavanserin. Pimavanserin had some moderate and mild adverse reactions, the most common of which were falls, urinary tract infection, mental, and psychological abnormalities[90].

Overall, there is conclusive evidence of the favorable therapeutic effect, safety, and tolerability of pimavanserin for PD psychosis[91]. Ten-week treatment with pimavanserin showed persistent efficacy in improving psychotic symptoms, as evaluated by SAPS-PD, and improved the quality of life of caregivers[92]. A meta-analysis of four randomized controlled trials (n = 680) in patients with PD psychosis showed that pimavanserin significantly recovered psychotic symptoms, as assessed by SAPS score[93].

A recent systematic review and Bayesian network meta-analysis of four antipsychotics showed that both pimavanserin and clozapine are effective antipsychotics that may improve the symptoms of PD psychosis compared to a placebo; however, the adverse effects of clozapine were a cause for concern[79,94].

Compared with quetiapine, pimavanserin exhibited lower discontinuation rate with in early duration and higher discontinuation rate with in late duration for treating DLB and PD psychosis[95] Moreno *et al*[96] retrospectively analyzed medical records of 676 PD patients treated with atypical psychotics, and found that patients receiving pimavanserin monotherapy showed a lower risk of mortality than patients receiving quetiapine or a combination of pimavanserin and quetiapine[96]. Coincidentally, in a multicenter, open-label extension safety study assessing the long-term impact of antipsychotics compared with pimavanserin, subjects treated with pimavanserin with an add-on antipsychotic drug showed higher mortality rate in comparison with pimavanserin monotherapy group[97].

The therapeutic responsiveness of pimavanserin may be enhanced or facilitated by other PD-related drugs or interventions, such as cholinesterase inhibitors and deep brain stimulation[98]. Currently, there is limited understanding of the discrepancy between pimavanserin and other antipsychotics with respect to efficacy, safety, and tolerability and further large-scale multicenter studies are required to confirm the clinical utility of pimavanserin in other clinical settings[84].

Cholinesterase inhibitors

An increasing body of evidence from experimental and clinical research has indicated a pivotal role of dysfunction of cholinergic system in addition to dysfunction of serotonergic and dopaminergic systems in the causation of PD psychosis. These findings indicate that the cholinergic system is a viable therapeutic target in the context of PD psychosis[99,100]. In a randomized controlled study, pimavanserin significantly improved PD psychotic symptoms (assessed by SAPS-PD score) either with or without accompanying cognitive dysfunction; the study also demonstrated that cholinesterase inhibitors as cognitive-enhancing medications may augment the efficacy of pimavanserin[101]. Long-term use of anticholinergic drugs (benzhexol) was strongly associated with high risk of developing PD psychosis, while cholinesterase inhibitors (donepezil) reduced the risk[56]. The cholinesterase inhibitor rivastigmine has been recommended as first-line drug for the treatment of PD dementia by the collaborators of the Parkinson's Disease Update on Non-Motor Symptoms Study Group[102]. Cholinesterase inhibitors may also ameliorate the gait disturbance and risk of falls in PD patients[103]. Furthermore, compared with PD dementia without psychosis, PD patients with concomitant dementia and psychosis were more likely to benefit from rivastigmine[104,105]. In a randomized, double-blind, placebo-controlled phase II single-center trial, donepezil showed a significant protective effect against the development of psychotic symptoms in PD patients with apolipoprotein E ε4 non-carriers, suggesting that ApoE ε4 allele status may contribute to the resistance of cholinesterase inhibitors[106].

Most Parkinson's hallucinations are accompanied by a decline in cognitive function, ranging from mild cognitive impairment to severe dementia. In addition to improving cognitive performance, cholinesterase inhibitors may significantly alleviate hallucinations in patients with PD. Because the reported incidence of adverse effects of cholinesterase inhibitors is much lower than that of atypical antipsychotics, cholinesterase inhibitors may be an alternative treatment for improving "benign or minor" hallucinations, especially in PD dementia with psychosis[104].

Other antipsychotics and N-methyl-D-aspartate receptors agonists

Ondansetron is a selective 5-HT3 receptor antagonist which can theoretically attenuate PD psychosis. Compared with other 5-HT receptors, the 5-HT3 receptor is the only ligand-gated 5-HT receptor which has a particular mechanism to mediate the release of neurotransmitters. Although a series of clinical studies on ondansetron in the treatment of PD psychosis were carried out in the 1990s, there are three open-label trials on the efficacy of ondansetron with contradictory results, to our knowledge. In two open-label trials enrolling 40 patients, ondansetron moderately improved the symptoms of hallucination and paranoid delusion with favorable tolerability, and without severe adverse effects; furthermore, ondansetron did not deteriorate motor functions of PD or attenuate the efficacy of levodopa. However, in another study of 5 patients with PD psychosis, a similar dose of ondansetron failed to show long-term benefit. Due to the high cost of ondansetron, no further clinical trials have been reported in the subsequent two decades[107]. Investigations of other antipsychotic drugs including rispehdone, ziprasidone, aripiprazole, however, have been confined to small open-label trials.

Dysfunction of N-methyl-D-aspartate receptors (NMDAR)-mediated neurotransmission is believed to contribute to neuropsychiatric symptoms of PD. Enhancing glutamatergic transmission through blocking of glycine re-uptake was found to ameliorate the psychosis-like behaviors in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced PD marmoset model[108]. NMDAR stimulation, accomplished through allosteric modulation *via* the glycine modulatory site, may be a potential therapeutic target for PD psychosis. As a glycine re-uptake inhibitor, sarcosine was found to increase synaptic glycine concentration to activate NMDAR glycine site, thereby enhancing NMDAR function. A small-scale randomized controlled study suggested that sarcosine may relieve the neuropsychiatric symptoms of PD with dementia[109].

Further high-quality randomized controlled trials examining the efficacy and tolerability of other antipsychotics and NMDAR agonists are required to confirm these findings.

Non-pharmacological interventions

A recent cross-sectional study showed that caregivers and partners of PD patients were more inclined to use non-pharmacological treatment strategies to cope with the occurrence of psychosis compared to the use of medications[110]. Nevertheless, there is inadequate clinical evidence supporting the use of non-pharmacological interventions for PD psychosis. The role of psychological therapies such as cognitive behavioral therapy, reasoning and rehabilitation is less certain than pharmacological interventions in the therapeutic strategy for PD psychosis. Physical activity can not only improve motor symptoms, but may also play a role in relieving non-motor symptoms of PD.

CONCLUSION

The current review suggests that PD psychosis is an important non-motor symptom that predicts poor outcome. Development of PD psychosis may involve dyshomeostasis of neurotransmitters, structural and network changes, genetic profiles, and cognitive impairment. The side effects of anti-Parkinsonism medications and patient-specific characteristics are both involved in the onset and progression of psychosis during the course of PD. Unfortunately, most of the studies included in this review were observational studies which did not distinguish between treated and non-treated PD patients, since treatment with antiparkinsonian medications (*e.g.*, DA agonists) is considered as a potential cause of PD psychosis. A follow-up prospective study investigating whether antiparkinsonian medications have a significant impact on the development and progression of PD psychosis in a cohort of patients receiving different kinds and doses of antiparkinsonian medications should be conducted in future. The therapeutic approaches for PD psychosis include reducing or ceasing the use of dopaminergic drugs, and use of antipsychotics, cholinesterase inhibitors, NMDAR agonist, and non-pharmacological interventions. Pharmacological interventions for PD psychosis remain an outstanding need in clinical practice. Emerging research on future targeted therapies based on new biomarkers and genetic factors may help inform tailored therapeutic strategies.

FOOTNOTES

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REVIEW

Underlying mechanisms of mindfulness meditation: Genomics, circuits, and networks

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Abstract

Understanding neuropsychological mechanisms of mindfulness meditation (MM) has been a hot topic in recent years. This review was conducted with the goal of synthesizing empirical relationships *via* the genomics, circuits and networks between MM and mental disorders. We describe progress made in assessing the effects of MM on gene expression in immune cells, with particular focus on stress-related inflammatory markers and associated biological pathways. We then focus on key brain circuits associated with mindfulness practices and effects on symptoms of mental disorders, and expand our discussion to identify three key brain networks associated with mindfulness practices including default mode network, central executive network, and salience network. More research efforts need to be devoted into identifying underlying neuropsychological mechanisms of MM on how it alleviates the symptoms of mental disorders.

Key Words: Mindfulness meditation; Gene expression; Neural circuits; Neural networks

Core Tip: Recently, understanding neuropsychological mechanisms of mindfulness meditation (MM) has been a hot topic. We describe progress made in assessing the effects of MM on gene expression in inflammatory processes, with particular focus on stress-related inflammatory markers and associated biological pathways. We then discuss primary brain circuits related to MM and effects on symptoms of mental disorders, and three brain networks associated with MM including default mode network, central executive network, and salience network. More research examining MM effects and outcomes at the potential molecular mechanisms, critical genes and the network level is necessary.

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INTRODUCTION

Mindfulness meditation (MM) refers to a conscious, non-judgmental way of concentrating on the present[1-3], which has originated from a systematically Buddhist notion 2550 years ago[4]. It is an instant and tranquil mental state with observing all mental contents (including virtually sensations, perceptions, cognitions and feelings) at any given moment[5,6]. MM was first introduced into the mainstream medical practices by Dr. Kabat-Zinn[7] of the Massachusetts Medical School in 1982. MM developing strategies include sustained attention training, somatic and non-judgmental awareness, emotion control, detaching from a self-centered view and acceptance of the "here-and-now"[8-10]. The great majority of MM research is about clinical practices[11], especially in mental disorders such as anxiety disorder, major depressive disorder, attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, eating disorder and substance abuse[12-16].

In recent years, there has been a burgeoning interest in underlying mechanisms of MM, mainly due to increasing evidence of its positive effects on mental disorders and physical well-being. In parallel to research evaluating the effectiveness of these MM approaches, a second line of investigation focuses on unraveling the neurophysiological and psychological processes involved[17]. Recent functional and structural neuroimaging studies are beginning to provide evidence that diverse brain areas have been congruously found in both beginners undergoing temporary practice and experienced meditators[18,19]. These areas have been determined to specialize in some of these critical functions[20]. However, many of these neural areas or correlates are much more complicated and the so-called "networks or neural circuits" are likely to perform higher-level processes and multiple mental functions[21].

Understanding neuropsychological mechanisms of MM has been a hot topic in recent years. This review was conducted with the goal of synthesizing empirical relationships *via* the genomics, circuits and networks between MM and mental disorders. We describe progress made in assessing the effects of MM on gene expression in immune cells, with particular focus on stress-related inflammatory markers and associated biological pathways. We then discuss key brain circuits related to MM and effects on symptoms of mental disorders, and three brain networks associated with MM including default mode network (DMN), central executive network (CEN), and salience network. More research examining MM effects and outcomes at the potential molecular mechanisms, critical genes and the network level is necessary.

GENETIC STUDIES OF MM

Genetic studies of MM showed that differential transcription occurs in genes involved in DNA damage response, oxidative stress, and inflammatory metabolism processes, in both short and long-term practitioners[22-24]. In most studies, these results were correlated with reduced stress and fatigue, improved immune response, and clinical symptoms. A few studies examined neurotrophins[25,26]. Transcriptomic analyses were performed in both healthy and clinical populations combining diverse MM activities in several longitudinal and mixed design studies and obtained similar results[24,27-29].

Creswell and colleagues reported NF-κB-related gene expression in older adults responding to the Mindfulness-Based Stress Reduction (MBSR) intervention compared to a wait-list control group, who in contrast, showed the gene to be up-regulated[30,31]. Bakker *et al*[32] showed that genetic variation in muscarinic acetylcholine receptor M2 (CHRM2) and the μ1 opioid receptor (OPRM1) moderate the positive impact on the level of positive affect following mindfulness-based cognitive therapy (MBCT) with depressive symptoms, and proposed that variation in genetic factors in response to MBCT may be contingent on the association with the regulation of positive affect[32].

In the study by Dada *et al*[33], intraocular pressure in primary open angle glaucoma appeared significantly decreased after MM. Significant upregulation of the anti-inflammatory genes and downregulation of the proinflammatory genes were found in glaucoma patients who underwent a 3-wk MM course. These results indicate that MM has a direct impact on trabecular meshwork gene expression in ocular tissues. Similarly, the practice of MM was shown to improve immune function by normalizing stress-related serum biomarkers, and positively modifying gene expression[25]. Moreover, increased blood levels of brain-derived neurotrophic factor indicated a positive impact on retinal ganglion cells rescue from death in patients with primary open angle glaucoma[26].

GENOME-WIDE ASSOCIATION STUDIES

Genome-wide approaches to gene activity have started to elucidate the effects of MM on gene modulation[34]. For example, utilizing microarray analysis of global mRNAs to study the methylome of peripheral blood mononuclear cells of 17 experienced meditators of one-day intensive MM practice, found 61 differentially methylated regions[35]. Similarly, studying the transcriptomic effects in six individuals after twice-daily transcendental MM practice revealed 200 genes differentially expressed [24]. Studies focusing on the impact of MM for treating hypertension, irritable bowel syndrome and inflammatory bowel disease showed that several genes related to fundamental pathways were differentially expressed[27,28].

Nevertheless, most previous studies were cross-sectional studies with small sample sizes[22,26,36, 37]. The large-scale genomic study, by Chandran *et al*[38], analyzed the meditation-specific core network of advanced MM practice, rather than changes in the expression of a few individual genes. They observed that the up-regulated RNA coexpression networks are directly related to the immune response, including 68 genes differentially expressed after MM. Interestingly, these authors reported that the top 10 hub genes in the up-regulated module included many previously identified genes known to regulate the immune system and related to the type I interferon signaling pathway. They identified nine coexpression and protein–protein interaction networks associated with MM using a multistage approach. This suggests that MM, as a behavioral intervention, may be an effective component in treating diseases characterized by increased inflammatory responsiveness with a weakened immune system.

NEURAL CIRCUITS RELATED TO MM

Feelings of fear circuit related to MM

The connections between the amygdala and key areas of the prefrontal cortex, specifically the anterior cingulate cortex (ACC) and orbitofrontal cortex can regulate the feelings of fear (Figure 1A). Specifically, the overactivation of these circuits may lead to feelings of fear. King *et al*[39] examined the neurobiological effects of 16-week mindfulness-based exposure therapy (MBET) compared with present-centered group therapy in task-evoked functional connectivity of combat veterans with posttraumatic stress disorder (PTSD). The MBET group showed higher neural activation in the rostral ACC, dorsal medial prefrontal cortex (mPFC), and left amygdala that were significantly associated with improvement in PTSD symptoms. The interactive results of group and time showed that MBET increased responses of the left medial PFC related to fearful faces, and greater post-therapy effects on the fusiform/lingual gyrus and amygdala to angry faces, suggesting that MM practices may be related to greater involvement in threat cues of patients with PTSD. It also found that MBET was associated with increased activation of the lingual/fusiform gyrus and amygdala to angry faces. It was proved that mindfulness-based art therapy is associated with significant changes in cerebral blood flow, including the insula, amygdala, hippocampus, and caudate nucleus, which is associated with a period of reduced anxiety within 8 wk[40]. These brain structures are involved in MM tasks and emotional processing related to anxiety[41-43].

The physiology of fear circuit related to MM

Hoge and colleagues provide some support that MM could mitigate the elevated response to acute stress observed in generalized anxiety disorder on the hypothalamic pituitary adrenal (HPA) axis, by measuring blood levels of cortisol and adrenocorticotropic hormone (ACTH) with treatment. Over the course of the treatment, participants in the MM group exhibited a reduction in their ACTH Area-Under-the-Curve concentrations[44]. Similarly, Pace *et al*[45] demonstrated that healthy participants who practiced more MM had a faster drop in cortisol after the Trier Social Stress Test than healthy participants who practiced MM less frequently[45]. The physiological reaction to a fearful stimulus involves activation of multiple systems, including the autonomic nervous system, respiratory system, and endocrine system[46,47]. Part of the characteristic of the fear response may be endocrine influence [48]. The HPA axis is responsible for endocrine output during the stress/fear response, and is regulated

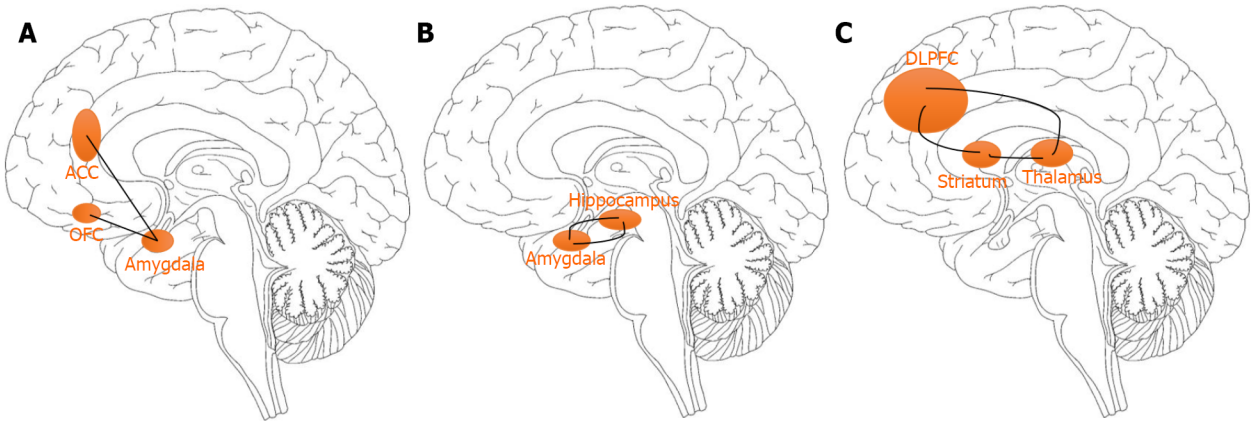

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Figure 1 Circuits associated with mindfulness meditation. A: Feelings of fear circuit related to mindfulness meditation; B: Re-experiencing circuit related to mindfulness meditation; C: Worry/obsessions circuit related to mindfulness meditation. DLPFC: Dorsolateral prefrontal cortex; ACC: Anterior cingulate cortex; OFC: Orbitofrontal cortex.

by the amygdala *via* reciprocal connections with the hypothalamus[49-51].

Activation of the autonomic system is regulated by connections between the amygdala, the locus coeruleus, and parabrachial nucleus and leads to an increase in heart rate, respiration rate and blood pressure that is necessary for a fight/flight reaction[52,53]. Several studies have consistently found an association between cardio-respiratory parameters and MM related to slow paced breathing[54]. Park and Park[55], and Stark *et al*[56] found an increase in the high frequency power paralleled during paced breathing of MM at 10 b/min as compared to spontaneous breathing. Generally, slow breathing techniques (such as MM exercises) enhance interactions between autonomic nerves, cerebral, and mental flexibility, linking parasympathetic and central nervous system activities with emotional control and well-being. Slow breathing techniques seem to promote a predominance of the parasympathetic autonomic system with respect to the sympathetic one, mediated by the vagal activity[57,58].

Re-experiencing circuit related to MM

Sevinc *et al*[59] investigated potential neural correlates of MM intervention and in extinction learning (the context-dependent recall of extinction) using MBSR training. Group-by-time interactions found that MBET was associated with greater increases in the hippocampus and the supramarginal gyrus during extinction recall. Also during the early phase, the MBSR training group showed increased hippocampal connectivity to the supramarginal gyrus. Increased connectivity between the hippocampus and primary somatosensory cortex during retrieval of extinguished stimuli following MBSR training was also observed[60]. Furthermore, Sevinc *et al*[61] demonstrated an association between functional changes in the hippocampal connectivity and changes in anxiety following MM training. These findings provide a better understanding of the mechanisms through which MM training relieves anxiety. Anxiety can be triggered not only by an external stimulus but also internally through traumatic memories stored in the hippocampus (Figure 1B), which can activate the amygdala, causing the amygdala, in turn, to activate other brain regions and generate a fear response[46,62]. This is known as re-experiencing and is a central feature of PTSD[63].

Worry/obsessions circuit related to MM

King *et al*[64] studied the potential neural relevance of MBET among combat veterans who suffered from PTSD following deployment to Afghanistan and/or Iraq. MBET showed increased connectivity with the dorsolateral prefrontal cortex (DLPFC) and dorsal ACC following therapy by a group × time interaction; and posterior cingulate cortex (PCC)-DLPFC connectivity was related to improvement of avoidant and hyperarousal symptoms in PTSD. Worry refers to anxious misery, apprehensive expectation, catastrophic thinking, and obsessions (Figure 1C). It is hypothetically related to a cortico-striatal-thalamic-cortical loop originating in the DLPFC and projecting the striatal complex, than the thalamus, and ending in the DLPFC[65,66]. Overactivation of the DLPFC can result in symptoms such as worry or obsessions[67-69].

MM AND BRAIN NETWORKS

In identifying the neural mechanism of MM, most inferences have focused on the role of isolated brain areas in supporting the observed cognitive processes and concurrently enhancing behavioral outcomes;

however, consisting of key areas that are temporally correlated with one another (a large-scale brain network) must be considered[70]. There are three key functional networks related to attention, cognitive control and interoceptive awareness: DMN, CEN, and salience network according to the former neuroimaging literature on MM[71].

The DMN is associated with task-irrelevant and mind-wandering thoughts[72,73]. Greater activations in core nodes of the PCC, mPFC, and bilateral parietal cortices, lead to introspective thought, including activities such as daydreaming or retrieving memories[74-77]. The CEN, with core nodes located in the bilateral parietal cortices and DLPFCs, is typically associated with increased activation during distractibility and goal-directed behavior[78-80]. The CEN is linked to decision making by converging external information with internal representations[75,81-83]. The salience network is responsible for changing and monitoring the states of the CEN and the DMN, and presumably accepts the distribution of attentional resources to support cognitive control[84].

Based on structural and functional neuroimaging studies, MM is related to the activities and connections in the three networks, each of which is responsible for different stages of MM in experienced practitioners[85-87]. The activity and connectivity of the DMN have been suggested as potential biomarkers for monitoring the effect of MM[88]. It describes that MM may improve DMN, CEN and salience network functions to target symptoms of anxiety disorders[9]. King *et al*[64] investigated potential neural correlates of MBET in patients with PTSD compared with an active control therapy. After MM training, the connection between the DMN and CEN increase, which may improve the ability to shifting of voluntary attention. There is increased connection between the DMN and the DLPFC areas in CEN before and after MBET.

FUTURE DIRECTIONS

Currently, few scientific studies have investigated the neural connections of MM at the level of critical genes and brain networks[89-93]. Notably, there has been a shift from isolated areas to large-scale networks, circuits or large-scale genetic changes[38,94,95]. Further research examining MM effects and outcomes at the potential molecular mechanisms, critical genes and the network level is necessary[96,97]. As the knowledge of brain function increases, we can better understand what the neural connections that affect clinical symptoms are. In turn, this will better characterize the specific deficiencies of any particular patient. We can predict that the development of neuroscience research on MM will help strengthen neuronal circuits that are damaged by mental disorders, and help develop personalized interventions for individuals' unique defects and strengths.

CONCLUSION

Recently, understanding neuropsychological mechanisms of MM has been a hot topic[98-100]. We describe progress made in assessing the effects of MM on gene expression in inflammatory processes, with particular focus on stress-related inflammatory markers and associated biological pathways. We then discuss primary brain circuits related to MM and effects on symptoms of mental disorders, and expand our discussion to identify three brain networks associated with MM including the DMN, CEN, and salience network. More research examining MM effects and outcomes at the potential molecular mechanisms, critical genes and the network level is necessary.

FOOTNOTES

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REVIEW

Depressive disorder and antidepressants from an epigenetic point of view

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Abstract

Depressive disorder is a complex, heterogeneous disease that affects approximately 280 million people worldwide. Environmental, genetic, and neurobiological factors contribute to the depressive state. Since the nervous system is susceptible to shifts in activity of epigenetic modifiers, these allow for significant plasticity and response to rapid changes in the environment. Among the most studied epigenetic modifications in depressive disorder is DNA methylation, with findings centered on the brain-derived neurotrophic factor gene, the glucocorticoid receptor gene, and the serotonin transporter gene. In order to identify biomarkers that would be useful in clinical settings, for diagnosis and for treatment response, further research on antidepressants and alterations they cause in the epigenetic landscape throughout the genome is needed. Studies on cornerstone antidepressants, such as selective serotonin reuptake inhibitors, selective serotonin and norepinephrine reuptake inhibitors, norepinephrine, and dopamine reuptake inhibitors and their effects on depressive disorder are available, but systematic conclusions on their effects are still hard to draw due to the highly heterogeneous nature of the studies. In addition, two novel drugs, ketamine and esketamine, are being investigated particularly in association with treatment of resistant depression, which is one of the hot topics of contemporary research and the field of precision psychiatry.

Key Words: Epigenetics; Depression; DNA methylation; Histone tail modification; microRNA; Antidepressants

Core Tip: Deeper knowledge on the biological background of depressive disorder could be achieved through understanding of epigenetic mechanisms that alter the response of cells to environmental stimuli. Antidepressants are of particular interest since it has been shown that they affect DNA methylation, histone modifications, and microRNA expression. As not all patients respond to prescribed antidepressants, it is of interest to discover specific biomarkers that could be used in a clinical setting.

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INTRODUCTION

Depressive disorder

Depressive disorder is a complex heterogeneous disease that affects more than 280 million people[1]. The principal form of depressive disorder is major depressive disorder (MDD). Symptoms of depressive disorder are persistent depressive mood, diminished ability to feel pleasure and rejoice, weight changing, disturbed sleep, loss of energy, lowered self-esteem, trouble with concentration, elevated emotional psychomotor activity in children and teenagers, psychomotor agitation or motor retardation, and self-injuring or suicidal ideation[2]. The suicidality phenotype includes ideation, suicide attempt, and death by suicide. MDD is, along with bipolar disorder, schizophrenia, and substance use disorder, one of the most common mental disorders in people who die by suicide[3]. Depression contributes to suicidality, and it increases mortality risk by 60%-80%[4]. According to the Diagnostic and Statistical Manual of Mental Disorder Diagnosis, MDD must exhibit five (or more) out of ten symptoms[2].

The prevalence of depression is higher for women (4.1%) than for men (2.7%)[5]. Sex differences are exhibited in multiple cells of the central nervous system (CNS), neurons, astrocytes, and microglia[6]. Emerging data is showing that besides hormones, epigenetic differences have considerable sexual dimorphism[7]. However, steroid hormone levels influence levels of DNA methyltransferases (DNMTs). For example, female rats had higher levels of DNMT3a and methyl CpG binding protein 2 (MeCP2) in the amygdala (an important center for modulating juvenile social play, aggression, and anxiety)[6] and the preoptic area[7]. As a result of a difference in DNMT3a, there is also a difference in the DNA methylation level[6].

Moreover, people aged 50 years and more have a 1.5 times higher risk for developing depression than younger people[5]. Modern lifestyle promotes independence of the environmental light/dark cycle, which leads to shifting in sleep-wake patterns. Circadian rhythm disruption is affected by the increase in nocturnal activity, decrease of sleep, and extended exposure to artificial light during the nighttime [8]. Limbic brain regions, monoamine neurotransmitters, and the hypothalamic-pituitary-adrenal (HPA) axis are under circadian regulation. It is thought that the perturbation of circadian rhythms contributes to the prevalence of depression and other mood disorders[9].

Depressive disorder is a result of the interplay of many different factors: Environmental, genetic, neurobiological, and cultural[10]. Known environmental risk factors for developing depressive disorder are poverty, negative experiences in the family (bad relationship, violence, divorce, child maltreatment), or other stressful life events. In the time after a stressful life event, the risk for depressive disorder is elevated but the effects of adversity can persist over time[4]. In depressive symptoms that persist over time, stable molecular adaptations in the brain, especially at the level of epigenetics, might be involved [11].

Genetic heritability for depressive disorder, estimated from twin studies, is around 35%–40%[10,12]. Genome-wide association studies have discovered multiple loci with small effects that contribute to MDD[13]. Pandya *et al*[14] collected results from neuroimaging, neuropsychiatric, and brain stimulation studies and showed similar results. In recent years, more and more studies are oriented towards epigenetics to understand new mechanisms and the way epigenetics is linked to a depressive state.

The nervous system is susceptible to shifts in the activity of epigenetic modifiers, which allow for significant plasticity and response to rapid changes in the environment[15]. Epigenetic mechanisms are dynamic. They are very important for early development of the organism as well as later in life, as a response to external factors[16].

From a biological perspective, there are four theories of depressive disorder: Monoamine theory, stress induced theory, neurotrophic theory, and cytokine theory (Figure 1).

Theories of depressive disorder

The monoamine theory of depressive disorder: Monoamine neurotransmitters (serotonin, norepinephrine, and dopamine) are chemical messengers involved in the regulation of emotion, arousal, and

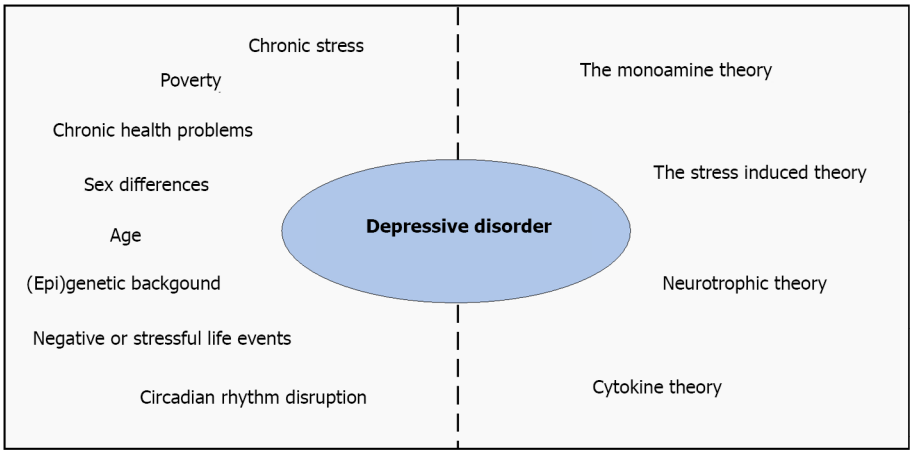

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Figure 1 Depressive disorder risk factors. Depressive disorders are influenced by various and often overlapping risk factors that form theories of depressive disorders.

certain types of memory. The monoamine hypothesis of depressive disorder proposes development of depressive disorder by signal dysfunction between neurons: A decreased level of neurotransmitters leads to the depressive state[2,17].

The stress induced theory of depressive disorder: Prenatal stress, early-life adversities, chronic stress, and stressful life events are all strong predictors of the onset of depressive disorder. The HPA axis, a neuroendocrine system, is responsible for adaptation to changing environments. Response to stress begins in the hypothalamus, with the secretion of corticotropin-releasing hormone, which affects the pituitary gland to release adrenocorticotropic hormone. Adrenocorticotropic hormone circulates in the blood and stimulates the release of glucocorticoid hormones (cortisol) in the adrenal cortex. Cortisol binds to glucocorticoid receptors in the brain, which are key regulators of the stress response. Cortisol with a negative loop inhibits the HPA axis. Dysregulation of the negative loop is associated with depressive disorder[2,17].

Neurotrophic theory of depressive disorder: Neurotrophic factors are peptides or small proteins that support the growth, survival, and differentiation of developing and mature neurons. Decreased neurotrophic support affects the development of depressive symptoms. Brain-derived neurotrophic factor (BDNF) is a very well examined neurotrophic factor. Many studies made on brain and blood showed decreased expression of *BDNF* in patients with depressive disorder. Also, decreased *BDNF* expression has been associated with epigenetic modifications of the *BDNF* gene[17].

Cytokine theory of depressive disorder: Cytokines are small secreting proteins important in cell signaling. Cytokines include chemokines, interferons, interleukins (IL), lymphokines, and tumor necrosis factors (TNF)[18]. The cytokine (or inflammation) theory of depressive disorder suggests that inflammation has a significant role in its pathophysiology. Patients with depressive disorder have increased inflammatory markers, IL-1β, IL-6, TNF-α, and C-reactive protein[19]. Depressive disorder is not a typical autoimmune disease, so the elevation of cytokines in patients with depressive disorder is lower than in autoimmune or infectious diseases[2].

There are several proposed theories by which the immune system (cytokines and immune cells) could affect depressive-like behavior[20]. For example, inflammation in peripheral tissue can signal the brain *via* the vagus nerve, cytokine transport systems, and a leaky blood-brain barrier caused by rising TNF-α, which leads to brain accessibility for other peripheral signals[19].

Cytokines in the brain elevate during chronic stress and depressive disorder, but besides peripheral cytokines they can also arise from the CNS. Cytokines IL-6 and TNF-α activate indoleamine-2,3-dioxygenase, which decreases tryptophan (a serotonin precursor) and consequently reduces serotonin. Moreover, indoleamine-2,3-dioxygenase is included in the kynurenine pathway. Metabolites from this pathway activate monoamine oxidase (MAO), which degrades serotonin, dopamine, and norepinephrine. Cytokines might also act directly on neurons, changing excitability, synaptic strength, and synaptic scaling. Furthermore, cytokine IL-1β can contribute to heightened activation of the HPA axis and lowering inflammatory response to stress. During chronic stress microglia (neural immune cells) enhance phagocytic activity and synaptic remodeling[20].

Microglia represent 10% of all brain cells[21]. During the development of the organism, microglia are extremely active. They significantly contribute to shaping and refining developing neural circuits by regulating neurogenesis, synaptogenesis, synaptic pruning, and behavior. Early life stress, which is strongly associated with depressive disorder and other mental disorders, can trigger microglia perturb-

ations and affect development through changed morphological and functional changes of microglia. For example, microglial phagocytic activity and neuronal-microglial signaling can disrupt neural circuits and alter the formation of behavior. Furthermore, aberrant functionality of maturing microglial cells can alter their developmental programs and have long-lasting consequences for their reactivity[22]. It is thought that innate immune memory is mediated through epigenetic reprogramming and can last *in vivo* for several months[23].

Epigenetics

In the 1940s, Waddington named the environmental influence of the genome epigenetics. Epigenetic modifications alter gene expression without changing the DNA sequence. The three key types of epigenetic change that occur in cells are DNA methylation, histone posttranslational modifications, and non-coding RNAs. The first two regulate gene transcription through altered chromatin structure and DNA accessibility, while the latter one regulates already transcribed messenger RNA (mRNA)[10]. Studies of epigenetics have escalated in the last 20 years and are gaining importance in the field of psychiatry. Through epigenetic studies, further understanding of depressive disorder is being achieved, but there are still many questions left to answer (Figure 2).

DNA methylation: DNA methylation is a process in which a single methyl group is added on the 5C of the cytosine DNA base. Methyl groups are transferred from S-adenosyl-L-methionine to cytosine by DNMTs[17]. In mammals, there are three groups of DNMTs; DNMT1, DNMT2, and DNMT3. DNMT1 maintains DNA methylation, DNMT3a and DNMT3b carry out *de novo* DNA methylation, and DNMT3L modulates DNMT3a and DNMT3b. DNMT2 has no DNA methylation activity. Instead it catalyzes RNA methylation, specifically on transfer RNAs[24]. DNA methylation mainly occurs at cytosine-phosphate-guanine (CpG) dinucleotides. When those dinucleotides are repeated many times in DNA sequence, they are called CpG islands. CpG islands have an average length of 1000 bp, and they contain more than 50% guanines and cytosines. Approximately 40% of genes contain CpG islands in promoter regions. Methylation of a promoter results in the inability of transcription factors to bind properly to regulatory elements and repression of gene transcription[17]. However, in mammals DNA methylation also occurs at CpA, CpT, and CpC. Those non-CpG methylation sites are common in brain tissue and several other tissue types[25] but at a three times lower rate than CpG methylation[26]. Besides methylation in promoter regions, it can also occur in the gene body and in intergenic regions and affect gene transcription[27]. DNA methylation is a stable cell state, but it can be reversed. Demethylation occurs when 5-methylcytosines are oxidized back to cytosines *via* three cytosine derivate forms: 5-hydoxymethylcytosine, 5-formylcytosine, and 5-carboxylcytosine[28].

Histone tail modification: The basic unit of chromatin is the nucleosome, which consists of negatively charged DNA and positively charged histone proteins. The nucleosome is an octamer, containing two copies of H2A, H2B, H3, and H4 proteins. Typically, a 147 bp long segment of DNA is wrapped around each nucleosome. H1 protein serves as a linker protein between the other histones that helps to condense nucleosomes even more[29]. Histone proteins have a long amino acid tail on their N-terminal end. In contrast with the core part of the histone protein, this extended part is very dynamic and is prone to chemical modifications[30]. To describe histone modifications we follow a standard nomenclature. First we write the name of the histone protein (H2A, H2B, H3, H4, or H1), then the modified amino acid residue (the name of amino acid and its site; for example, K4–lysine at site 4), and finally the type of modification (for example trimethylation–me3). An example of a final structure is H3K4me3. Specific proteins chemically modify histones and change chromatin conformation. Changes in conformation lead to the opening or closing of the chromatin, which allows or prevents transcription.

There are many different types of histone posttranslational modification, such as acetylation, methylation, phosphorylation, ubiquitination, *etc*, that can be modified differently and by different proteins called "writers" and "erasers." Furthermore, "readers" are proteins important for cross-talk between different epigenetic modifications. For example, DNA methylation and histone modifications mutually influence each other. There are many different reader domains that recognize histone modifications[31]. The most studied histone modifications are acetylation and methylation[29].

Histone acetyltransferases are proteins that transfer acetyl groups to lysine residues on the amino acid tail of histone proteins, while histone deacetylases (HDACs) are proteins that remove acetyl groups from the histone tails. Addition of a negative acetyl group loosens the tight bond between the negatively charged DNA and positively charged histones. This enables access of transcriptional machinery to the regulatory parts of DNA and consequently gene transcription[10].

Histone methylation is the adding of methyl groups to lysine and arginine residues on the histone tail. Histone methyltransferases add methyl groups to the histone tail, and histone demethylases remove methyl groups. Methylation of the histone tail can work in two ways. It can open chromatin or condense it. This depends on the position of the lysine/arginine residue in the histone tail and the number of methyl groups added to the amino acid[10].

MicroRNAs: Non-coding RNAs include many different RNAs: PIWI-interacting RNAs, small nucleolar RNAs, long non-coding RNAs and the most studied, microRNAs (miRNAs). MiRNAs are noncoding, 19–24 nt long RNAs that bind to mRNAs. A mature miRNA goes through biogenesis before it achieves

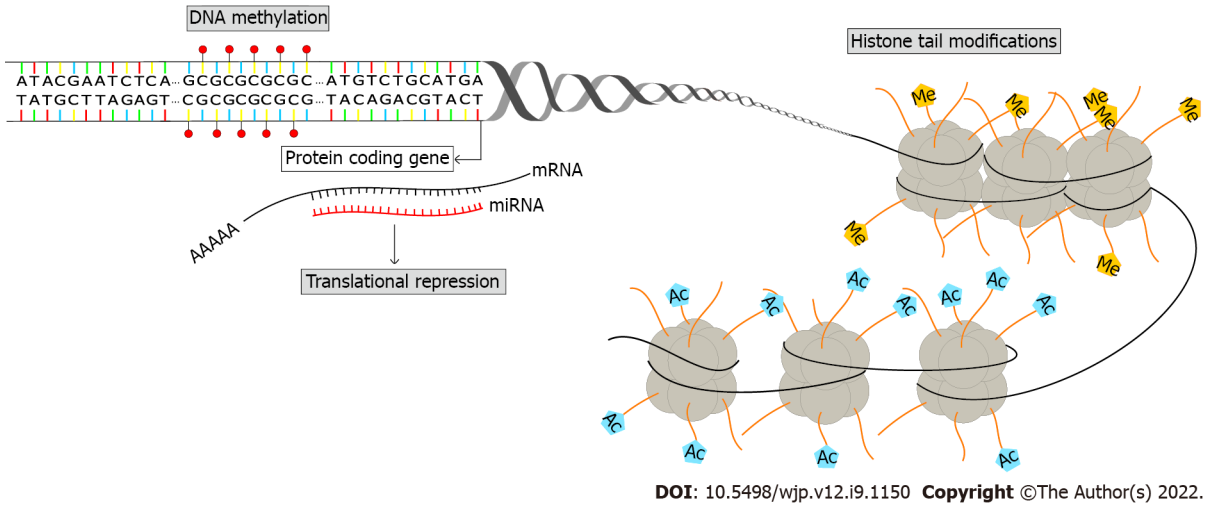

Figure 2 Epigenetic mechanisms. Epigenetic mechanisms include DNA methylation, noncoding RNA activity (such as microRNA), and posttranslational histone tail modifications. Ac: Histone acetylation; Me: Histone methylation; mRNA: Messenger RNA.

its final form. Briefly, it is transcribed as a 1 kb long primary RNA with a stem and loop structure. Primary miRNA is cleaved by Drosha ribonuclease III into a 60–100 bp long precursor miRNA. Precursor miRNA is then translocated from the nucleus into the cytoplasm where the endonuclease Dicer converts it into an unstable, double stranded small RNA. One strand of the duplex is degraded and the other, the mature miRNA, incorporates into the RNA-induced silencing complex along with Argonaut protein. Mature miRNA is complementary to one or more mRNAs. It binds to the 3′ untranslated region of the target mRNA and silences targeted mRNA or sends mRNA to degradation when binding is highly complementary[32].

EPIGENETICS AND DEPRESSIVE DISORDER

Biomarkers that could be associated with MDD are BDNF, the cortisol response, cytokines, and neuroimaging. However, due to the complex nature of depressive disorder a single biomarker is not sufficient for use in diagnosis or monitoring of the disorder. Therefore, it has been proposed to examine multiple biomarkers and use them for patient examination[33]. In genetic studies several polymorphisms associated with a depressive state were found in genes of the monoaminergic system (the gene that encodes for serotonin transporter, receptor genes for dopamine and serotonin, genes involved in signaling of noradrenaline and dopamine…), and genes involved in the functioning and regulation of the HPA axis[2] but did not reveal the role of the DNA sequence itself in the etiology of depressive disorder. Future epigenetics may present new findings, which could be included as possible biomarkers for MDD[33].

Epigenetic modifications were studied in the saliva and blood of the depressed patients, postmortem brain tissue of depressed patients who died by suicide, and rodent animal models (rats and mice). There are several ways to induce stress and a depressed state in animal models[34]. Chronic stress is induced with "bullying" by a bigger more aggressive mouse or witnessing another mouse being physically aggressed for several days[10]. Early life stress from humans can be evoked on animal models by maternal separation of offspring during early postnatal periods. Such induced stress in animals results in mimicking certain behavioral features of human depressive disorder. It has been shown that these methods evoke epigenetic changes, similar to those seen in humans[34].

Tables 1–4 show selected studies of epigenetic changes detected in samples of depressed patients and animal models. The most studied epigenetic modification is DNA methylation, and it has been rather extensively investigated in the *BDNF* gene, specifically exon I. In studies of depressive disorder induced by stress in the prenatal and early stages of life, methylation of glucocorticoid receptor gene (*NR3C1*) was the most analyzed. Lately, more studies are also considering histone 3 modifications among which are methylation of lysines 27, 9, and 4 and acetylation of lysine 14. Studies of miRNAs are diverse and are showing that a more standardized approach is needed.

DNA methylation studies (Table 1 and Table 4) were performed on blood, buccal swabs, or brain tissue of humans and brain tissue of animal models. As we can see from Table 1, there are a lot of studies investigating DNA methylation in the *BDNF* gene (different parts of the *BDNF* gene were tested; exon I, IV, IX, promoter region, whole gene). Most studies showed elevated DNA methylation in the *BDNF* gene in depressed patients. However, a few studies showed that DNA methylation is decreased.

Table 1 DNA methylation studies on depressed subjects, also associated with suicidality and life adversities

Gene (region)	Alteration	Subjects and collected tissue	Ref.
NR3C1 1-F and *FKBP5* intron 7 promoter	↑ DNA methylation at *NR3C1* 1-F, without significant differences at any of the measured individual CpG site in depressed patients. Association in salivary cortisol level and DNA methylation. ↑ DNA methylation in *NR3C1* 1-F at CpG 38 site in depressed patients, with early life adversity. No differences in *FKBP5* intron 7 promoter	33 depressed patients (24 females, 9 males), 34 controls (21 females, 13 males). Whole blood and saliva	Farrell *et al*[67], 2018
MAOA and *NR3C1* exon 1-F	↓ DNA methylation at *MAOA*'s first exon/intron junction; significantly ↓ at CpG 8 site from the intron region. ↑ DNA methylation at *NR3C1* 1-F's promoter and exon in individuals experienced early parental death; significant ↑ at CpG 35 and 10.11 (sites close to NGFI-A binding site)	82 (for *MAOA* gene) and 93 (for *NR3C1* 1-F gene) depressed females, victims of early-life adversity and 92 or 83 controls. Saliva	Melas *et al*[35], 2013
BDNF, *NR3C1*, and *FKBP5*	Significant alteration in DNA methylation at 9 sites in *BDNF* gene body, at 6 sites in *NR3C1* promoter region, and at 4 sites in *FKBP5* gene body, 3'UTR and promoter	94 maltreated and 96 non-traumatized children. Saliva	Weder *et al*[68], 2014
BDNF exon I	↓ DNA methylation; differences at loci 87, 88 and 92–94, located within the CpG island region on the promoter of the exon I	360 depressed patients (32 females, 328 males). Saliva	Song *et al*[69], 2014
BDNF promoter between –694 and –577 relative to the transcriptional start site (12 CpG sites). *SLC6A4* promoter adjacent to exon 1a between –479 and –350 relative to the transcriptional start site (10 CpG sites)	Depressed mood in 2nd trimester associated with ↓ DNA methylation at maternal *SLC6A4* promoter methylation status. ↓ DNA methylation at *SLC6A4* promoter in infants, from mothers with higher depressed mood during 2nd trimester. No difference in *BDNF* gene	82 female and male infants exposed to prenatal maternal stress–33 mothers treated with SRI and 49 mothers not treated with SRI. Blood	Devlin *et al*[70], 2010
NR3C1 exon 1-F and *BDNF* promoter IV	↑ DNA methylation within *NR3C1* 1-F gene (male infants). ↓ DNA methylation within *BDNF* promoter IV region (female and male infants)	20 female and male infants exposed to prenatal maternal stress and 37 controls. Buccal tissue	Braithwaite *et al*[71], 2015
NR3C1 exon 1-F	Depressed mood in 2nd trimester associated with ↑ DNA methylation of CpG 2 site (relative to translational start site) at *NR3C1* exon 1-F in infants. Depressed mood in 3^{d} trimester associated with ↑ DNA methylation of CpG 2 and CpG 3 site (relative to translational start site) at *NR3C1* exon 1-F in infants	46 depressed females (33 treated with SRI and 13 not medicated), 36 controls, and their infants. Blood	Oberlander *et al*[72], 2008
BDNF, *NR3C1*, *CRHBP*, *CRHR1*, *FKBP5* promoter	Hypermethylated *BDNF*, *NR3C1*, *CRHBP* and *FKBP5* promoter. mRNA down regulation of *BDNF, NR3C1, FKBP5* and *CRHBP* in MDD-suicidal ideation group	15 females and 9 males with MDD (14 with and 10 without suicidal ideation) and 20 controls (14 females and 6 males). PBMC	Roy *et al*[73], 2017
BDNF exon I promoter	↑ percentage of methylated reference values	207 female and male MDD patients and 278 controls. PBMC	Carlberg *et al*[58], 2014
BDNF exon I promoter	↑ at CpG 1, CpG 3 and CpG 5 site, ↓ BDNF serum level	49 female and male MDD patients and 57 controls. Blood	Schröter *et al*[74], 2020
BDNF exon I and IV promoter	↑ methylation at CpG site 3 of promoter IV	251 female and male MDD patients aged 65 > and 773 controls. Buccal tissue	Januar *et al*[75], 2015
BDNF exon IX	Changes in DNA methylation; ↑ at CpG site 217, ↓ at CpG site 327, and 362. ↓ BDNF level and mRNA levels	51 MDD patients (35 females and 16 males) and 62 controls (39 females and 23 males). Venous blood	Hsieh *et al*[60], 2019
BDNF upstream of exon I and IV	Changes in DNA methylation within CpG exon I promoter	20 MDD patients (12 females and 8 males) and 18 controls (8 females and 10 males). Blood	Fuchikami *et al*[76], 2011
MYO16 and *IDE*	↑ 5hmc in one CpG position of *MYO16* and two CpG positions of *IDE* in the PFC. ↑ gene expression of *MYO16*. ↓ gene expression of *IDE*	19 depressed male suicide victims and 19 controls. Brain tissue (PFC; inferior frontal gyrus)	Gross *et al*[77], 2017
$GABA_A$ receptor α1 subunit promoter	↑ DNA methylation of the CpG 2 and CpG 4 site (500 bp from transcriptional start site). ↑ DNMT-3B expression in FPC. ↓ expression of *DNMT1* mRNA and ↑ expression of *DNMT3b* mRNA in FPC. ↓ expression of *DNMT3b* and *DNMT1* mRNA in AMG	10 male suicide victims and 10 controls. Brain tissue (FPC, AMG)	Poulter *et al*[78], 2008

SLC6A4 promoter	↑ mean methylation level	28 MDD patients (20 females and 8 males) and 29 controls (21 females and 8 males). Blood	Iga *et al*[79], 2016
NR3C1 exon 1 promoter	↑ methylation at CpG 30 and 32 site. ↓ expression of total *NR3C1* mRNA and *NR3C1*-1F mRNA in suicide victims without childhood abuse and control group	12 suicide victims with traumatic childhood experience, 12 suicide victims without traumatic childhood experience, and 12 controls. Brain tissue (HPC)	McGowan *et al* [80], 2009

↓: Decreased expression; ↑: Increased expression; AMG: Amygdala; *BDNF*: Brain derived neurotrophic factor; bp: Base pair; CpG: Cytosine-phosphate-guanine; *CRHBP*: Corticotropin releasing hormone binding protein; *CRHR1*: Corticotropin releasing hormone receptor 1; *DNMT3B*: DNA methyltransferase 3; *FKBP5*: FK506 binding protein 5; FPC: Frontopolar cortex; $GABA_A$: γ-aminobutyric acid; H3K14ac: Acetylation of lysine 14 on histone 3; *HDAC2*: Histone deacetylase 2; HPC: Hippocampus; *IDE*: Insulin-degrading enzyme; MDD: Major depressive disorder; *MAOA*: Monoamine oxidase A; mRNA: Messenger RNA; *MYO16*: Myoxin XVI; NGFI-A: Nerve growth factor-induced protein A; *NR3C1*: Nuclear receptor subfamily 3 group C member 1; PFC: Prefrontal cortex; PBMC: Peripheral blood mononuclear cells; *SLC6A4*: Solute carrier family 6 member 4; SRI: Serotonin reuptake inhibitor antidepressant; UTR: Untranslated region; 5hmc: 5-hydroxymethylcytosine.

Table 2 Histone tail modifications studies on depressed suicide victims

Gene (region)/histone tail modification	Alteration	Subjects and collected tissue	Ref.
BDNF, H3K9/14ac, H3K27me2	↓ H3K9/14ac, ↑ HDAC2, ↑ HDAC3, ↑ H3K27me2, ↓ BDNF in HPC and NAc. ↑ Sin3a in HPC	14 suicide victims (5 females and 9 males) without psychiatric diagnosis and 8 controls (3 females and 5 males). Brain tissue (HPC, NAc, and FCx; BA10)	Misztak *et al*[53], 2020
H3K4me3	↑ In H3K4me3 at promoter of *SYN2*. ↑ expression *SYN2b*; no changes in *SYN2a* expression	7 females and 11 males with MDD suicide victims and 14 controls (3 females and 12 males). Brain tissue (PFC; BA10)	Cruceanu *et al*[81], 2013
H3K14ac	↑ H3K14ac. ↓ *HDAC2* mRNA expression	8 depressed females and males. Brain tissue (NAc)	Covington *et al*[11], 2009

↓: Decreased expression; ↑: Increased expression; BA10: Brodmann area 10; *BDNF*: Brain derived neurotrophic factor; FCx: Frontal cortex; H3K14ac: Acetylation of lysine 14 on histone 3; H3K9/14ac: Acetylation of lysine 9/14 on histone 3; H3K27me2: Dimethylation of lysine 27 on histone 3; H3K4me3: Trimethylation of lysine 4 on histone 3; HDAC2: Histone deacetylase 2; HDAC3: Histone deacetylase 3; HPC: Hippocampus; MDD: Major depressive disorder; mRNA: Messenger RNA; NAc: Nucleus accumbens; Sin3a: SIN3 transcription regulator family member A; PFC: Prefrontal cortex; *SYN2*: Synapsin II; *SYN2b*: Synapsin IIb; *SYN2a*: Synapsin IIa.

The main conclusion is that alteration in *BDNF* methylation is associated with a depressive state.

The gene *NR3C1* is included in many studies of early life adversities (childhood abuse, parental loss, exposure to maternal depression during pregnancy and after birth). Results show an association between increased methylation of the exon 1-F of the *NR3C1* gene, decreased total *NR3C1* mRNA, and early life adversities[35]. *NR3C1* encodes for the glucocorticoid receptor and is responsible for the effects of cortisol on peripheral tissues. It is self-regulated by a negative feedback loop within the HPA axis [36]. The glucocorticoid receptor can work as a transcription factor that binds to glucocorticoid receptor elements in the promoters of glucocorticoid responsive genes or as a regulator of other transcription factors[37].

In terms of the histone modification data presented in Table 2 and Table 4, H3K27me and H3K14ac are the most studied. The majority of the studies are carried out on animal models and a few on postmortem brain tissue. Studies include information of whole tissue histone modifications and not of single genes. From studies on animal models (Table 4), we can see that the histone tail modifications change over time and are different regarding tissue type.

Many studies in the last 15 years took into consideration miRNAs as important contributors either to the depressive state or as a biomarker of the depressive state. Studies examining humans (Table 3) are in correlation with studies performed on rodents (Table 4). For example, miR-218 and miR-511 are both downregulated in the prefrontal cortex of depressed subjects who died by suicide and in rodent models (mice or rat). On the other hand, miR-16 and miR-376b were oppositely regulated in humans *vs* animal models. This might be due to different tissues tested. There are several more miRNAs regulated in the same direction in human *vs* animal (rodent) models[38]. Upregulation of miR-139-5p is seen in blood-derived exosomes from MDD patients and in brain tissue from chronically depressed mice. Upregulation of miR-323-3p is seen in lateral habenula and Brodmann area 24 in depressed subjects. Consistently, there is also upregulation of miR-323-3p in the brains of rats exposed to prenatal stress. MiR-155 is downregulated in peripheral blood mononuclear cells of depressed subjects and serum of mice exposed to restraint stress. Furthermore, blood-derived exosomes with increased levels of miR-

Table 3 MicroRNA expression studies on depressed suicide victims

miRNAs	Alteration	Subjects and collected tissue	Ref.
miR-218	↓ miR-218 and ↑ *DCC* in PFC	11 male suicide victims with MDD and 12 male controls. Brain tissue (PFC; BA44)	Torres-Berrío *et al*[82], 2017
↓ miR-142-5p, miR-137, miR-489, miR-148b, miR-101, miR-324-5p, miR-301a, miR-146a, miR-335, miR-494, miR-20b, miR-376a*, miR-190, miR-155, miR-660, miR-130a, miR-27a, miR-497, miR-10a, miR-20a, miR-142-3p. ↓ by 30% or more: miR-211, miR-511, miR-424, miR-369-3p, miR-597, miR-496, miR-517c, miR-184, miR-34a, miR-34b-5p, miR-24-1*, miR-594, miR-34c-5p, miR-17*, miR-545, miR-565	Globally ↓ miRNAs expression by 17% on average in depressed subjects. miR-148b targets *DNMT3B*, protein level was upregulated in depressed subjects. miR-34a targets *BCL2*, protein level was downregulated in depressed subjects	18 suicide victims (2 females and 16 males) with depression and 17 male control subjects. Brain tissue (PFC; BA9)	Smalheiser *et al*[83], 2012
miR-1202	↓ miR-1202, and ↑ *GRM4* mRNA expression in BA44	25 suicide victims (2 females and 23 males) with MDD and 29 control subjects (4 females and 25 males). Brain tissue (PFC; BA44). 32 subjects with MDD (24 females and 10 males) and 18 control subjects (8 females and 10 males). Blood	Lopez *et al* [84], 2014
miR-30e	↑ miR-30e, ↓ ZDHHC21 protein	16 suicide victims (7 females and 9 males) with MDD and 16 controls (6 females and 10 males). Brain tissue (PFC; BA9)	Gorinski *et al*[85], 2019
miR-19a-3p	↑ miR-19a-3p (might be involved in the modulation of TNF-α signaling)	12 depressed patients with severe suicidal ideation, 12 control subjects. PBMC	Wang *et al* [86], 2018
More than 10 miRNAs	↑ miR-17-5p, miR-20b-5p, miR-106a-5p, miR-330-3p, miR-541-3p, miR-582-5p, miR-890, miR-99b-3p, miR-550-5p, miR-1179. ↓ miR-409-5p, let-7g-3p, miR-1197	9 depressed suicide victims (3 females and 6 males) and 11 control subjects (2 females and 9 males). Brain tissue (*locus coeruleus*)	Roy *et al* [37], 2017
miR-326	↓ miR-326, ↑ UCN1	5 male suicide victims with MDD and 8 male controls. Edinger-Westphal nucleus	Aschrafi *et al*[87], 2016
10 miRNAs tested	↑ miR-34c-5p, miR-139-5p, miR-195, miR-320c. ↓ *SAT1* and *SMOX* mRNA	15 male suicide victims with MDD and 16 male control subjects. Brain tissue (BA44)	Lopez *et al* [88], 2014
miR-204-5p, miR-320b, miR-323a-3p, miR-331-3p	↑ miR-204-5p, miR-320b, miR-323a-3p, miR-331-3p in ACC and lateral habenula. miR-323a-3p influences the expression of *ERBB4*. Decreased expression in ACC and lateral habenula	39 suicide victims with MDD (13 females and 26 males) and 41 control subjects (10 females and 31 males) for ACC region. 24 suicide victims with MDD (10 females and 14 males), 13 control subjects (5 females and 8 males) for lateral habenula. Brain tissue (ACC and lateral habenula)	Fiori *et al* [89], 2021
171 miRNA differently expressed	↑ 117 miRNAs. ↓ 54 miRNAs	22 (10 females and 12 males) MDD subjects (10 died by suicide, 12 died from cause other than suicide) and 25 control subjects (10 females and 15 males). Brain tissue (ACC)	Yoshino *et al* [90], 2020
miR-128-3p	↑ miR-128-3p. ↓ WNT5B, DVL1 and LEF1	20 MDD (10 females and 10 males) subjects and 22 control subjects (9 females and 13 males). Brain tissue (AMG)	Roy *et al* [91], 2020
miR-16	↓ miR-16	36 MDD (21 females and 15 males) subjects and 30 controls (17 females and 13 males). CSF	Song *et al* [92], 2015

↓: Decreased expression; ↑: Increased expression; ACC: Dorsal anterior cingulate cortex; AMG: Amygdala; BA44: Brodmann area 44; BA9: Brodmann area 9; *BCL2*: B-cell lymphoma 2; CSF: Cerebrospinal fluid; *DCC*: Developmental netrin-1 guidance cue receptor; *DNMT3B*: Gene coding for DNA methyltransferase 3; DVL1: Dishevelled segment polarity 1; *GRM4*: Gene coding for metabotropic glutamate receptor 4; LEF1: Lymphoid enhancer binding factor 1; MDD: Major depressive disorder; miR: MicroRNA; mRNA: Messenger RNA; PBMC: Peripheral blood mononuclear cells; PFC: Prefrontal cortex; *SAT1*: Gene coding for spermidine/spermine N1 -acetyltransferase 1; *SMOX*: Gene coding for spermine oxidase; TNFα: Tumor necrosis factor; UCN1: Urocortin; WNT5B: Wingless-related integration site, member 5B.

139-5p collected from depressed subjects, evoked depressive-like behavior when administered intravenously in mice[38].

However, from all the data currently available, it is hard to pinpoint particular miRNAs that could be used as biomarkers for depressive disorder. Studies presented in Table 4 show lack of overlap between

Table 4 Epigenetic (DNA methylation, histone tail modifications, and microRNAs) studies on animal models of depressive disorder

Epigenetic modification	Gene (region)/histone tail modification/miRNA	Alteration	Organism and collected tissue	Ref.
DNA methylation	*Crf* promoter of exon 1 and intronic region between exon 1 and exon 2 (relative to exon 1 start site)	Overall ↑ DNA methylation, and specific ↑ in CpG –147 and CpG –101 site of the *Crf* gene in stressed female rats in the PVN. No changes in male rats. ↓ DNA methylation in CpG –15 (male and female rats), ↓ DNA methylation in CpG –226, CpG –55 and ↑ in CpG +485 and CpG +494 (male rats) and ↓ DNA methylation in CpG –95 site (female rats) in BNST. ↑ DNA methylation in CpG –232 and CpG –226 (male rats), ↓ CpG –226 and CpG +535 (female) in the CeA	Male and female Wistar-R Amsterdam rats; sacrificed 2 h after stress. Brain tissue (PVN, BNST, CeA)	Sterrenburg *et al* [93], 2011
DNA methylation	*Crf* promoter (relative to exon 1 start site)	Chronic social stress induced ↑ DNA methylation in *Crf* promoter region at CpG site –226 and ↓ DNA methylation level in intronic region of the gene *Crf* in the PVN. Long term effect of social defeat in mice susceptible to social defeat: ↑ in *Crf* mRNA levels in PVN and ↓ DNA methylation level at CpG –226, –101, –95, and –79	Chronically stressed adult mice C57BL/6. Brain tissue (PVN)	Elliott *et al*[94], 2010
DNA methylation and histone tail modification	*Gdnf*	↑ DNA methylation at CpG site 2. ↓ H3ac in NAc of BALB mice and C57BL/6 mice. C57BL/6 mice had higher H3ac and higher *Gdnf* expression	BALB/c mice with maladaptive response to stressful stimuli and stress resilient strain C57BL/6. Brain tissue (NAc)	Uchida *et al*[95], 2011
Histone tail modification	H3K14ac	↓ H3K14ac 1 h after final stress. ↑ H3K14ac 24 h and 10 d after final stress. ↓ *Hdac2* mRNA expression 24 h and 15 d after final stress in NAc	Chronically social defeated adult male mice C57BL/6J. Brain tissue (NAc).	Covington *et al* [11], 2009
Histone tail modification	H3K14ac	H3K14ac ↑ after 24 h and ↓ at longer time in HPC. H3K14ac ↑ after 1 h and 24 h, no changes 10 d and longer in AMG	Chronically social defeated adult male mice C57/BL6J. Brain tissue (HPC and AMG)	Covington *et al* [96], 2011
Histone tail modification	*Bdnf* exon IV, H3ac, H4ac	↓ exon IV *Bdnf* mRNA. ↓ H3ac and H4ac. ↑ MeCP2 levels. ↑ *Hdac* mRNA	Rats (early life adversity induced by maternal separation). Brain tissue (HPC)	Seo *et al*[97], 2016
Histone tail modification	*Bdnf* III and IV promoter, H3K27me2	↑ H3K27me2 at promoter *Bdnf* III and IV. ↓ total *Bdnf* mRNA. No change at H3K9me2	Chronic social defeat stress mice. Brain tissue (HPC)	Tsankova *et al* [62], 2006
Histone tail modification	H3K9me2	↑ H3K9me2 in HPC and mPFC. ↓ *Bdnf* expression in HPC and mPFC	Wistar rats exposed to maternal separation and chronic unpredicted mild stress. Brain tissue (HPC and mPFC)	Jiang *et al*[98], 2021
Histone tail modification	H3K4me3, H3K9me3, H3K27me3	Acute restrain stress: ↑ in H3K9me3 in CA1 and DG; no changes in CA3; ↓ in H3K27me3 in DG and CA1; not significantly altered in CA3. No significant changes for H3K4me3. Subchronic 7-d restraint stress: The basal level of H3K9me3 on day 7 increased in DG, CA1 and CA3. ↓ in H3K9me3 in CA1, CA3 and DG. ↓ in H3K27me3 in DG	Adult male Sprague–Dawley rats (acute stress/7 d restraint stress). Brain tissue (HPC parts: DG, CA1, CA3)	Hunter *et al*[99], 2009
miRNA	miR Let-7a-1, miR-9, miR-25a/b	↑ miR Let-7a-1, miR-9, miR-25a/b after acute stress in FCx. No changes in HPC	Male CD1 mice with induced acute or repeated stress. Brain tissue (FCx and HPC)	Rinaldi *et al* [100], 2010
miRNA	miR-218	↓ miR-218 and ↑ *DCC* in PFC	Chronically social defeated adult male mice C57BL/6. Brain tissue (mPFC)	Torres-Berrío *et al*[82], 2017
miRNA	miR-16	↑ miR-16. ↓ *Bdnf* mRNA	Sprague-Dawley rats exposed to maternal deprivation. Brain tissue (HPC)	Bai *et al*[101], 2012
miRNA	342 miRNAs differently expressed (response to gestational stress) and 336 miRNAs differently	↑ 147 miRNAs and ↓ 195 miRNAs in FCx of female rats. ↑ 205 miRNAs and ↓ 131 miRNAs in offspring	Stress induced through pregnant female Long-Evans rats. Offspring	Zucchi *et al*[102], 2013

	expressed in offspring (response to prenatal stress)		(decapitated 1 to 5 h after parturition). Brain tissue (FCx)	
miRNA	AMG: 10 miRNAs under acute stress and 28 after chronic stress; HPC CA1: 16 after acute stress and 22 after chronic stress	The overlap: ↑ miR Let-7a-1 in AMG affected by acute and chronic stress. ↑ miR-376b and miR-208, ↓ miR-9 in HPC by acute and chronic stress. Other changes are unique to acute/chronic stress or brain region analyzed	Adult male rats with induced acute or chronic stress. Brain tissue (AMG, HPC CA1 region)	Meerson *et al* [103], 2010
miRNA	miR-124a, miR-18a, miR-511	↑ miR-124a, miR-18a in PFC and HPC persistently. ↓ miR-511 in PFC (in adult rats experienced CUMS)	Adolescent male Wistar rats were stressed with CUMS. Brain tissue (PFC and HPC)	Xu *et al*[104], 2019

↓: Decreased expression; ↑: Increased expression; AMG: Amygdala; *Bdnf*, brain derived neurotrophic factor; BNST: Bed nucleus of the stria terminalis; CeA: Central amygdala; CpG: Cytosine-phosphate-guanine; *Crf*: Corticotropin releasing factor; CUMS: Chronic unpredictable mild stress; *DCC*: Gene coding developmental netrin-1 guidance cue receptor; DG: Dentate gyrus; FCx: Frontal cortex; *Gdnf*: Glial cell-derived neurotrophic factor; HDAC: Histone deacetylase; H3ac: Acetylation of histone 3; H4ac: Acetylation of histone 4; H3K14ac: Acetylation of lysine 14 on histone 3; H3K9me2: Dimethylation of lysine 9 on histone 3; H3K9me3: Trimethylation of lysine 9 on histone 3; H3K27me2: Dimethylation of lysine 27 on histone 3; H3K27me3: Trimethylation of lysine 27 on histone 3; H3K4me3: Trimethylation of lysine 4 on histone 3; *Hdac2*: Histone deacetylase 2; HPC: Hippocampus; HPC CA1: Hippocampal CA1 region; HPC CA3: Hippocampal CA3 region; MeCP2: Methyl CpG binding protein 2; mPFC: Medial prefrontal cortex; miR: Micro RNA; miRNA: Micro RNA; mRNA: Messenger RNA; NAc: Nucleus accumbens; PFC: Prefrontal cortex; PVN: Hypothalamic paraventricular nucleus.

studies; there are several different tissues used, and the number of miRNAs interrogated vary from whole RNome studies to single miRNA studies. Although many limitations exist in the miRNA research, current results are promising enough to persist with the search for miRNAs or even miRNA networks that could serve as biomarkers.

Due to variation in study design, comparisons between the obtained results are limited. In particular, criteria for subject inclusion are very diverse (inclusion of one/two sexes, age, ethnic background, and so on), and studies are frequently underpowered. In addition, the background of the depressive state is not the same for all depressed patients. Some studies analyze the consequences of early life adversity, others include patients with depressive disorder at older age or depressed patients without a known cause. When working with animal models the study design is more standardized and controlled, while the trigger of depressed state is selected based on the interest of the study.

POSSIBLE TREATMENTS OF DEPRESSIVE DISORDER

There are pharmacological and nonpharmacological (psychotherapy, lifestyle interventions, and neuromodulatory treatment) ways of treating depressive disorder. For pharmacological treatment, there are many different antidepressants available, and they are a cornerstone for treating depressive disorder [39]. The main drug classes of antidepressants are selective serotonin reuptake inhibitors (SSRIs), selective serotonin and norepinephrine reuptake inhibitors, norepinephrine and dopamine reuptake inhibitors, noradrenergic and specific serotonergic agents, tricyclic antidepressants, MAO inhibitors, and melatonin modulators (agomelatine)[40]. However, there is no universally effective treatment for all depressed patients[39].

People suffering from depressive disorder can recover in a year or not recover in more than 20 years. Furthermore, depressive episodes recur in almost half of recovered patients[5]. Even though there are many different antidepressants available and many different treatment options, 34%–46% of MDD patients still do not respond effectively to one or more antidepressant treatments (*i.e.* fail to achieve remission). That is why there is still a great need for new antidepressants for curing treatment-resistant depression[41]. Among novel drugs, ketamine and eskatemine are being extensively used. Also, the HDAC inhibitors (HDACis) are being tested on animal models as one possibility of treatment.

Selective serotonin inhibitors

SSRIs are the most commonly prescribed antidepressants and are used as the first treatment step for depressive disorder. Serotonin or 5-hydroxytryptamine (5-HT) is a monoamine neurotransmitter that modulates mood, reward, learning, and memory. Deficiency in serotonin release is not associated with serotonin biosynthesis. The serotonin deficit is more likely due to less serotonin neuron firing and less serotonin release. However, SSRIs block the reabsorption of serotonin into presynaptic neuron cell and with that improve message transmission between cells[40].

Fluoxetine was the first SSRI to be developed and is the most used antidepressant for children and adolescents. Many different SSRIs have now been developed that vary in binding affinity; some are more specific to serotonin than others. It became clear that using the available antidepressants targeting specific monoamines also have side effects. Those side effects come from neurotransmitters binding to different receptors. For example, when serotonin binds to the 5HT1A receptor, there is an antide-

pressant and anxiolytic effect; when it binds to 5HT2A/C receptor, there is an effect on sexual dysfunction. Multimodal antidepressants directly target specific serotonin receptors and inhibit reuptake of serotonin. Vilazodone is an example of a multimodal antidepressant, which targets a specific receptor (5HT1A). Still, vilazodone is not as superior as it was expected to be compared to other antidepressants[40,42]. Vortioxetine is more promising since it shows superior efficacy compared to the other antidepressants in trials. Vortioxetine is an agonist of 5HT1A, (partial) antagonist of other receptors, and a potent serotonin reuptake inhibitor. Besides the antidepressant effect, it also improves cognitive function[40,42].

Ketamine

Novel treatments that target outside of the monoaminergic system are ketamine [targeting the glutamate system through N-methyl-aspartate (NMDA) receptor antagonism] and agomelatin (a melatonin receptor agonist)[40]. Agomelatin is a melatonin agonist and a selective serotonin antagonist. For antidepressant effect, both actions are necessary. Agomelatin showed good antidepressant effect for people with seasonal affective disorder[43].

Ketamine is used in many clinical studies for treatment-resistant patients who fail to respond to SSRIs. Ketamine showed good results, with a response rate between 40% and 90%[43]. Intravenous infusion of ketamine produces a rapid and prolonged effect within a few hours of administration. It is accompanied by psychotomimetic effects, which subside within 2 h. The effect of a single intravenous insertion lasts 2–14 d, and it has an anti-suicide effect[41]. Ketamine is restricted for routine clinical use due to its side effects: Dissociative effects, changes in sensory perception, intravenous administration, and risk of abuse[44].

Ketamine is a mixture of two enantiomers, S-ketamine and R-ketamine. In the past few years, esketamine (S-ketamine) has been studied as a better option than ketamine because of its easier administration. Esketamine can be inserted intranasally and is therefore easier for at home administration. Recently, researchers investigated R-ketamine. Preclinical and clinical studies on intravenously infused R-ketamine elicit a fast and sustained antidepressant state, without psychotic symptoms[45].

Ketamine's action: Ketamine affects the glutamate system. Glutamate is an excitatory neurotransmitter and is involved in neurodevelopment, neurocognitive (memory learning) function, and neuroplasticity (neurogenesis, neuronal growth and remodeling, maintenance, and synaptic plasticity). Dysregulation of neuroplasticity can contribute to MDD and other neuropsychiatric conditions. The majority of neurons use glutamate as a neurotransmitter. Two types of glutamate receptors (ionotropic or metabotropic glutamate receptors) are categorized into four major classes: α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid receptors, NMDA receptors (NMDAR), kainate receptors, and metabotropic glutamate receptors[46]. NMDARs are located at the postsynaptic and presynaptic side of glutamatergic synapses in the CNS[47]. In postmortem brains of MDD patients, many studies have revealed alteration in NMDAR. Several changes were discovered, such as NMDAR dysfunction (reduced glutamate recognition and allosteric regulation) and altered expression of NMDAR subunits. The latter might be manifested by altered glutamatergic input and abnormal glutamate neurotransmission[46].

There are several mechanisms of ketamine action, which may act complementarily. Ketamine can bind to NMDAR on presynaptic or postsynaptic glutamatergic neuron and on GABAergic interneurons. Binding leads to blockade and inhibition of NMDAR. For the antidepressant effects of ketamine, cascades of actions happen: γ-aminobutyric acid decrease, glutamate release, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors activation, BDNF release, tropomyosin receptor kinase B activation, and mammalian target of rapamycin complex 1 activation. The result is an acute change in synaptic plasticity and sustained strengthening of excitatory synapses[44]. The process of synaptogenesis is activated and further probably affects cognition, mood, and thought patterns[48].

HDACis

Decreased acetylation is associated with a depressive state and because of that, HDACs (as erasers of acetylation) might become a novel treatment target[10]. HDACs, "erasers" of histone acetylation, are classified into two categories: The zinc-dependent and nicotinamide-adenine-dinucleotide–dependent sirtuins (Table 5)[49].

HDACs I, II, and IV are expressed in the brain, primarily in neurons. Class I and II regulate histone deacetylation at most genes, and class III deacetylates nuclear and cytoplasmic substrates beside histones[50]. The balance between histone acetyltransferases and HDAC activity determines the (de)condensation status of the chromatin and gene transcription[10].

HDACis are potent to specific classes of HDACs. The United States Food and Drug Administration has approved a few HDACis [vorinostat (SAHA), belinostat, panobinostat, and romidepsin] for treatment of some types of cancers. Many preclinical studies on mice showed an antidepressant effect of HDACis by reversing the acetylated state. Moreover, HDACis also promote neuronal rewiring and recovery of motor functions after traumatic brain injury. Use in clinical practice is limited due to severe side effects including thrombocytopenia and neutropenia[51].

Table 5 Histone deacetylase classification and localization

HDAC category	HDAC class	HDAC type	Localization
Zinc-dependent HDACs	Class I	HDACs 1, 2, 3, 8	Localized in nucleus
	Class II	HDACs 4, 5, 7, 9, 10	Pass between nucleus and cytoplasm
		HDAC6	Localized in the cytoplasm
	Class IV	HDAC11	
NAD-dependent SIRTs	Class III	SIRTs 1, 2, 6 and 7	Localized in the nucleus
		SIRTs 3, 4 and 5	Localized in the mitochondria

HDACs: Histone deacetylases; NAD-dependent sirtuins: Nicotinamide-adenine-dinucleotide–dependent sirtuins; SIRTs: Sirtuins.

DEPRESSIVE DISORDER ASSOCIATED GENES AND CLASSICAL ANTIDEPRESSANT DRUGS

How different antidepressants affect depressive symptoms can be measured by a subject's phenotype (behavior for animals and psychiatric evaluation for humans). Epigenetic alterations might become one of the tools to check how well specific subjects respond to the antidepressant[52].

BDNF and depressive disorder

One of the most studied genes of depressive disorder is *BDNF*. BDNF is one of the most important neurotrophins. The human *BDNF* gene contains nine exons (I–IX), each regulated by its own promoter. All the different transcripts are translated into an identical BDNF protein[53]. It is highly expressed in the CNS[54] and plays an important role in proper brain development and functioning, including neuronal proliferation, migration, differentiation, and survival[53]. BDNF binds to p75 neurotrophin receptor (p75NTR) and tropomyosin receptor kinase B[54]. In many studies, exon I and IV showed alteration in expression levels in depressed subjects. Splice variant tropomyosin receptor kinase B.T1 is an astrocytic variant and has gained a lot of interest in the study of the depressive state[10]. Two single nucleotide polymorphisms, Val66Met and *BE5.2*, of *BDNF* reduce BDNF release. In addition, studies show significant effects of epigenetic changes on the depressive state[53]. Treatment with SSRIs and HDACi antidepressants increases levels of BDNF in peripheral tissues. If BDNF does not increase early after administration, this predicts non-response to antidepressants[55].

BDNF and antidepressants: Human studies: The studies on DNA methylation and antidepressant effect in general include a rather low number of subjects but several different antidepressants.

Two studies analyzed H3K27me3 modification, and both reported decreased H3K27me3 in patients with MDD. Chen *et al*[56] performed a study on Caucasians (French Canadian origin, 9 control subjects, 11 MDD subjects without a history of antidepressant use, and 7 MDD subjects who used antidepressants). All MDD subjects died due to suicide. Several different antidepressants were administered: Fluoxetine (n = 1), venlafaxine (n = 2), clomipramine (n = 1), amitriptyline (n = 1), citalopram (n = 1), and doxepin (n = 1). Analysis of the epigenetic modification H3K27me3 in brain tissue from Brodmann area 10 between the control group and the non-medicated MDD group showed no differences. Subjects with a history of antidepressant use showed an increase in *BDNF* IV expression but not *BDNF* I, II, and III expression and a decreased level of H3K27me3 at the *BDNF* IV promoter[56].

Lopez *et al*[57] investigated 25 MDD patients (13 females and 12 males) whose blood levels of total BDNF and H3K27me3 were measured before antidepressant treatment and after 8 wk of citalopram administration. After treatment, there was an elevation of peripheral *BDNF* mRNA in patients responsive to antidepressant treatment and a decrease in H3K27me3 level at promoter IV of the *BDNF* gene[57].

An increase of *BDNF* DNA methylation level after antidepressant administration was shown in three studies. Carlberg *et al*[58] (2014) studied *BDNF* methylation on peripheral blood mononuclear cells of 207 MDD patients and 278 control subjects from Vienna, Austria. From 207 MDD patients, 140 subjects were treated with antidepressant medication and 25 subjects were not. There was an alteration in DNA methylation at the *BDNF* exon I promoter. After antidepressant administration, there was an increase in methylation in MDD patients compared with patients without antidepressant medication and healthy controls[58].

D'Addario *et al*[59] reported that there was an increase in DNA methylation at the *BDNF* promoter in 41 MDD patients with stable pharmacological treatment in comparison to 44 healthy control subjects. In addition, there was a significant reduction in expressed *BDNF* from peripheral blood mononuclear cells in MDD patients than in the control group. Patients who took only SSRIs or selective serotonin and norepinephrine reuptake inhibitors had a higher methylation level of the *BDNF* promoter than patients

who received antidepressants and mood stabilizers[59].

In a study by Wang *et al*[16], 85 Chinese Han patients with MDD (females and males) were treated with escitalopram. Blood samples were tested for DNA methylation in the *BDNF* region. DNA methylation before treatment was significantly lower than after 8 wk of treatment. A difference was seen between remitted and non-remitted patients. Patients with remission had higher DNA methylation than non-remitters[16].

Two studies included analysis of patients who responded and those who did not. In both, higher methylation level was an important contributor to treatment response. Hsieh *et al*[60] included 39 patients with MDD (females and males) and 62 healthy controls (females and males). Higher methylation levels were detected at CpG site 217 and lower methylation level at CpG sites 327 and 362 in the *BDNF* exon IX promoter in MDD patients compared to controls. After drug administration (SSRIs; fluoxetine, paroxetine, and escitalopram), 25 patients who responded to SSRIs had a higher methylation level at CpG sites 24 and 324 than patients who did not respond (n = 11). Methylation analysis results also showed consistent results of BDNF protein level and mRNA level in peripheral blood[60].

A study by Tadić *et al*[52] (2014) included 46 MDD patients (females and males) with different monoaminergic antidepressants prescribed: Escitalopram (n = 5), fluoxetine (n = 2), sertraline (n = 6), venlafaxine (n = 19), duloxetine (n = 2), mirtazapine (n = 6), amitriptyline (n = 1), clomipramine (n = 3), trimipramine (n = 1), or tranylcypromine (n = 1). Although different antidepressants were used, the main observation of the study was the response or non-response to the antidepressant treatment. From 13 CpG sites checked for methylation status on blood samples within the *BDNF* IV promoter, one stood out; antidepressant non-responders had lower methylation at CpG position –87 (relative to the first nucleotide of exon IV). There were no other DNA methylation changes after treatment[52].

Animal studies: In animal models, it has been shown that histone tail modifications significantly affect gene expression and that they are changed after antidepressant administration.

In the study by Park *et al*[34], male Sprague-Dawley rat pups were separated from mothers during early life. Maternal separation evoked a decrease of exon I mRNA *Bdnf*, H3 acetylation (ac) levels and an increase in *Dnmt1* and *Dnmt3a* mRNA level in the hippocampus. After 3 wk of escitalopram administration in adult rats subjected to maternal separation, the result was an increase in BDNF protein, exon I mRNA, levels of H3ac, and a decrease in *Mecp2*, *Dnmt1*, and *Dnmt3a* mRNA levels[34].

Xu *et al*[61] showed that mice stressed in the adolescent period show epigenetic changes also in adult life. Stress in tested male C57BL/6J mice were induced by confrontation of aggressor mice CD1. The expression level of total *Bdnf* and *Bdnf* IV mRNA were decreased in the medial prefrontal cortex (the same results were observed in the hippocampus). *Bdnf* I and VI mRNA levels changed over time in the medial prefrontal cortex. Adult mice had upregulated H3K9me2 in a region downstream of the promoter of the gene *Bdnf* IV, but there were no differences in H3K4me3, H3K9ac, and H3K4ac. Tranylcypromine administration reversed this change and increased levels of H3K4me3. Tranylcypromine is a non-selective MAO inhibitors[61].

Tsankova *et al*[62] showed decreased expression of *Bdnf* III and IV, which manifested in the total level of *Bdnf* mRNA in the hippocampus in chronically defeated BL6/C57 mice. Changes in *Bdnf* III and IV expression persisted a month after cessation of the chronic defeat stress. On the promoter of *Bdnf* III and *Bdnf* IV there was an increase of H3K27me2 but not H3K9me2. Chronic imipramine (a tricyclic antidepressants) administration reversed changes of *Bdnf* expression but did not reverse H3K27me2 to the base level. After chronic social defeat stress and imipramine administration, H3 was hyperacetylated (H3K9/14ac) at the promoter *Bdnf* III and IV, which affected mRNA expression. Furthermore, H3K4me2 was similarly enriched in the *Bdnf* III promoter and correlated with transcriptional activation. There were no changes in H4ac. There was a decrease in *Hdac5* mRNA level but only on chronically stressed mice treated with chronic imipramine. Acute imipramine did not influence *Hdac* level[62].

Solute carrier family 6 member 4 and depressive disorder

Solute carrier family 6 member 4 (*SLC6A4*) is a gene that codes for serotonin transporter. The protein's name comes from the name of the monoamine neurotransmitter serotonin (5-HT) that binds to it. The gene *SLC6A4* was associated with the protein later. Serotonin transporter is an integral membrane protein that transports serotonin from synapse to presynaptic neurons. Besides involvement in regulation of the serotonergic system, *SLC6A4* also acts as an important element of stress susceptibility. Serotonin transporter linked promoter region polymorphism at gene *SLC6A4* has 2 variants, a short allele and a long allele. The short allele results in lower gene transcription and is therefore associated with a depressive state[63]. In addition, there are also several epigenetic studies explaining its dysfunction. Some studies have shown how treatment with classical antidepressants affects epigenetic changes of the *SLC6A4* gene. Therefore, *SLC6A4* is a key target for antidepressant treatment research.

***SLC6A4* and antidepressants:** Human studies: There is a difference in the response to antidepressants seen when analyzing DNA methylation in *SLC6A4* gene. Two studies reported higher methylation status after antidepressant administration and one lower methylation status.

Booij *et al*[64] included in their study 33 MDD patients (females and males). MDD patients who were taking SSRIs had higher methylation levels at CpG 11 and 12 within the regulatory region upstream of the promoter of the *SLC6A4* than patients who did not use antidepressants (n = 36). Research was done

on whole blood samples. There was no association between mRNA expression and DNA methylation [64]. In the study of Okada *et al*[65], peripheral blood was taken from 50 Japanese MDD patients (females and males) before and after antidepressant treatment. Different antidepressants (paroxetine, fluvoxamine, milnacipran) were used in this study. There were no differences in DNA methylation of *SLC6A4* exon I promoter between the healthy control group (n = 50) and patients without antidepressant administration. There was a significant increase in methylation at the CpG 3 site after 6 wk of antidepressant treatment[65].

Domschke *et al*[66] included 61 Caucasian MDD patients who were tested for changes in DNA methylation from blood cells. Administration of escitalopram was evaluated 6 wk after treatment. There was lower average methylation in the transcriptional control region upstream of exon 1A of *SLC6A4* gene. The CpG 2 site specifically stood out from these results[66].

CONCLUSION

Depressive disorder is affected by dysregulation of many different genes, each contributing a small effect. All hypotheses of depressive disorder involve a variety of changes that can occur in a depressive state. These are a consequence of gene variations or epigenetic changes that affect DNA transcription and/or mRNA translation resulting in imbalanced protein levels regulating the processes in the CNS. With the development of technologies and new knowledge, epigenetic research has become accessible for investigation in the field of psychiatry. Among candidate genes particular interest was placed on *BDNF, NR3C1,* and *SLC6A4*, as their roles in CNS regulation have been identified in association with response to external stress stimuli and mood regulation. Although the research has been fairly extensive, we still cannot identify a reliable biomarker or a set of them, either proteomic or (epi)genetic, to be used in a clinical setting.

However, in many studies scientists discuss the importance of epigenetic factors (DNA methylation and histone modifications) as playing a key role in predicting antidepressant response. The aggregation of subthreshold levels of the epigenetic changes in several different genes might show alterations caused by a depressive state. It appears that to date we have uncovered a few pieces of the jigsaw puzzle but that more studies are needed for understanding this complex disorder. For example, it has been determined that classical antidepressants change the epigenome, and it has been proposed that this effect might be an important contributor to treatment. These results have triggered further investigation of drugs targeting epigenetic modifiers (HDACs, histone methyltransferases). HDACis seem to be promising drugs, but there are no HDACis used for depression treatment.

Further research in clinical settings will be important to determine which epigenetic markers are informative for treatment response prediction and which markers actually change as a response to treatment. Although the field of pharmacoepigenetics is only starting to develop, we can already identify some potential genes that we can expect to become biomarkers with clinical value. With rapid technological advancement, enabling determination of markers from multi-omic data with the use of artificial intelligence and carefully designed studies in the growing field of psychiatry, we could expect to obtain relevant biomarkers that could be used by clinicians as meaningful guidance in addition to clinical interviews in the future. With the development of the field of pharmacoepigenetics, it will be possible to move towards personalized treatments, where combinations of genetic and environmental factors will need to be incorporated in treatment selection.

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ORIGINAL ARTICLE

Case Control Study

Delayed improvements in visual memory task performance among chronic schizophrenia patients after high-frequency repetitive transcranial magnetic stimulation

Xiang-Dong Du, Zhe Li, Nian Yuan, Ming Yin, Xue-Li Zhao, Xiao-Li Lv, Si-Yun Zou, Jun Zhang, Guang-Ya Zhang, Chuan-Wei Li, Hui Pan, Li Yang, Si-Qi Wu, Yan Yue, Yu-Xuan Wu, Xiang-Yang Zhang

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Abstract

BACKGROUND

Cognitive impairments are core characteristics of schizophrenia, but are largely resistant to current treatments. Several recent studies have shown that high-frequency repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex (DLPFC) can reduce negative symptoms and improve certain cognitive deficits in schizophrenia patients. However, results are inconsistent across studies.

AIM

To examine if high-frequency rTMS of the DLPFC can improve visual memory deficits in patients with schizophrenia.

METHODS

Forty-seven chronic schizophrenia patients with severe negative symptoms on

stable treatment regimens were randomly assigned to receive active rTMS to the DLPFC (n = 25) or sham stimulation (n = 22) on weekdays for four consecutive weeks. Patients performed the pattern recognition memory (PRM) task from the Cambridge Neuropsychological Test Automated Battery at baseline, at the end of rTMS treatment (week 4), and 4 wk after rTMS treatment (week 8). Clinical symptoms were also measured at these same time points using the Scale for the Assessment of Negative Symptoms (SANS) and the Positive and Negative Syndrome Scale (PANSS).

RESULTS

There were no significant differences in PRM performance metrics, SANS total score, SANS subscores, PANSS total score, and PANSS subscores between active and sham rTMS groups at the end of the 4-wk treatment period, but PRM performance metrics (percent correct and number correct) and changes in these metrics from baseline were significantly greater in the active rTMS group at week 8 compared to the sham group (all $P < 0.05$). Active rTMS treatment also significantly reduced SANS score at week 8 compared to sham treatment. Moreover, the improvement in visual memory was correlated with the reduction in negative symptoms at week 8. In contrast, there were no between-group differences in PANSS total score and subscale scores at either week 4 or week 8 (all $P > 0.05$).

CONCLUSION

High-frequency transcranial magnetic stimulation improves visual memory and reduces negative symptoms in schizophrenia, but these effects are delayed, potentially due to the requirement for extensive neuroplastic changes within DLPFC networks.

Key Words: Cognition; High-frequency repetitive transcranial magnetic stimulation; Non-invasive brain stimulation; Randomized controlled study; Schizophrenia; Visual memory deficits

Core Tip: The main objective of this study was to evaluate the efficacy of high-frequency repetitive transcranial magnetic stimulation (rTMS) in the treatment of visual memory disorders in schizophrenia. Forty-seven patients with chronic schizophrenia who had significant negative symptoms during stabilization therapy were randomly assigned to two groups: Active rTMS over dorsolateral prefrontal cortex (n = 25) or false stimulation (n = 22) for 4 wk, followed by 4 wk of follow-up. Our results suggest that high-frequency transcranial magnetic stimulation improves visual memory function and relieves negative symptoms in patients with schizophrenia, but with a delay.

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INTRODUCTION

Schizophrenia is a chronic psychiatric disorder characterized by distorted thinking and perception[1]. A comprehensive epidemiological survey reported a median prevalence of 15.2/100000 persons, but individual prevalence estimates in various regions have varied from 7.7–43.0/100000[2], potentially due to genetic factors, diagnostic standards, and the heterogeneity of symptom presentation. The clinical symptoms of schizophrenia are divided into three groups or domains: Positive symptoms such as hallucinations, negative symptoms such as flat affect and anhedonia, and cognitive symptoms, and the predominance of different symptom clusters in individual patients determines the treatment strategy and influences long-term outcome[1,3]. At present, the main treatments for schizophrenia are antipsychotics, but these agents are effective only against positive symptoms[3], while it remains more difficult to improve the negative and cognitive symptoms of chronic schizophrenia even during long-term hospitalization.

Cognitive impairments in schizophrenia include deficits in attention, executive functions such as response inhibition and working memory, verbal learning and memory, and social memory[4] that vary

markedly in severity among individual patients. These symptoms may be detectable prior to clinical disease onset and remain relatively stable over time despite improvements in other symptoms[4,5]. Further, these cognitive deficits contribute to functional disability and predict poor life outcome[4,6,7]. Visual memory is a critical faculty for various forms of learning and for daily activities such as employment. Although prior research has indicated that visual memory impairments are minor in comparison to other cognitive impairments[8], a recent study found that patients with a family history of schizophrenia have considerably worse visual memory scores[9]. Furthermore, several earlier studies reported that patients with schizophrenia have poor visual memory[10,11] and that improvement is associated with better job retention and successful recovery[8]. Thus, any improvement in visual memory that occurs during treatment could be broadly beneficial, especially to patients with a family history of schizophrenia[9].

The prefrontal cortex (PFC) is critical for executive functions such as working memory, cognitive flexibility, and behavioral inhibition; some or all of which may be disrupted in psychiatric disorders including depression, anxiety and schizophrenia. A recent study of patients with bilateral lesions in the ventromedial (vm)PFC[12,13] revealed deficits in the acquisition of Pavlovian threat conditioning (*i.e.*, emotional learning). A recent theoretical review[14,15] on the neurobiology of emotional conditioning concluded that the vmPFC is fundamental for the representation and evaluation of safety- and threat-related information and thus for the relative influence of this information on sustained physiological responses. Imaging studies of patients with depression exhibiting executive dysfunction also revealed damage to dorsolateral prefrontal circuits[16,17]. Therefore, the PFC is a promising target for therapeutic interventions aimed at treating the cognitive and emotional symptoms of schizophrenia. In addition, some scholars proposed that the anatomical–functional interplay between the PFC and heart-related dynamics in human emotional conditioning (learning) and proposes a theoretical model to conceptualize these psychophysiological processes, the neurovisceral integration model of fear, that can be impaired in the context of psychiatric disorders (as schizophrenia)[18-20].

While antipsychotic drugs clearly benefit positive symptoms, they may also disrupt attention and memory in unimpaired subjects. In this regard, atypical antipsychotics are less deleterious than conventional antipsychotics. Nonetheless, cognitive dysfunction is still a major predictor of poor clinical and life outcome among patients with schizophrenia, necessitating the continued development of interventions for improving cognitive function[21]. Among potential treatments, nonpharmaceutical and noninvasive treatments may be particularly effective as patient noncompliance to drug treatment is a major obstacle to effective long-term patient management. Repetitive transcranial magnetic stimulation (rTMS) is one such alternative as it is noninvasive, well-tolerated, and has demonstrated efficacy for the treatment of various psychiatric and neurological diseases, in particular in treatment-resistant depression (TRD), for which it has received United States Food and Drug Administration approval[22,23]. However, studies of clinical efficacy for schizophrenia treatment have thus far reported inconsistent results, possibly to heterogeneity in illness factors (such as duration of illness and baseline psychopathology), assessment methods (such as the assessment tool used and evaluation of bias), and stimulation parameters (such as stimulus location, frequency, intensity and duration)[24,25]. Due to these discrepancies, several meta-analyses have been conducted to investigate the impact of rTMS on the clinical symptoms of schizophrenia[5,26], and a recent report concluded that rTMS of the dorsolateral PFC (DLPFC) is an effective method for the treatment of negative symptoms[24]. A more recent meta-analysis concluded that 1-Hz rTMS had a significant therapeutic effect on auditory hallucinations[27]. In contrast, the same study found no significant effect of 10-Hz rTMS on negative symptoms compared to sham treatment. However, there has been no examination on the efficacy of rTMS targeting the DLPFC on cognitive symptoms such as visual memory. Here, we examined this question and presented possible reasons for the differential efficacy of previous protocols[8-11].

Given the major influence of cognitive dysfunction on long-term outcome, cognitive improvement should be a primary treatment goal[27,28]. Second-generation antipsychotic drugs have been shown to improve positive symptoms, but have little effect on negative symptoms and cognitive deficits[7,28,29]. Alternatively, nonpharmacological interventions such as cognitive remedial training and aerobic exercise have shown promising results for the treatment of cognitive impairment[30]. As well, a previous open label study reported that 1-Hz rTMS of the left temporal parietal cortex and 10-Hz rTMS of the DLPFC improved short-term auditory verbal memory[31]. Wölwer *et al*[21] also reported improved facial affect recognition, a critical component of social cognition, in schizophrenia patients following 10 Hz rTMS to the left DLPFC[21]. A double-blind sham-controlled randomized treatment trial found that 20-Hz rTMS of the bilateral DLPFC improved working memory as measured by the three-back task[32]. However, Mittrach *et al*[33] did not find any beneficial effect of 10-Hz rTMS of the DLPFC on long-term verbal memory, attention, or frontal executive functioning. Similarly, a recent randomized sham-controlled trial including schizophrenia patients with prominent negative symptoms found that active 10-Hz rTMS of the left DLPFC was no more effective than sham treatment for improving cognitive performance[34]. In contrast, we found that rTMS of the left DLPFC can improve the negative symptoms of schizophrenia[35].

Therefore, the primary objective of the current randomized, double-blind sham-controlled study was to examine if a similar rTMS protocol improved visual memory performance. Accordingly, chronic schizophrenia patients with marked negative symptoms among the Chinese Han population were

randomized to receive five sessions *per* week of high-frequency rTMS to the left DLPFC or sham stimulation and were examined periodically for visual memory performance. We hypothesized that visual memory performance would be improved to a greater degree by real rTMS than sham treatment. The secondary objective was to analyze the association between improvement in visual memory and negative symptoms during and following rTMS treatment. This study highlighted the therapeutic potential of rTMS targeting the DLPFC for schizophrenia patients with predominant negative and cognitive symptoms. More broadly, rTMS may be an effective component of more precise and individualized treatment regimens for neurologic and psychiatric disorders.

MATERIALS AND METHODS

Subjects

The subjects of this study also participated in our previous clinical trial published in 2016[35]. Forty-seven schizophrenia inpatients were recruited from Suzhou Guangji Hospital, a city-owned psychiatric hospital in Suzhou City, from June 2013 to May 2015. The inclusion criteria were: (1) Meeting ICD-10 diagnostic criteria for schizophrenia according to two senior psychiatrists; (2) Eight-handed; (3) Aged 20–60 years and Han Chinese ancestry; (4) ≥ 5-years' duration of illness; (5) Antipsychotic medication fixed for at least 12 mo before enrollment; and (6) Marked negative symptoms as evidenced by a score ≥ 20 on the Scale for the Assessment of Negative Symptoms (SANS). Baseline demographic and clinical characteristics of the study population are summarized in Table 1.

All subjects received a complete medical history review and detailed physical examinations. We excluded candidates with physical diseases such as aneurysm, seizure, stroke, and cardiovascular disorders as well as patients with illegal drug or alcohol abuse/dependence.

This study was approved by the Institutional Review Board of Suzhou Guangji Psychiatric Hospital and each subject provided written informed consent prior to participation following a full explanation of project goals, methods, and risks by a research staff member. All study procedures were performed in accordance with the Declaration of Helsinki. This clinical trial was registered with https://www.clinicaltrials.gov/ on September 5, 2017 as NCT03273439 (5/9/2017).

Design

This was a single-center, randomized, sham-controlled, double-blinded study conducted as described in our previous report[35]. Briefly, participants received active or sham rTMS on all weekdays for 4 wk (20 sessions in total). Antipsychotic medications and all other medications remained unchanged during treatment. Clinical assessments and cognitive tests were performed at baseline, after the 4-wk treatment (week 4) and 4 wk post-treatment (week 8).

Active and sham rTMS

Repetitive TMS was delivered through a figure-of-eight coil connected to a MAGPRO-R30 magnetic stimulator (Medtronic DantecNeuroMuscular, Skovlunde, Denmark). Prior to each TMS or sham administration, motor threshold (MT) at the left primary motor cortex (M1) was determined as the lowest possible energy required to produce at least five potentials ≥ 0.05 mV in 10 trials from the X. During each active rTMS session, thirty 5-s trains of 10 Hz stimulation were delivered in 30-s intervals at 110% of MT over the left DLPFC (defined as the F3 position of the 10–20 electroencephalogram system). These trains were administered once each weekday for four consecutive weeks (for a total of 30000 individual stimuli). The left DLPFC was chosen as the rTMS target because the majority of previous studies performed rTMS on DLPFC[5,24]. For sham rTMS, all procedures were identical except that the figure-of-eight coil was rotated 180° during stimulator activation. Since rTMS machine was used in a blinded fashion in this study, the coil was thick enough and had a magnetic shielding function (Figure 1).

Psychopathological measures

General psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS). Negative symptoms were also assessed with the SANS, which consists of 19 items assessing five symptoms of the negative dimension: Affect flattening, alogia, avolition-apathy, anhedonia-asociality, and poor attention. Two clinical psychiatrists blinded to treatment condition (real *vs* sham rTMS) assessed PANSS and SANS scores at baseline, at weeks 4 and 8. Inter-rater reliability was satisfactory for both tests (κa = 0.88 for PANSS and κa = 0.86 for SANS).

Cognitive performance

The Cambridge Neuropsychological Test Automated Battery (CANTAB) is a widely used computerized assessment tool for cognition in schizophrenia. Since the patients in this study had relatively long disease histories (> 20 years) and most had not received any higher education (Table 1), only the pattern recognition memory (PRM) component of the CANTAB, a relatively straightforward two-choice forced

Table 1 Demographic and baseline clinical characteristics of active and sham repetitive transcranial magnetic stimulation groups

	Active rTMS (*n* = 25)	Sham rTMS (*n* = 22)	χ^2 or F	*P* value
Sex (male/female)	12/13	11/11	0.02	0.89
Age (yr)	45.9 ± 10.0	45.1 ± 10.4	0.05	0.83
Education (yr)	13.0 ± 4.7	12.5 ± 5.7	0.11	0.74
Age of onset (yr)	22.3 ± 6.3	25.2 ± 7.5	2.48	0.13
Antipsychotics			0.42	0.94
Clozapine	14	12		
Quetiapine	3	4		
Aripiprazole	3	2		
Risperidone	3	1		
Olanzapine	1	2		
Chlorpromazine	1	1		
Daily antipsychotic dose (mg) (chlorpromazine equivalent)	323.5 ± 193.1	341.7 ± 168.7	0.08	0.78
PANSS total score	72.1 ± 15.3	69.3 ± 11.5	0.45	0.51
P-subscore	12.6 ± 4.0	10.0 ± 3.3	3.52	0.07
N-subscore	26.7 ± 7.5	25.9 ± 6.9	0.25	0.62
G-subscore	33.8 ± 6.0	33.4 ± 5.4	0.01	0.91
SANS total score	88.1 ± 17.9	88.1 ± 15.2	0.18	0.68
Affect flattening	23.5 ± 5.8	24.1 ± 5.8	0.09	0.76
Alogia	16.0 ± 4.6	16.3 ± 3.4	0.12	0.73
Avolition-apathy	14.0 ± 3.1	14.6 ± 3.1	0.05	0.83
Anhedonia-Asociality	21.4 ± 3.3	21.7 ± 3.2	0.27	0.61
Attention	11.6 ± 2.3	11.4 ± 3.0	0.2	0.66
PRM-number correct	14.7 ± 4.0	15.5 ± 3.7	0.47	0.5
PRM-percent correct (%)	61.3 ± 16.9	64.6 ± 15.6	0.47	0.5

rTMS: Repetitive transcranial magnetic stimulation; P: Positive symptom; N: Negative symptom; G: General psychopathology; SANS: Scale for the Assessment of Negative Symptoms; PRM: Pattern recognition memory; PANSS: Positive and Negative Symptom Scale.

discrimination task, was administered. Subjects were presented with a series of 12 visual geometric patterns, one at a time, at the center of the screen (first presentation phase) and then were required to choose between an already seen pattern and a novel pattern (first recall phase). In the recall phase, previously viewed patterns were presented in reverse order from original presentation. Then, a new series of patterns was presented, followed by a second recognition test given either immediately or after a delay (20 min) to test delayed recognition memory. Performance on the PRM is measured as the number and proportion (%) of correct responses, with a maximum score of 100 (best pattern recognition memory).

Statistical analysis

Continuous variables were first tested for normality using the Kolmogorov–Smirnov one-sample test ($P < 0.05$). All continuous datasets met this criteria, so they were presented as mean ± SD. Continuous baseline variables were compared between active and sham rTMS groups by independent samples *t*-test. Categorical variables were presented as frequency and compared by χ^2 test. Data were analyzed using the intention-to-treat principle so missing data points were replaced with the last observation.

The primary objective of this study was to evaluate the effect of rTMS on visual recognition memory in patients with schizophrenia. Since all variables were normally distributed according to the Kolmogorov–Smirnov one-sample test, the principal outcome (visual memory performance as measured by % correct) was analyzed by repeated-measures analyses of variance with measurement time (baseline and weeks 4 and 8) as the within-group factor and active *versus* sham rTMS as the

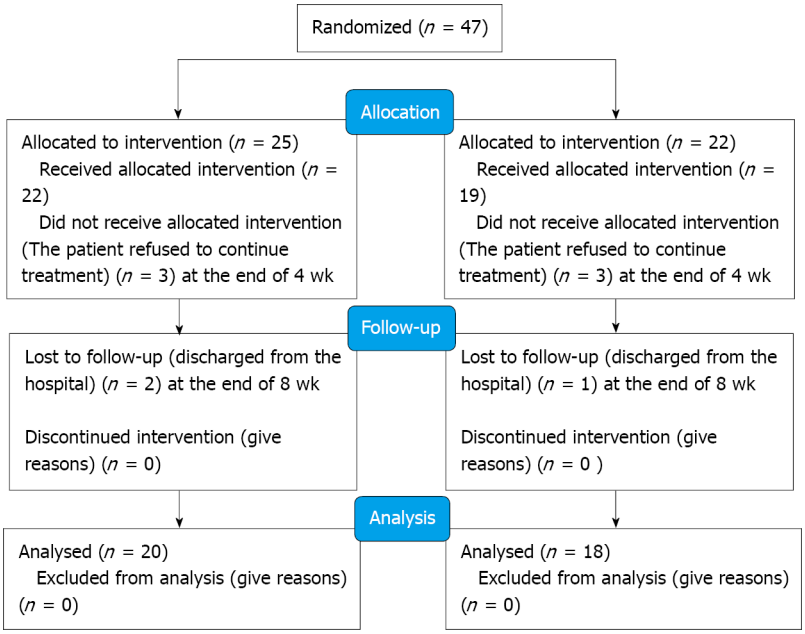

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Figure 1 Flow diagram.

between-group factor. If the time × group interaction was significant, analysis of covariance (ANCOVA) was used to test for differences between groups at the end of weeks 4 and 8, with baseline score as the covariate. If the interaction was not significant, no further statistical tests were performed. The same method was used to analyze changes in PANSS and SANS scores.

The second objective was to determine whether negative symptoms (SANS scores) were correlated with PRM performance (number and proportion correct) in the active and sham rTMS groups before and after treatment. Correlations between changes in SANS scores and visual memory performance were examined by Pearson correlation coefficients, and when significant, the Bonferroni correction was used. Finally, multiple linear regression was used to investigate potential response predictors associated with changes in visual memory scores.

All statistical analyses were conducted using SPSS version 18.0. $P \leq 0.05$ (two-tailed) was considered significant for all tests. In cases with multiple comparisons, P values were adjusted by Bonferroni correction.

RESULTS

Demographic and basic descriptive data

The full details of this clinical trial examining the effects of DLPFC-targeted rTMS on schizophrenia symptoms were reported previously[35]. In total, 47 patients were randomly divided into an active rTMS group (n = 25) and sham rTMS group (n = 22). However, six subjects withdrew their consent before starting treatment (three in the active and three in the sham rTMS groups). Therefore, 41 participants completed the full set of clinical trial, including 22 in the active rTMS group and 19 in the sham rTMS group.

At baseline, there were no significant differences in demographic variables, PANSS total and subscale scores, SANS total and subscale scores, PRM-number correct, and PRM-percent correct between active and sham rTMS treatment groups (Table 1). Consistent with a potential association between negative symptoms and poor visual memory, PRM performance metrics (number correct and percent correct) at baseline were negatively correlated with SANS total score and all subscale scores (P < 0.05–0.001) except for the affect flattening subscale (P > 0.05).

Efficacy of rTMS treatment for improving cognitive performance

Three participants were lost to follow-up due to premature discharge before week 8 (2 in the active group and 1 in the sham rTMS group), so treatment efficacy analysis included 20 patients in the active group and 18 in the sham group. Repeated measures ANCOVA revealed a significant test time (baseline *vs* week 4 *vs* week 8) × group interaction (F = 22.1, df = 274, P < 0.001) and a significant main effect of test time (F = 13.2, df = 274, P < 0.001) on PRM performance, but no significant effect of group (F =1.37, df = 137, P = 0.25). However, the PRM-number correct was significantly higher in the active rTMS group

than the sham group at week 8 (F = 16.8, df = 137, $P < 0.001$; effect size = 1.35) but not immediately after the 4-week treatment period (F = 0.49, df = 136, $P = 0.48$). The difference at week 8 was still significant after controlling for the effects of sex, age, disease duration, and drug dose (chlorpromazine equivalent) (F = 19.2, df = 133, $P < 0.001$), while the difference at week 4 did not reach significance (F = 0.63, $P = 0.43$).

In the active rTMS group, the mean number of correct answers on the PRM test increased by 4.54 ± 2.98 from baseline to week 8, while the correct number in the sham group decreased slightly (-0.92 ± 2.72) and the difference between these changes was highly significant (mean 5.46 ± 0.92, 95%CI: 3.43–7.14, F = 33.3, df = 137, $P < 0.0001$, effect size = 0.474) (Table 2). However, from baseline to week 4, there was no significant difference in the correct response change between groups (0.41 ± 4.1 *vs* −0.62 ± 2.8, F = 0.75, $P = 0.39$). rTMS treatment also significantly shortened select time (Figure 2A) and interval time (Figure 2B) in PRM from baseline to week 8 compared to the sham group. We can see that the treatment group decreased with the selection time and interval time in PRM compared with the control group at week 8.

rTMS treatment for psychopathological symptoms

Changes in PANSS and SANS total scores as well as subscale scores (secondary outcomes) are also summarized in Table 2. These SANS results are included from our previous study[35] for comparison and to assess the relationship between effects on negative symptoms and visual recognition memory following rTMS. By the end of 4 wk of treatment, there were no significant differences in SANS total score, all five SANS subscale scores, PANSS total score, and PANSS subscale scores between active and sham rTMS groups (all $P > 0.05$). At 8 wk, however, SANS total score as well as avolition/apathy, anhedonia/asociality, and attention subscores were significantly lower (improved) in the active rTMS group compared to the sham group (all $P < 0.05$) (Table 2). Alternatively, there were no between-group differences in PANSS total and subscale scores at week 4 and week 8 compared to baseline (all $P > 0.05$).

Relationship between improvement in cognitive ability and changes in psychopathological symptoms

The increase in PRM-number correct from baseline to week 8 was significantly correlated with the changes in SANS total score ($r = 0.34$, df = 38, $P = 0.034$; Figure 3), SANS alogia subscale score ($r = 0.37$, df = 38, $P = 0.024$), and SANS avolition/apathy subscale score ($r = 0.34$, df = 38, $P = 0.037$). However, none of these univariable correlations were significant after Bonferroni correction (all $P > 0.05$). Multiple regression analysis revealed a significant association between the increase in PRM-number correct and the change in SANS total score from baseline to week 8 (= 0.42, $t = 2.53$, $P = 0.017$).

DISCUSSION

The key results of this study were as follows. (1) DLPFC-targeted 10-Hz rTMS (20 single weekday sessions over 4 wk) had a significant therapeutic effect on the visual recognition memory deficit exhibited by schizophrenia patients with strong negative symptoms, but this response was delayed until several weeks after the end of treatment; and (2) This improvement in visual recognition memory was associated with a reduction in negative symptoms. The delay between treatment and response may help explain previous inconsistencies among studies on the therapeutic efficacy of rTMS.

There is growing acceptance of noninvasive brain stimulation (NIBS) techniques for the treatment of cognitive deficits[7], but only a few studies have examined the efficacy of rTMS for cognitive impairments in schizophrenia. Here, we showed that this specific NIBS regimen can mitigate multiple core symptoms of schizophrenia. Furthermore, this regimen may be a promising therapeutic option for other disorders presenting with emotional dysregulation and cognitive dysfunction. Recent studies have reported that NIBS stably mitigates psychiatric symptoms by noninvasively modulating the abnormal activity of neural circuits (*i.e.*, amygdala–PFC–hippocampus pathways) involved in the regulation of mood and cognition[36]. For instance, a recent review suggested that NIBS can improve mood by modulating emotional memories, while others[37,38] have reported that NIBS can suppress abnormally persistent fear memories in anxiety disorder patients that do not respond to psychotherapy and/or anxiolytic drugs. Multiple studies have also demonstrated the value of NIBS as a research tool for examining the neurological mechanisms underlying depression and anxiety in schizophrenia and other psychiatric disorders[39,40]. For instance, NIBS to the DLPFC after memory reactivation was reported to reduce the subsequent response to learned fear, suggesting that stimulation alters the synaptoplastic processes re-engaged during memory retrieval (term reconsolidation)[41-43]. In accordance with the current study, Barr and colleagues reported that daily 20-Hz rTMS of the DLPFC for 4 wk significantly improved working memory compared to sham stimulation in schizophrenia patients as measured by a three-back task[32]. More impressively, three-back accuracy was similar to that of healthy subjects after treatment[32]. Taken together, these findings suggest that high-frequency rTMS may be an effective treatment for visual and working memory deficits in patients with schizophrenia. In contrast, however, Prikryl and colleagues reported that 15-Hz rTMS over the left DLPFC for 4 wk had no significant effect

Table 2 Cognitive performance measures and clinical symptoms at baseline, week 4, and week 8 in active repetitive transcranial magnetic stimulation and sham multichannel transcranial magnetic stimulation groups

	Baseline (n = 47)	Week 4 (n = 41)	Week 8 (n = 38)	Group F (P value)	Time F (P value)	Group × Time F (P value)
PRM-number correct				1.37 (0.25)	13.2 (< 0.001)	22.1 (< 0.001)
rTMS (n = 25)	14.7 ± 4.0	15.1 ± 3.8	19.2 ± 2.7[c]			
Sham (n = 22)	15.5 ± 3.7	14.9 ± 4.4	14.6 ± 4.1			
SANS total score				0.89 (0.35)	38.11 (< 0.001)	11.36 (0.002)
rTMS	88.1 ± 17.9	79.0 ± 21.5	72.5 ± 16.8[a]			
Sham	88.1 ± 15.2	83.6 ± 19.2	83.5 ± 20.5			
Affect flattening				0.39 (0.54)	43.56 (< 0.001)	6.83 (0.013)
rTMS	23.5 ± 5.8	20.1 ± 6.7	18.8 ± 4.8			
Sham	24.1 ± 5.8	22.5 ± 5.9	21.9 ± 6.7			
Alogia				0.23 (0.64)	8.27 (0.007)	5.30 (0.027)
rTMS	16.0 ± 4.6	15.0 ± 4.7	13.6 ± 3.6			
Sham	16.3 ± 3.4	15.9 ± 4.1	16.1 ± 5.1			
Avolition-apathy				1.56 (0.22)	29.56 (< 0.001)	10.00 (0.003)
rTMS	14.0 ± 3.1	12.4 ± 3.5	11.4 ± 2.6[a]			
Sham	14.6 ± 3.1	14.1 ± 3.9	14.0 ± 3.9			
Anhedonia-Asociality				1.48 (0.23)	1.48 (0.23)	3.84 (0.058)
rTMS	21.4 ± 3.3	20.0 ± 3.9	29.9 ± 6.5[a]			
Sham	21.7 ± 3.2	20.8 ± 3.8	31.9 ± 6.0			
Attention				0.70 (0.41)	37.00 (< 0.001)	11.61 (0.002)
rTMS	11.6 ± 2.3	9.9 ± 2.9	8.7 ± 2.2[a]			
Sham	11.4 ± 3.0	10.4 ± 3.7	10.6 ± 3.5			
PANSS total score				0.03 (0.86)	60.02 (< 0.001)	8.42 (0.006)
rTMS	72.1 ± 15.3	65.3 ± 15.9	64.6 ± 16.8			
Sham	69.3 ± 11.5	61.9 ± 16.6	63.1 ± 14.3			
P-subscore				2.99 (0.09)	1.05 (0.313)	0.50 (0.49)
rTMS	12.6 ± 4.0	12.4 ± 4.0	12.5 ± 4.0			
Sham	10.0 ± 3.3	10.5 ± 3.9	10.3 ± 3.6			
N-subscore				0.01 (0.93)	77.76 (< 0.001)	10.12 (0.003)
rTMS	26.7 ± 7.5	22.8 ± 8.8	21.0 ± 7.1			
Sham	25.9 ± 6.9	22.6 ± 7.5	23.1 ± 7.6			
G-subscore				0.31 (0.58)	37.90 (< 0.001)	5.38 (0.026)
rTMS	33.8 ± 6.0	30.3 ± 6.6	29.9 ± 6.5			
Sham	33.4 ± 5.4	31.7 ± 6.2	31.9 ± 6.0			

[a]P < 0.05.
[c]P < 0.001.
rTMS: Repetitive transcranial magnetic stimulation; PANSS: Positive and Negative Symptom Scale; P: Positive symptom; N: Negative symptom; G: General psychopathology; SANS: Scale for the Assessment of Negative Symptoms; PRM: Pattern recognition memory.

on working memory performance in schizophrenia patients[44]. Thus, the efficacy of different rTMS regimens for the cognitive deficits of schizophrenia requires further investigation in larger clinically heterogenous populations.

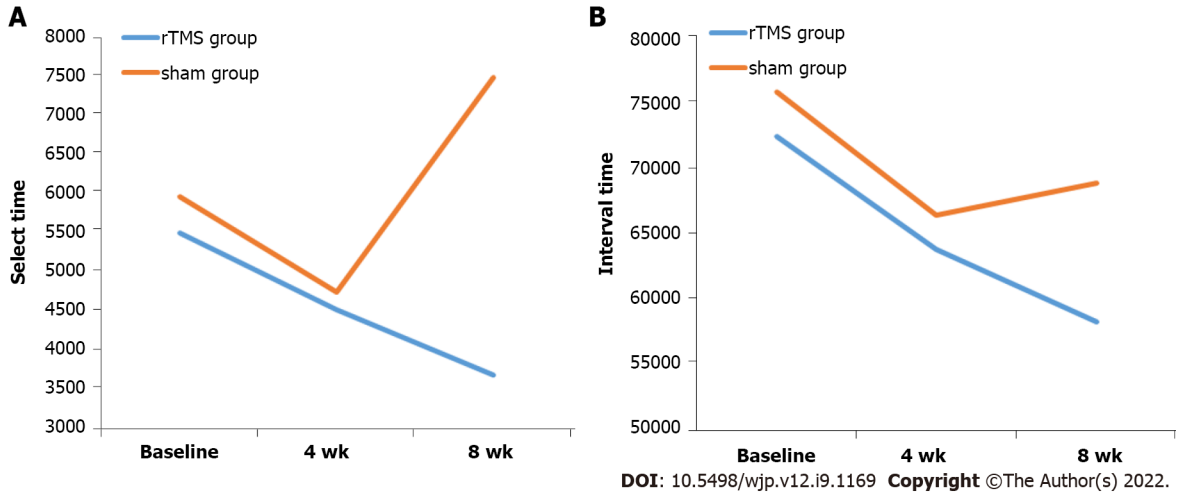

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Figure 2 Repetitive transcranial magnetic stimulation treatment also significantly shortened select and interval time in pattern recognition memory from baseline to week 8 compared to the sham group. A: Select time; B: Interval time. rTMS: Repetitive transcranial magnetic stimulation.

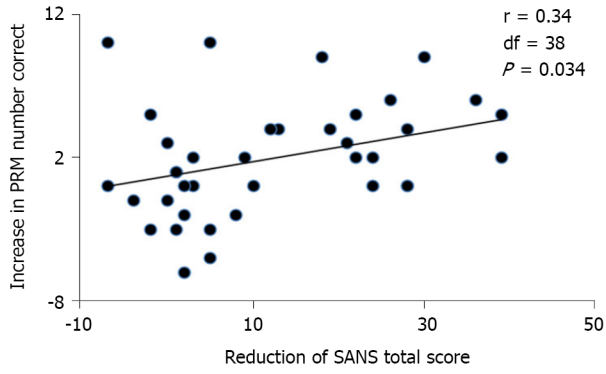

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Figure 3 The increase in pattern recognition memory-number correct from baseline to week 8 was significantly correlated with the reduction in Scale for the Assessment of Negative Symptoms total score ($P < 0.05$). This association was confirmed by multiple regression analysis (beta = 0.42, $t = 2.53$, $P = 0.017$). PRM: Pattern recognition memory; SANS: Scale for the Assessment of Negative Symptoms.

In our recently published study[35], we reported that high-frequency rTMS over the left DLPFC for four consecutive weeks reduced the negative symptoms of schizophrenia compared to sham rTMS[42-45], consistent with numerous studies using rTMS to treat the negative symptoms of schizophrenia[42,43,46-50] but in contrast to many others[34,42,43,51,52]. Further, multiple meta-analyses have also found mixed results[26,53-55]. Our previous and current findings provide a potential explanation for these discrepancies as the effects of multichannel TMS (mTMS) on both SANS scores and PRM task performance were not statistically significant until several weeks post-treatment. The exact reasons for these delayed effects are unclear but are not unusual following NIBS. For example, a recent randomized, sham-controlled two-arm study reported that active intermittent theta burst transcranial stimulation (iTBS) of the left DLPFC significantly reduced negative symptom severity in treatment-resistant schizophrenia patients compared to sham iTBS at 6 mo after the end of treatment[56]. Similarly, a randomized, double-blind, sham-controlled crossover study of accelerated iTBS for 2 wk in patients with TRD found a greater response rate (defined as a 50% reduction in Hamilton Depression Rating Scale score) after two additional weeks compared to immediately after treatment[57]. We speculate that this delay is due to the slow nature of the changes underlying reversal of negative symptoms, such as circuit-level plasticity and improvements facilitated by interpersonal relationships and social activities occurring over an extended period after treatment. In addition, plasticity may also take longer in older patients such as those examined in the current study. Further studies are warranted to test these and other potential mechanisms.

The improvement in visual recognition memory performance (increased number of correct responses) correlated significantly with a decrease in SANS total score at week 8 but not week 4. Moreover, PRM-number correct was correlated with SANS total score and all subscale scores except the affect flattening

subscale at baseline, suggesting shared neurological mechanisms. It is known that both cognitive deficits and negative symptoms of schizophrenia are associated with generalized dopamine (DA) signaling deficits in cortical and extrastriatal regions[58], and recent studies have shown that prefrontal hypodopaminergia can cause striatal DA disorders that in turn can lead to cognitive impairments[59,60]. Conversely, increasing DA release by administering low or moderate doses of psychostimulants improved negative symptoms and cognitive deficits in schizophrenia[60]. High-frequency rTMS applied over the left PFC also increased the release of DA in mesostriatal brain pathways[46] possibly accounting for improved negative symptoms and cognitive deficits. However, a host of other therapeutic mechanism may contribute, warranting further clinical and preclinical investigations.

This study had several limitations. First, the sample size was small, limiting statistical power and precluding exploratory subgroup analyses. Second, due to the homogeneity of the study population, these findings may not be applicable to other ethnic groups, patients in earlier phases of the disease including untreated first-episode patients, and those with distinct symptom clusters. Third, 180° rotation of the figure-of-eight coil did not completely prevent brain stimulation, so a real sham coil should be used in subsequent studies. Fourth, carrying forward the last observation is less suitable for small samples, although this was necessary in only a small portion of individual datasets. Fifth, the 4-wk follow-up period may not be sufficient to measure the full extent (or stability) or symptom improvement. Indeed, previous studies have monitored patients for 3 to 12 mo following treatment. Sixth, it is possible that visual recognition memory is particularly responsive to rTMS, so more comprehensive evaluations are required to establish clinical efficacy, including effects on executive functions, which are markedly impaired in many patients with schizophrenia. Seventh, it is uncertain if some patients recognized the specific treatment (active or shame) as we did not compensate for possible somatosensory effects. Eighth, we chose the left DLPFC based on past studies but other sites may be more effective. In addition, we did not use neuronavigation to determine the location of the DLPFC, which may introduce response heterogeneity. Finally, although antipsychotic drugs were included as covariates in statistical analysis, the different antipsychotic regimens may have distinct effects on the efficacy of rTMS.

CONCLUSION

High-frequency rTMS targeting the DLPFC can improve visual recognition memory in patients with schizophrenia. This high-frequency rTMS protocol may be of substantial clinical value because cognitive deficits are a major barrier to recovery and predict adverse clinical outcomes in patients with schizophrenia and other psychiatric disorders. Although the results of our study are encouraging, larger-scale studies with longer follow-up are needed to confirm the effectiveness of DLPFC-targeted rTMS for the treatment of cognitive deficits in first-episode schizophrenia patients and patients of different ethnicities. Moreover, therapeutic effects on other cognitive domains and the underlying mechanisms warrant further investigation.

ARTICLE HIGHLIGHTS

Research background

At present, antipsychotic drug therapy has little effect on the improvement of some psychiatric symptoms in schizophrenia patients, and drug therapy is not acceptable due to the unbearable adverse drug reactions. There is growing evidence that repetitive transcranial magnetic stimulation (rTMS) is effective for both positive and negative symptoms of schizophrenia.

Research motivation

Schizophrenia has brought great burden to the whole society with high morbidity and disability rate. The United Kingdom and the United States spend around 2% of GDP each year on the treatment, care and rehabilitation of people with schizophrenia. In particular, long-term hospitalization of patients wastes a large number of medical resources, and the existence of negative symptoms is one of the important reasons for long-term hospitalization of patients. Therefore, the use of rTMS adjuvant therapy to explore the possibility of improving the negative symptoms of patients, to promote the remission of patients, improve the social function and quality of life of patients, has good social and economic benefits.

Research objectives

In this study, we assessed the therapeutic effects and safety of left dorsolateral prefrontal cortex (DLPFC) high-frequency rTMS on negative symptoms of schizophrenia. We evaluated the efficacy of rTMS on recognition in patients with chronic schizophrenia.

Research methods

This was a randomized, sham-controlled, double-blinded trial. Patients diagnosed with schizophrenia on stable antipsychotic treatment were randomly assigned to active rTMS treatment group (n = 25) or a sham rTMS treatment group (n = 22). 25 patients in the active rTMS group received 10-Hz 110% motor threshold rTMS, while 22 patients were subjected to sham rTMS, both being given 4-wk treatment (5 d/wk). Efficacy of negative symptom was assessed with the Scale for the Assessment of Negative Symptoms (SANS), the Positive and Negative symptom scale (PANSS) at baseline, the end of 4 and 8 wk. The cognitive function was assessed with Cambridge Neuropsychological Test Automated Battery at baseline, the end of 4 and 8 wk. The side effects were assessed with TESS at baseline and the end of 4 wk.

Research results

There were no significant differences in pattern recognition memory (PRM) performance metrics, SANS total score, SANS subscores, PANSS total score, and PANSS subscores between active and sham rTMS groups at the end of the 4-wk treatment period, but PRM performance metrics (percent correct and number correct) and changes in these metrics from baseline were significantly greater in the active rTMS group at week 8 compared to the sham group (all $P < 0.05$). Active rTMS treatment also significantly reduced SANS score at week 8 compared to sham treatment. Moreover, the improvement in visual memory was correlated with the reduction in negative symptoms at week 8. In contrast, there were no between-group differences in PANSS total score and subscale scores at either week 4 or 8 (all $P > 0.05$).

Research conclusions

High-frequency TMS can improve visual memory and reduce negative symptoms in patients with schizophrenia, but these effects are delayed, potentially due to the requirement for extensive neuroplastic changes within DLPFC networks.

Research perspectives

In the future, it is necessary to further explore more scientific treatment parameters and more sensitive assessment tools (such as SANS and neuropsychological assessment kits) for rTMS in the treatment of negative symptoms of schizophrenia, and carry out multicenter, large-sample studies.

FOOTNOTES

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ORIGINAL ARTICLE

Case Control Study

Galectin-3 mediated risk of inflammation in stable schizophrenia, with only possible secondary consequences for cognition

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Abstract

BACKGROUND

Evidence suggests that cytokines cause immune disturbances, shape immunological sequelae later in life, and modulate the risk of schizophrenia (SC). Galectin-3 (Gal-3), a multifaceted molecule of the glycan family, is involved in the formation of the immunological synapse and modulates the signalling pathway and effector functions of T lymphocytes, which are major producers of cytokines. We have previously reported elevated serum Gal-3 levels in stable SC patients. However, Gal-3 as a link between cognitive functioning and inflammation has not yet been investigated in SC.

AIM

To investigate the relationship between serum Gal-3 levels and cognitive performance, serum cytokines, and white blood cell count in three-month stably treated SC patients.

METHODS

Twenty-seven patients with SC in remission and 18 healthy volunteers participated in this case-control and correlational study. Clinical assessment was performed using the Positive and Negative Syndrome Scale and the Montreal-Cognitive Assessment. The results of previously measured serum levels of Gal-3, interleukin (IL)-33, soluble suppression of tumorigenicity 2 (sST2), tumor necrosis factor-alpha (TNF-α), IL-6 and IL-17 were used for further statistical analyses, and IL-4, IL-23, IL-1β and transforming growth factor-beta (TGF-β) were now additionally measured with a sensitive enzyme-linked immunosorbent assay. The number of leukocytes in the blood and the percentage of neutrophils, lymphocytes, and monocytes were determined with a standardized routine measurement procedure (Sysmex Technology). Statistical analyses were performed using SPSS 20.0 software.

RESULTS

We found no correlation between serum Gal-3 levels and cognitive functioning in SC patients. A positive correlation was found between the levels of Gal-3 and TNF-α (r = 0.476; P = 0.012), Gal-3 and IL-23 (r = 0.417; P = 0.031), and Gal-3 and sST2 (r = 0.402; P = 0.038). The binary logistic model, which included all nine cytokines measured in this patient sample, indicated the particular role of Gal-3 and TGF-β in the duration of SC. In the stabilization phase of SC, we observed a moderate and negative correlation between serum Gal-3 levels and leukocytes (r = -0.449; P < 0.019). Additional linear regression analysis showed a positive correlation between Gal-3 expression and risperidone dose (F: 4.467; P < 0.045; r^2 = 0.396).

CONCLUSION

The combined activity of Gal-3 and proinflammatory cytokines, TGF-β downregulation and lower counts of leukocytes influence the SC duration. Gal-3 likely manifests indirect immunometabolic regulation of cognition in SC.

Key Words: Schizophrenia; Galectin-3; Cytokines; Leukocytes; Antipsychotics

Core Tip: In clinical sampling, there is an urge to place the results of biological measurements in a much broader context. Elevated serum galectin-3 (Gal-3) levels in schizophrenia (SC) have not been studied in relation to other peripheral biomarkers and subsequent neuroinflammation. We found that Gal-3 contributes to ongoing peripheral systemic inflammation and disease duration in patients with SC. All of this may be an underlying indirect immunometabolic mechanism for cognitive performance in patients with SC.

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INTRODUCTION

Immune dysregulations during prenatal and postnatal life are increasingly associated with neurodevelopmental disorders and have also recently been shown to be an important etiological construct of schizophrenia (SC)[1,2]. Multiple post-mortem brain and neuroimaging studies have also provided evidence for neuroinflammation in SC[3,4]. One of the best-known hypotheses, proposed by Bechter, links SC to mild and localized encephalitis[5]. There is strong evidence that cytokines cause these immune disturbances, shape immunological sequelae later in life, and modulate SC risk. In particular, T lymphocytes are one of the major producers of cytokines, and it has been reported that blood levels of cytokines derived from various lineages of T lymphocytes such as T helper 1 (Th1), Th2, Th17 and regulatory T cells (Treg) are altered in SC[6-8]. Studies have shown that patients with SC have increased serum concentrations of proinflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor-alpha (TNF-α)[9,10].

Studies have also shown that Gal-3, a multifaceted molecule in the glycan family, is directly involved in the formation of the immunological synapse and appears to play a pivotal role in modulating the signalling pathway and effector functions of T lymphocytes[11]. It is noteworthy that Gal-3 has both

immune and non-immune functions in the brain. Gal-3 appears to play a neuroprotective role in neuronal tissue and is involved in the reparative processes of brain lesions and ischemia. In contrast, Gal-3 may promote microglia-mediated neuroinflammation and contribute to neuroprogression[12]. Gal-3 increases the secretion of proinflammatory cytokines from microglia and astrocytes[13] and is also required for leukocyte recruitment during an acute inflammatory response[14].

Biomarkers that can be conveniently measured in blood may also reflect changes in the central nervous system and dysfunction of the blood-brain barrier (BBB). There is evidence of BBB dysfunction in brain disorders, including SC. Brain microvascular endothelial cells (BMECs) are a key element of the microvasculature that forms the BBB and shields the brain from toxins and reactive immune cells. However, it is not known whether BMECs themselves are functionally compromised and lead to BBB dysfunction in brain disorders[15]. An increased ratio of cerebrospinal fluid to serum albumin in patients with SC suggests increased permeability of the BBB[16]. Given the important role of galectins in cell adhesion, migration, polarity, and chemotaxis, it is likely that modulation of galectin levels in BMECs that form the BBB could compromise BBB integrity and consequently contribute to neuroinflammation[17]. Plasma levels of Gal-3 have been shown to be increased after aneurysmal subarachnoid hemorrhage (SAH), and a Gal-3 inhibitor could potentially prevent post-SAH BBB disruption by inhibiting Gal-3[18].

We have previously reported elevated serum Gal-3 levels in patients with SC who received stable 3-mo antipsychotic therapy[19]. We wanted to go further in exploring Gal-3 interactions and not only measure serum levels during stabilisation of SC. Recently, such an association between Gal-3 and cognition was found in Alzheimer's disease[20]. In this additional analysis, we tested the hypothesis that serum Gal-3 levels in patients with stable SC might be related to cognitive functioning and different white blood cell counts and types of cytokines in stable SC patients. In this way, we aimed to investigate the possible involvement of this glycan in peripheral systemic inflammation and disease duration, but also its position as a link between cognitive functioning and inflammation, which has not yet been investigated in SC.

MATERIALS AND METHODS

Participants

Patients with SC in remission (SC in remission) were recruited in 2016 in the Psychiatric Day Hospital of the Kragujevac Clinical Centre. Participants were between 18 and 65 years old. Diagnoses were made using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) criteria[21] for SC (F20). The major inclusion criterion was stable mental functioning and adherence to three months of stable antipsychotic depot therapy with risperidone or paliperidone. Add-on therapy for patients included anxiolytics or hypnotics only. A complete medical history was obtained from each patient.

Exclusion criteria were current infections during the three-month remission period, allergies or autoimmune disorders, current anti-inflammatory or antiviral medications, or dual diagnoses of other mental illnesses. Healthy controls (HCs) were recruited during blood donation at the Blood and Blood Products Service of the Kragujevac Clinical Centre, and controls with a family history of psychosis were excluded. All laboratory measurements and immunoassays were performed at the Centre for Molecular Medicine and Stem Cell Research, Faculty of Medical Sciences, University of Kragujevac. The study was conducted after the Ethics Committee of the Kragujevac Clinical Centre gave its approval. Participants were able to give informed consent, and each patient signed the informed consent form before participating in the study.

The study sample was estimated considering the first type error (α) of 0.05 and the power of the study of 0.8 for the two-tailed t-test for two independent samples using the statistical softer G* Power 3.1.9.2. Considering previous studies and similar methods for measuring serum cytokine levels[22], the minimum number of participants required in each group was estimated to be 14.

Clinical assessment

Psychological assessment was performed by trained raters. Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS)[23]. Cognition was assessed using the cognitive factor of the PANSS (consisting of items P2-N5-G11)[24], which primarily refers to sustained attention, and executive functioning such as mental flexibility and problem-solving as components of executive functioning[25]. In addition, cognitive impairment was assessed using the Montreal-Cognitive Assessment (MoCA)[26], a cognitive screening tool for older population with mild cognitive impairment and dementia that has also been shown to be useful in patients with psychosis[27]. The MoCA test assesses multiple cognitive domains including attention, concentration, executive functions, memory, language, visual-constructive skills, conceptualization, and orientation, with a maximum total score of 30 and a lower limit for normal cognition of 26.

Blood collection and cytokine measurements

Blood samples were taken in the morning (approximately 8 am) after overnight fasting. The blood clot was cut and then centrifuged. After separation, serum samples were stored at -20° until analysis. The results of previously measured serum levels of Gal-3, IL-33, soluble suppression of tumorigenicity 2 (sST2), TNF-α, IL-6 and IL-17[19,28] were used for further statistical analyses, and IL-4, IL-23, IL-1β and transforming growth factor-beta (TGF-β) were now additionally measured using sensitive Enzyme-Linked Immuno-Sorbent Assay kits specific for the human cytokines according to the manufacturer's instructions (R&D System, Minneapolis, MB). The procedure has been described in detail previously [19]. Briefly, 96-well plates coated with capture antibody and incubated overnight were washed with wash buffer and incubated with blocking buffer for 1 h at room temperature. Serum samples or standard recombinant IL-4/IL-23/IL-1β/TGF-β were added to the plates for 2 h before a biotinylated detection antibody and streptavidin peroxidase were applied for 1 h each at room temperature. The plates were developed with substrate reagent for 20 min, and the reaction was stopped by addition of 4 mol/L sulfuric acid. The absorbance was read at 495 nm using a microplate reader. The exact concentration of the above biomarkers was measured by interpolating a standard curve with a series of known concentrations according to the manufacturer's instructions. The values of the measured cytokines are expressed in pg/mL. Blood cell populations were determined using a standardized routine laboratory procedure (Sysmex Technology).

Statistical analysis

Demographic and clinical data were presented descriptively. Various covariates were included in linear and multiple linear regression models to examine the effects of these variables on the results. Pearson's or Spearman's correlation analysis was used to examine the significance of the correlation between serum Gal-3 levels and blood cell counts, serum cytokine levels, and clinical scores and subscores of PANSS and MoCA. To determine the best prediction of serum cytokine levels for the presence of illness, binary logistic regression analysis was performed. A P-value of ≤ 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0. Armonk, NY: IBM Corp.

RESULTS

Demographic and clinical characteristics

There were no statistically significant differences in age (P = 0.886) and sex (P = 0.851) between patients (n = 27) and HC subjects (n = 18). The demographic and clinical characteristics of the patients were the same as those presented previously[19,28] and are listed in Table 1. Among patients with SC, the duration of illness was 9.95 ± 7.71 years, with 2.18 ± 1.92 years as multiple previous hospitalizations. Most patients were individuals with high school education (n = 22). The mean PANSS total score and subscores, MoCA total score and subscores, and medications taken in the SC group are shown in Table 1.

Differentiation of serum cytokine levels between groups

In this study, lower TGF-β levels (272.09 ± 101.59 *vs* 360.41 ± 45.13, P = 0.003) were observed in patients with SC (Figure 1A), with no difference in serum IL-4, IL-23 and IL-1β levels (data not shown). The binary logistic model, which included the presence of illness as a dependent variable and all measured cytokine serum levels as covariates in a stepwise Backward-Wald method, highlighted the particular role of Gal-3 and TGF-β in SC, both of which have an impact on disease presentation with an odds ratio for Gal-3: 1.002 (95%CI: 1.000-1.004; P = 0.022) and TGF-β: 0.982 (95%CI: 0.9968-0.997; P = 0.015) (Figure 1B), suggesting that higher Gal-3 levels are associated with stabilization in later phases of SC.

Serum Gal-3 levels correlate significantly with proinflammatory mediators and risperidone dosing

The correlation between Gal-3 serum levels and cognitive functioning considering MoCA total score, subscores, and PANSS Cog was not significant (data not shown). In addition, we now examined the relationship between systemic Gal-3 levels and cytokines with divergent immune properties. A positive and moderate correlation was observed between Gal-3 and TNF-α (r = 0.476; P = 0.012), Gal-3 and IL-23 (r = 0.417; P = 0.031), and Gal-3 and sST2 (r = 0.402; P = 0.038) levels (Figure 2).

Moreover, linear regression analysis revealed a positive correlation between Gal-3 and risperidone dose (F: 4.467; P < 0.045; r^2 = 0.396).

Serum levels of Gal-3 inversely correlate with leukocyte count

We also examined the correlation between Gal-3 and the number of leukocytes (neutrophils, lymphocytes, and monocytes) involved in the immune response. A negative correlation was found between Gal-3 and total leukocyte count (r = -0.449, P < 0.019), with no other significant correlations with the percentages of specific populations.

Table 1 Demographic and clinical characteristics of subjects

Characteristics	SC in remission (*n* = 27)	Healthy control (*n* = 18)	*P* value
Age (yr), mean ± SD	36.18 ± 9.27	37.67 ± 9.96	0.862
Sex (male/female)	16/11	12/6	0.851
Duration of illness (yr), mean ± SD	9.95 ± 7.71	-	-
Number of previous hospitalizations	2.18 ± 1.92	-	-
PANSS			
PANSS total score	99.22 ± 18.2	-	-
Positive syndrome scale	22.26 ± 5.97	-	-
Negative syndrome scale	27.52 ± 6.09	-	-
General psychopathology scale	49.44 ± 7.83	-	-
MoCA			
MoCA total score	22.74 ± 4.76	-	-
Visuospatial/Executive	4.11 ± 1.25	-	-
Naming	2.78 ± 0.69	-	-
Attention	5.07 ± 1.21	-	-
Language	1.89 ± 0.69	-	-
Abstraction	1.41 ± 0.84	-	-
Delayed recall	1.81 ± 1.62	-	-
Orientation	5.74 ± 0.81	-	-
Medications			
Long-acting risperidone/paliperidone	22/5	-	-
Long-acting risperidone dosage 25/37.5/50 mg	3/9/13	-	-
Cell counts			
Leukocytes (× 10^9/L)	6.67 ± 2.06	-	-
Neutrophils (%)	0.61 ± 0.07	-	-
Lymphocytes (%)	0.31 ± 0.07	-	-
Monocytes (%)	0.08 ± 0.02	-	-

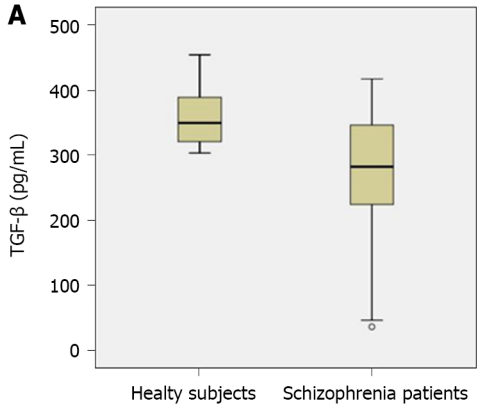
PANSS: Positive and Negative Syndrome Scale of Schizophrenia; MoCA: Montreal-Cognitive Assessment; SC: Schizophrenia.

DISCUSSION

The current study contains several new and interesting findings. One of the salient findings was a significant correlation between serum Gal-3 levels and levels of proinflammatory cytokines in a stable phase of SC. Serum Gal-3 correlated positively with TNF-α, IL-23, and soluble ST2 in SC in remission (Figure 2) and was associated with downregulation of the counterregulatory cytokine TGF-β and appears to play a role in disrupting leukocyte migration. In addition, the increase in Gal-3 might be influenced by risperidone dosing.

This study was the first to investigate a possible relationship between Gal-3 and cognitive functioning in SC patients. No correlation was found between serum Gal-3 levels and cognitive performance, suggesting a more indirect immunometabolic regulation of cognition in SC, as we have recently discussed[12]. It has been demonstrated that proinflammatory cytokines and mediators of oxidative stress could influence serum Gal-3 levels, and a reciprocal role of Gal-3 in these cascades could not be excluded[29]. Recently, Dal Lin *et al*[30] (2020) pointed out the close relationship and regulatory effect of cognitive functioning on some molecular processes in the human body, including acute attenuation of oxidative stress and inflammation, which inversely affect Gal-3 levels. Based on these findings, Gal-3 may prove to be a potential therapeutic target in SC.

Currently, there are no studies on the correlation between Gal-3 and proinflammatory cytokine levels in SC patients. In our previous study on the same cohort, we found higher systemic Gal-3 levels[19] and



B

Cytokine impact on illness[1]	B	SE	Wald	df	Sig.	Exp(B)	95%CI	
							Lower	Upper
TGF-β	-0.018	0.007	5.902	1	0.015	0.982	0.968	0.997
Gal-3	0.002	0.001	5.279	1	0.022	1.022	1.000	1.004

[1]Binary logistic regression, 9 steps analysis included cytokines representing different types of immune responses [galectin-3, interleukin (IL)-33, soluble suppression of tumorigenesis, tumor necrosis factor-alpha, IL-4, IL-6, IL-23, IL-1β and transforming growth factor-beta]

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Figure 1 Transforming growth factor-beta and galectin-3 levels impact the illness. A: Lower transforming growth factor-beta (TGF-β) levels (272.09 ± 101.59 *vs* 360.41 ± 45.13 pg/mL, *P* = 0.003) were measured in patients; B: These parameters of serum concentrations of galectin-3 and TGF-β both had an impact on disease presentation. TGF-β: Transforming growth factor-beta; IL: Interleukin; Gal-3: Galectin-3.

TNF-α[24]. In addition to our study, Kajitani *et al*[31] (2017) also reported elevated serum Gal-3 levels in a stable phase of SC. In one study, Gal-3 was tested for its capacity to induce proinflammatory cytokines such as TNF-α and IL-6 from plasmacytoid dendritic and form myeloid dendritic cells isolated from blood. This lectin was found to activate both, TNF-α and IL-6[32]. In addition, a pre-clinical model of intracerebral haemorrhage (ICH) also demonstrated increased expression of Gal-3 in perihematomal brain regions after ICH and Gal-3-induced release of IL-6, suggesting a role for Gal-3 in inflammatory responses after ICH[33]. These findings suggest the hypothesis that neuronal damage could be followed by inflammation involving Gal-3. The elevated serum Gal-3 levels observed in SC patients in the current study could lead to BBB disruption and contribute to the persistence of mild chronic neuroinflammation suspected in SC.

In particular, somatic comorbidities common in SC, such as obesity, hyperlipidaemia, dyslipidaemia and type 2 diabetes, could be monitored by measuring Gal-3[34]. Gal-3 correlates positively with obesity and inflammation, as measured by the inflammatory markers IL-6 and C-reactive protein (CRP)[35]. Contrary to this finding, the IL-6 axis was not active in this phase and in the specific subpopulation of patients, but rather overweighted type-1 immune response with representative TNF-α. Taken together, these findings suggest potential systemic inflammatory properties of Gal-3 through its interactions with proinflammatory markers in SC that contribute to immunometabolic processes in SC.

The association of Gal-3 and sST2 and their changes at follow-up with the development of heart failure in patients with ST-segment elevation myocardial infarction showed that the levels of Gal-3 and sST2 were significantly increased at one-year follow-up[36]. Interestingly, the increased serum Gal-3 concentration correlated with the production of IL-17 and exhibited a significant correlation with neutrophil/lymphocyte ratio, white blood cell count, and CRP, but inversely correlated with the production of IL-10 and IL-12 in patients with untreated colorectal cancer[37]. Some findings suggest that Gal-3 is required to efficiently recruit leukocytes during an acute inflammatory response[14]. These findings may indicate the diverse role of Gal-3 in this SC chronic inflammation, as we have previously discussed that Gal-3 plays a predominant role in the resolution of inflammation[12]. In chronic SC, our studies have shown that serum Gal-3 levels are elevated and that Gal-3 is negatively correlated with leukocyte count. This lower leukocyte count may be related to the decline in immunity of patients with SC in later stable phases and their greater susceptibility to infection.

Although the Gal-3 signalling pathway is not well understood, Gal-3 can be secreted into the extracellular space, where it can interact with different structures such as cell surface and extracellular matrix glycoproteins[38]. In autoimmune neuroinflammation, endogenous Gal-3 may potentiate its severity by decreasing the frequency of Treg cells, controlling IL-10 production, and modulating Notch activation[39]. The Notch and TGF-β signalling crosstalk, which plays an important role in regulating endothelial and neural development[40], could also be influenced by Gal-3. Our findings might shed important light on the Notch-TGF-β axis in SC (Figure 1B). As for TGF-β, our previous data indicate that serum levels of TGF-β are significantly increased in patients with SC in relapse and first-episode psychosis compared to healthy subjects[41,42]. However, in the current study, significantly lower TGF-β levels were observed in SC patients in remission compared to a group of HC subjects (Figure 1A), suggesting that TGF-β levels vary during the course of SC.

Regarding the possible influence of antipsychotics, a recent *in vitro* study reported that the atypical antipsychotic risperidone reduced the production of proinflammatory cytokines by lipopolysaccharide-stimulated glial cells but had no effect on IL-10[43]. However, paliperidone increased TGF-β and IL-10 during acute stress and during prolonged chronic stress[44]. Our recent hypotheses about the

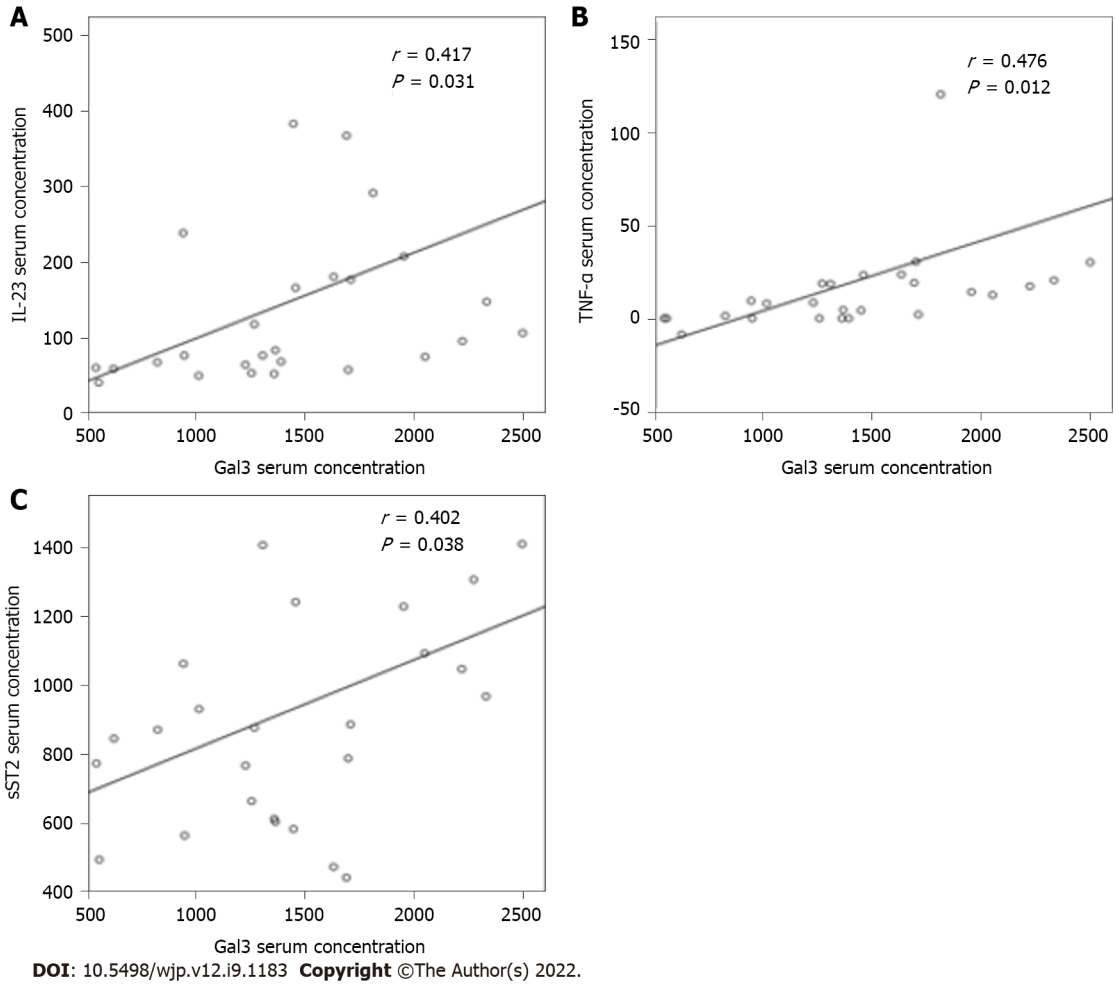

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Figure 2 Correlations of serum concentrations of galectin-3 with proinflammatory mediators. A positive and moderate correlation was observed between serum concentrations of galectin-3 (Gal-3) and interleukin-23 (IL-23), Gal-3 and tumor necrosis factor-alpha (TNF-α), and Gal-3 and soluble suppression of tumorigenicity 2 (sST2). A: IL-23 serum concentration; B: TNF-α serum concentration; C: sST2 serum concentration. IL: Interleukin; TNF-α: Tumor necrosis factor-alpha; sST2: Soluble suppression of tumorigenicity 2.

involvement of antipsychotics in the processes of glycosylation can be explained by the effects of their higher doses on serum Gal-3 levels. The findings of the current study suggest that higher doses of prescribed risperidone may lead to an increase in Gal-3 levels. Whole-serum proteins show increased glycosylation after antipsychotic use, indicating the usefulness of these processes for understanding the pathogenesis and monitoring the treatment of patients with SC[34,45].

A higher percentage of Gal-3-expressing innate and adaptive immune cells in the lamina propria was observed in patients with comorbid ulcerative colitis and metabolic syndrome[46]; this encouraged us to explore other immune biomarkers in patients with SC. N-acetylcysteine (NAC) has been proposed for the adjunctive treatment of SC and ulcerative colitis[47]. Oral intake of NAC was shown to lower inflammatory biomarkers, CRP and Gal-3 in patients with acute myocardial infarction receiving fibrinolytic therapy[48]. Preliminary results indicated the usefulness of NAC in improving all domains of SC functioning[49].

As a limitation of our study in terms of cognitive assessment, we must consider that only specific domains of cognitive functioning were assessed, using available validated and brief instruments to detect cognitive impairment in SC in our population. Although we tried to exclude all somatic states, we should be aware that comorbidity and psychotropic medication could influence the results of both cognitive functioning and serum measurements. We believe that it is necessary to investigate these issues further in a larger sample with a much more thorough analysis of confounding factors, which has not been done within the scope of this manuscript, but these results are valuable to guide us in the future.

CONCLUSION

In clinical sampling, there is an urge to place the results of biological measurements into a much wider concept. Higher serum levels of Gal-3 in SC have not been explored in interaction with other peripheral biomarkers reflecting possible inflammatory changes. We observed that Gal-3 contributes to ongoing peripheral systemic inflammation and disease duration in patients with SC. Moreover, its influence on BBB permeability and consequent neuroinflammation should be explored. Our data revealed some new complex roles of Gal-3, such as its possible involvement in neuroinflammation and cognitive processing, contributing to a better understanding of the specific immune profile in patients with SC. Inflammation also appears to be the potential pathway by which Gal-3 may affect cognitive functioning in SC. The efficacy of antipsychotics could be improved and their adverse effects corrected if the role of Gal-3 in glycosylation processes were considered. These findings provide a rationale for further strategies targeting Gal-3 for therapeutic intervention in SC.

ARTICLE HIGHLIGHTS

Research background

Galectin-3 (Gal-3), a multifaceted molecule of the glycan family, modulates T lymphocytes' signalling pathway and effector functions. We have previously reported elevated serum Gal-3 levels in stable schizophrenia (SC) patients, but Gal-3 as a link between cognitive functioning and inflammation has not yet been investigated in SC.

Research motivation

Elevated serum Gal-3 levels in SC have not been studied in relation to other peripheral biomarkers and subsequent neuroinflammation. All of this may be an underlying indirect immunometabolic mechanism for cognitive performance in patients with SC.

Research objectives

Investigating the relationship between serum Gal-3 levels and cognitive performance, serum cytokines, and white blood cell count in three-month stably treated SC patients could contribute to a better understanding of the specific immune profile in patients with SC.

Research methods

Twenty-seven patients with SC in remission and 18 healthy volunteers participated in this case-control and correlational study. Clinical assessment was performed using the Positive and Negative Syndrome Scale and the Montreal-Cognitive Assessment. The results of previously measured serum levels of Gal-3, interleukin (IL)-33, soluble suppression of tumorigenicity 2 (sST2), tumor necrosis factor-alpha (TNF-α), IL-6 and IL-17 were used for further statistical analyses, and IL-4, IL-23, IL-1β and transforming growth factor-beta (TGF-β) were now additionally measured with a sensitive enzyme-linked immunosorbent assay. The number of leukocytes in the blood and the percentage of neutrophils, lymphocytes, and monocytes were determined with a standardized routine measurement procedure. Statistical analyses were performed using SPSS 20.0 software.

Research results

Serum Gal-3 correlated positively with TNF-α, IL-23, and soluble sST2 in SC in remission and was associated with downregulation of the counterregulatory cytokine TGF-β and appears to play a role in disrupting leukocyte migration. The increase in Gal-3 might be influenced by risperidone dosing.

Research conclusions

The combined activity of Gal-3 and proinflammatory cytokines, TGF-β downregulation and lower counts of leukocytes influence the SC duration. Gal-3 likely manifests indirect immunometabolic regulation of cognition in SC.

Research perspectives

We observed that Gal-3 contributes to ongoing peripheral systemic inflammation and disease duration in patients with SC. Moreover, its influence on blood-brain barrier permeability and consequent neuroinflammation should be explored. Inflammation also appears to be the potential pathway by which Gal-3 may affect cognitive functioning in SC.

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FOOTNOTES

Author contributions: Minic Janicijevic S and Borovcanin MM presented the design of this project, recruited the participants, performed the psychological and somatic assessment, collected the samples for laboratory measurements, structured the manuscript and incorporated all parts of the manuscript; Jovanovic IP, Gajovic NM and Arsenijevic NN performed the cytokine measurements; Jurisevic MM and Borovcanin MM did the statistical analysis and prepared tables and figures; All authors, especially Debnath M, additionally searched the literature and provided new insights into specific areas of their expertise, made a final revision of the manuscript, and corrected the figures; All authors read, discussed, and approved the final version of the manuscript.

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Institutional review board statement: The study was reviewed and approved by the Ethics Committee of the Kragujevac Clinical Centre.

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: Minic Janicijevic S, Jovanovic IP, Gajovic NM, Jurisevic MM, Arsenijevic NN and Borovcanin MM has received research funding from Ministry of Science and Technological Development of the Republic of Serbia, No. 175069 and Faculty of Medical Sciences, University of Kragujevac, No. JP15-05. Debnath M declared no conflict of interest.

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ORIGINAL ARTICLE

Observational Study

Associations between social support and anxiety during the COVID-19 lockdown in young and middle-aged Israelis: A cross-sectional study

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Abstract

BACKGROUND

This study examined the associations between social support and anxiety during the coronavirus disease 2019 (COVID-19) in an Israeli sample.

AIM

To examine the associations between social support and anxiety during the COVID-19 in an Israeli sample.

METHODS

Data for this cross-sectional study were retrieved from an online survey. Linear regression, logistic regression and restricted cubic spline models were conducted to test for associations between social support and anxiety.

RESULTS

A total of 655 individuals took part in the present study. In the univariate linear regression model, there is a negative correlation between the Generalized Anxiety Disorder-7 score (GAD-7) and the Multidimensional Perceived Social Support Scale (MSPSS) score. For MSPSS score, the multivariable adjusted regression coefficient and 95% confidence interval (CI) of GAD-7 score were -0.779 (-1.063 to -0.496). In the univariate logistic regression model, there was a negative correlation between anxiety (GAD-7 ≥ 9) and MSPSS score, and there was still a negative correlation in multivariate logical regression analysis. The odds ratios and 95%CI were 0.709 (0.563-0.894).

CONCLUSION
Social support was inversely correlated with anxiety during COVID-19 in an Israeli sample.

Key Words: Cross-sectional study; Social support; Anxiety; COVID-19; Lockdown; Correlation

Core Tip: Coronavirus disease 2019 (COVID-19) is a worldwide pandemic caused by the severe acute respiratory syndrome coronavirus 2. Due to the massive spread and high infectivity of the virus, most countries have adopted various lockdown measures to control the epidemic. Anxiety disorder is one of the most common mental disorders. To examine the associations between social support and anxiety during the COVID-19 in an Israeli sample. A total of 655 individuals took part in the present study. Our results show that in the Israeli sample social support is negatively correlated with anxiety during COVID-19. This underscores the importance of social support for anxiety prevention during COVID-19 locking.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a worldwide pandemic caused by the severe acute respiratory syndrome coronavirus 2. COVID-19 was first reported in Wuhan, China, causing pneumonia and other respiratory complications. Due to the massive spread and high infectivity of the virus, most countries have adopted various lockdown measures to control the epidemic. Changes in social distance and daily life activities during the blockade can affect personal well-being, mental health, and increase the risk of mental illness[1]. Anxiety disorder is one of the most common mental disorders.

Anxiety disorder is a common mental disorder with a global incidence of 7.3%[2]. Patients with anxiety disorders often feel excessive fear, anxiety or aim to avoid threats in the environment and within themselves, which can lead to disability and places a heavy burden on individuals and society[3]. Adequate social support is always significantly important for an individual's mental health. There are no significant side effects associated with social support, as compared to typical drug therapy. In addition, social support is one of the social resources to deal with stressful life events[4]. Social support is defined as allowing individuals to take advantage of the positive effects of social interactions to directly protect their mental health and directly resist stressful situations. Social support, as a function of interpersonal emotion regulation, can reduce the risk of mental illness[5]. In a trial of 947 colorectal cancer patients in Spain, patients with more social support were more likely to have better results in anxiety and depression one year after surgery[6]. In patients with multiple sclerosis, higher social support was associated with lower depression and anxiety[7]. In a cross-sectional study of young pregnant women, pregnant adolescents with anxiety disorders were found to have less social support in all areas[8]. Similarly, adolescents' exposure to negative life events was shown to be associated with social anxiety disorder, whereas changing social support can reduce anxiety symptoms in at-risk adolescents[4]. It is, thus, assumed that this inverse association exsits between the absence of social support and anxiety in different negative events and various populations.

It is not clear whether social support is equally protective of anxiety disorders in the context of the unique features of the first wave of COVID-19 pandemic in Israel in particular during lockdown. This study used data from an interim study on the lockdown enforced during the first wave of the COVID-19 pandemic in Israel to clarify the potential associations between social support and anxiety disorders.

MATERIALS AND METHODS

Data collection

The Qualtrics^{XM} platform (https://www.qualtrics.com/) digital questionnaire for data collection method was implemented in this study. It included a sociodemographic and personal questionnaire, the Generalized Anxiety Disorder-7 (GAD-7), the Multidimensional Perceived Social Support (MSPSS) and other measures and was administered using a snowball sampling method to recruit participants across

Israel *via* email and mobile phone applications. All responses were anonymous. The responses to the questionnaire were collected from April 19 to May 2, 2020, when Israel was experiencing the peak of the first wave of the COVID-19 epidemic. During that time, the government imposed three weeks of strict lockdown measures, banning social gatherings. The experimental procedure was approved by the Ethics Committee of the Academic College of Tel-Aviv Yafo, Israel (Approval No. 2020085), and all participants an signed electronic informed consent, allowing access to the full set of questionnaires[9].

Sample

A total of 655 participants took part. 200 participants did not complete the questionnaire. Of these, 45% did not complete sociodemographic and personal questionnaire. Of the remaining 55% of participants, only 1.3% completed the GAD-7 questionnaire. Participants who failed to complete all the questionnaires were excluded. The inclusion criteria were over 18 years of age and fluent in Hebrew.

Demographic information

The demographic information included the participants' age, gender, and socioeconomic status (based on question assessment of educational level, subjective perception of socioeconomic status, and financial resources for the next three months).

Assessment of anxiety

The GAD-7 is a self-reported anxiety questionnaire that can measure the anxiety level of the general population with sufficient validity and accuracy[10]. The Hebrew version was used, which contains 7 items, with scores ranging from 0 to 21. These scores represent 0-4 (minimal anxiety), 5-9 (mild anxiety), 10-14 (moderate anxiety), and 15-21 (severe anxiety). In this study, anxiety was defined as an overall score ≥ 9[11]. The internal consistency of the current sample was $\alpha = 0.892$.

Assessment of social support

Social support was evaluated on the Hebrew version of the MSPSS, which assesses participants' subjective feelings about their degree of social support[12]. The scale consists of three sub-scales related to family, friends, and significant others, with a total of 12 items. The higher the participants' scores, the more social support they felt.

Covariates

Covariates includes demographic variables (age, gender) and other background factors, including number of children, education, socioeconomic status, occupation, exercise and use of antidepressants.

Statistical analysis

SPSS 20.0 and R 3.5.1 were used for analysis. Linear regression was performed to analyze the association between social support and anxiety symptoms. Logistic regression was performed to examine the association between social support and anxiety disorders (GAD-7 score ≥ 9). To further investigate the relationship between social support and anxiety, a restricted cubic spline analysis was performed in the fully adjusted model. *P* values of less than 0.05 (two-tailed) were considered statistically significant.

RESULTS

Sample characteristics according to GAD score

Table 1 shows the characteristics of the 655 participants in terms of GAD-7 scores. The sample was composed of 246 men and 409 women, with a median age of 30. There were significant differences in age, gender, number of children, education, socioeconomic status, occupation, history of depression, and use of antidepressants between those with and without anxiety disorders (GAD-7 score ≥ 9). Those classified as exhibiting anxiety were younger than those who were classified as not exhibiting anxiety. Anxiety was also more common among women. Of the participants classified as anxious, 80% had no children, 50% had a bachelor's degree, 41.1% had an average economic status and 54.2% had a full-time or part-time job.

Association of MSPSS with the GAD-7 score

Table 2 uses linear regression to analyze the association between social support and anxiety symptoms. In the univariate linear regression model, GAD-7 score was negatively correlated with MSPSS score, and the regression coefficient and 95% confidence interval (CI) were -0.692 (-0.990 to -0.394). Further multivariate linear regression analysis showed that there was still a negative correlation between GAD-7 score and MSPSS score, and the regression coefficient and 95%CI was -0.779 (-1.063 to -0.496). This negative correlation was independent of age, sex, socio-economic status and the use of antidepressants.

Table 1 Characteristics of participants according to Generalized Anxiety Disorder-7 score, represented by medians and interquartile range

Variable	Total (*n* = 655)	GAD-7 score < 9 (*n* = 585)	GAD-7 score ≥ 9 (*n* = 70)	*P* value
Age (yr)	30 (26-47)	31 (26-49)	27 (23-33)	< 0.001
Gender				0.007
Male	246 (37.6%)	230 (39.3%)	16 (22.9%)	
Female	409 (62.4%)	355 (60.7%)	54 (77.1%)	
Number of children				0.008
Zero	392 (59.8%)	336 (57.4%)	56 (80.0%)	
One	37 (5.6%)	34 (5.8%)	3 (4.3%)	
Two	95 (14.5%)	91 (15.6%)	4 (5.7%)	
Three	100 (15.3%)	94 (16.1%)	6 (8.6%)	
Four	31 (4.7%)	30 (5.1%)	1 (1.4%)	
Education				0.003
Without diploma	23 (3.5%)	21 (3.6%)	2 (2.9%)	
12 years or less	125 (19.1%)	102 (17.4%)	23 (32.9%)	
Bachelor	295 (45.0%)	260 (44.4%)	35 (50.0%)	
Master (or higher)	187 (28.5%)	178 (30.4%)	9 (12.9%)	
Other	25 (3.8%)	24 (4.1%)	1 (1.4%)	
Socio-economic status				< 0.001
Low	21 (3.2%)	16 (2.7%)	5 (7.1%)	
Low-average	79 (2.1%)	60 (10.3%)	19 (27.1%)	
Average	281 (42.9%)	252 (43.1%)	29 (41.1%)	
Average-high	224 (34.2%)	209 (35.7%)	15 (21.4%)	
High	50 (7.6%)	48 (8.2%)	2 (2.9%)	
Occupation				0.029
Full-time job	280 (42.7%)	261 (44.6%)	19 (27.1%)	
Partially employed	109 (16.6%)	90 (15.4%)	19 (27.1%)	
Unpaid vacation	4 (0.6%)	4 (0.7%)	0 (0.0%)	
Lost job	33 (5.0%)	31 (5.3%)	2 (2.9%)	
Unemployed	55 (8.4%)	47 (8.0%)	8 (11.4%)	
Retired	174 (26.6%)	152 (26.0%)	22 (31.4%)	
Exercise				0.112
Yes	190 (29.0%)	164 (28.0%)	26 (37.1%)	
No	465 (71.0%)	421 (72.0%)	44 (62.9%)	
History of depression				< 0.001
Yes	538 (82.1%)	494 (84.4%)	44 (62.9%)	
No	117 (17.9%)	91 (15.6%)	26 (37.1%)	
Use of antidepressants				0.001
Yes	563 (86.0%)	512 (87.5%)	51 (72.9%)	
No	92 (14.0%)	73 (12.5%)	19 (27.1%)	
MSPSS score	6.08 (5.25-6.67)	6.08 (5.33-6.75)	5.75 (4.67-6.50)	0.009
GAD-7 score	3 (1-6)	3 (1-5)	13 (11-15)	< 0.001

MSPSS: Multidimensional Perceived Social Support Scale; GAD-7: Generalized Anxiety Disorder-7.

Table 2 Associations of Generalized Anxiety Disorder-7 score with Multidimensional Perceived Social Support Scale score (regression coefficient and 95% confidence intervals)

Variable	Univariate linear regression		Multivariate linear regression	
	β (95%CI)	*P* value	β (95%CI)	*P* value
MSPSS	-0.692 (-0.990, -0.394)	< 0.001	-0.779 (-1.063, -0.496)	< 0.001
Age	-0.056 (-0.077, -0.035)	< 0.001	-0.048 (-0.068, -0.028)	< 0.001
Sex	1.888 (1.246, 2.529)	0.316	1.641 (1.021, 2.261)	< 0.001
Number of children	-0.524 (-0.760, -0.289)	< 0.001	-	-
Education	-0.399 (-0.763, -0.034)	0.032	-	-
Occupation	0.142 (-0.006, 0.289)	0.059	-	-
Socio-economic status	-0.952 (-1.300, -0.603)	< 0.001	-0.514 (-0.854, -0.174)	0.003
Exercise	-0.460 (-1.162, 0.241)	0.198	-	-
Use of antidepressants	2.589 (1.781, 3.397)	< 0.001	2.046 (1.279, 2.813)	< 0.001

MSPSS: Multidimensional Perceived Social Support Scale; CI: Confidence interval.

Association of MSPSS with anxiety

Table 3 shows the odds ratios (OR) and the 95%CI for social support and anxiety disorders (GAD-7 score ≥ 9). In the univariate logistic regression model, the occurrence of anxiety was negatively correlated with MSPSS score. Multivariate logical regression analysis with backward method showed that the occurrence of anxiety was still negatively correlated with MSPSS score, and the OR and 95%CI were 0.709 (0.563-0.894). This negative correlation is independent of gender, age, education level, socio-economic status and the use of antidepressants.

Restricted cubic spline analyses

To further clarify the relationship, a restricted cubic spline analysis was used to analyze the association between social support and anxiety (Figure 1). The results showed that social support was inversely correlated with anxiety symptoms (GAD-7 score ≥ 9). Anxiety symptoms decreased with increasing social support scores.

DISCUSSION

In this study, a cross-sectional analysis was conducted using data from an interim study conducted while Israel was in lockdown during the first wave of the COVID-19 pandemic to assess the relationship between social support and anxiety symptoms. The data included 655 participants. The results showed that participants' social support scores were inversely correlated with GAD-7 scores. Social support was inversely associated with anxiety (GAD-7 score ≥ 9) in logistic regression model, and this negative correlation is independent of gender, age, education level, socio-economic status and the use of antidepressants.

During the COVID-19 pandemic, people in most countries were placed under tight lockdown measures due to the dangers of the rapid spread of the disease and the severe shortage of medical resources. In instances of insufficient supply and personnel, medical workers tend to give priority to serious physical diseases and ignore patients' mental symptoms[13]. At the same time, for quarantined individuals, the panic caused by the COVID-19 outbreak, as well as the economic losses caused by the lockdown, the lack of protective gear and other complications all exacerbated the psychological difficulties. In an epidemiological survey conducted in Hong Kong, 25.4% of the population's mental health was reported to have deteriorated since the outbreak of COVID-19, and 14% of the population suffers from anxiety[14]. Anxiety is an emotion characterized by physical changes such as tension, anxious thoughts and elevated blood pressure, with a lifetime prevalence rate of more than 20%[15]. When severe acute respiratory syndrome broke out in Hong Kong in 2013, 13% of the population developed anxiety disorders after discharge from hospital[16]. Anxiety disorders often occur at the same time as post-traumatic stress disorder (PTSD). Pre-existing anxiety has been proved to be a risk factor

Table 3 Odds ratios (95% confidence intervals) of anxiety (Generalized Anxiety Disorder-7 score ≥ 9) across Multidimensional Perceived Social Support Scale score

Variable	Univariate logistic regression		Multivariate logistic regression	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
MSPSS	0.747 (0.605, 0.921)	0.006	0.709 (0.563, 0.894)	0.004
Age	0.965 (0.944, 0.986)	0.001	0.976 (0.953, 0.999)	0.041
Sex	2.187 (1.222, 3.913)	0.008	2.151 (1.142, 4.053)	0.018
Number of children	0.658 (0.514, 0.842)	0.001	-	-
Education	0.617 (0.464, 0.822)	0.001	0.615 (0.445, 0.851)	0.003
Occupation	1.096 (0.980, 1.227)	0.109	-	-
Socio-economic status	0.539 (0.409, 0.710)	< 0.001	0.628 (0.465, 0.849)	0.003
Exercise	0.659 (0.393, 1.106)	0.114	-	-
Use of antidepressants	2.613 (1.461, 4.672)	0.001	2.588 (1.384, 4.841)	0.004

MSPSS: Multidimensional Perceived Social Support Scale; CI: Confidence interval; OR: Odds ratio.

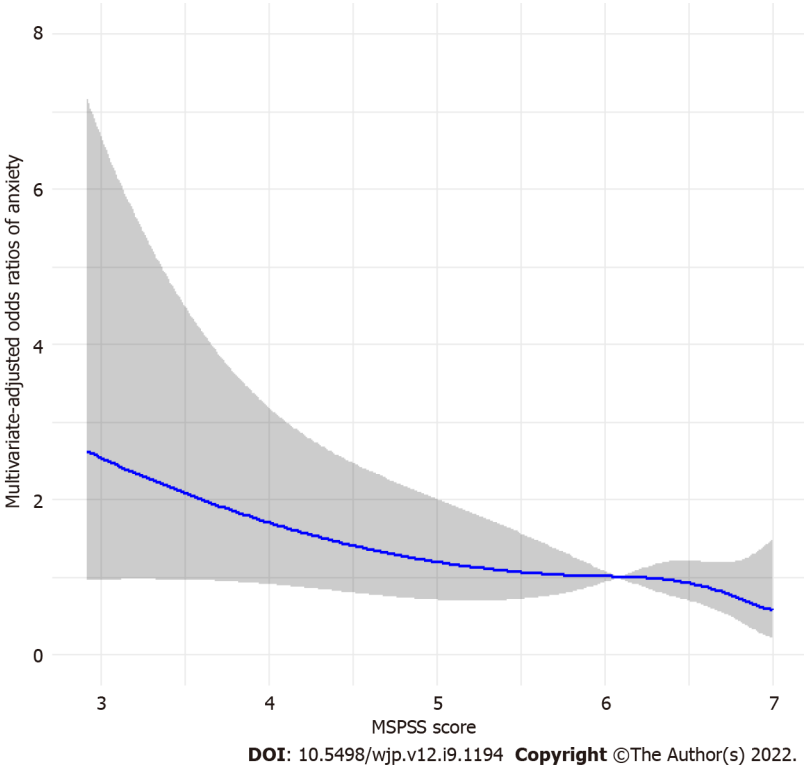

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Figure 1 A restricted cubic spline model of the odds ratio between anxiety (Generalized Anxiety Disorder-7 score ≥ 9) and Multidimensional Perceived Social Support Scale score. The grey area represents a 95% confidence interval. Adjusted for age, gender, number of children, education, socioeconomic status, occupation, exercise, history of depression, and use of antidepressants. MSPSS: Multidimensional Perceived Social Support Scale.

for the development of urban population into PTSD[17]. Studies have shown that participants with higher symptoms of depression and anxiety are more likely to develop more severe PTSD symptoms, and higher social support may be associated with lower PTSD[18].

Social support, as a way to foster a sense of belonging and love, is crucial for the mental health of the population. Social support can promote mental health in several ways. First social support can enable people receive more information and care from others. Certain specific groups, such as pregnant and postpartum mothers and parents of young children with special medical needs can obtain social support from social media to relieve negative emotions such as psychological anxiety and glean useful suggestions[19,20]. During the lockdown period, people mainly used social media to get social support from a range of sources to ease anxiety and fight the epidemic collectively. Second, social support can

alleviate people's pain, and can encourage physical activity, including those who are physically limited by pain, and thus have a positive impact on people's health behaviors[21]. Finally, social support can improve individuals' physical condition and promote mental health by directly influencing the body's pathophysiological mechanisms. Studies have found that people with higher social support and integration have lower mortality rates, and a comprehensive meta-analysis has shown that social support is inversely correlated with inflammation levels *in vivo*[22]. In addition, social support can significantly reduce the cardiovascular response of the population and lower cardiovascular recovery to its pre-stress level[23]. All these studies thus suggest that social support not only provides information and care from the outside world, but also modulates the mental health of the population by reducing physical pain and improving inflammation levels.

In a cross-sectional study of women who had undergone a therapeutic abortion, more than half reported symptoms of anxiety, and social support from these women's family and friends significantly reduced anxiety levels. Furthermore, social support from partners can also reduce women's anxiety symptoms[24]. Another longitudinal cohort study of caregivers of patients diagnosed with cancer showed that accurate information and social support from other members of the community, as well as physical activity reduced anxiety in partners in the first months after a cancer diagnosis[25]. These epidemiological studies underscore the positive effects of social support on anxiety disorders. Similarly, during the special period of COVID-19's outbreak, in a cross-sectional survey of 3500 Spanish adults, it was found that for those without pre-pandemic mental disorders, higher levels of social support decreased the odds of GAD-7[26]. During the COVID-19 pandemic in Turkey, it was also found that anxiety levels decreased significantly when perceived social support increased[4]. This study conducted a survey during Israel's first blockade in 2020, taking into account the effects of age, sex, number of children, education level, socio-economic status, occupation, exercise and antidepressant use, the results here show that social support is negatively correlated with post-blockade anxiety.

This study makes several contributions beyond its limitations. Using data collected during the first wave of COVID-19 lockdown in Israel, this study reports on relationship between social support and anxiety during COVID-19 lockdown. In addition, we considered the impact of confounding factors such as age, gender, education, socioeconomic status and other potential influences. Note, however, that the cross-sectional design of this study is a major limitation because it is difficult to make causal inferences. Second, the results were adjusted for a variety of major potential confounding factors; however, the existence of unmeasured factors and some unknown factors cannot be ruled out. Third, randomly distributed questionnaires may lead to age selection bias of the study population, which may make the results not generalized. Fourth, this study does not include the limitations on generalization to younger and older ages. Fifth, this study does not include people who have been infected with COVID-19, whether infected with COVID-19 may have an impact on the correlation coefficient between social support and anxiety.

Prolonged home confinement may be the main reason that affects people's mental health during the blockade of the COVID-19 pandemic, and it is very important to give proper physical and mental care and social support. In addition, the long epidemic period of COVID-19 and the continuous mutation of virus strains undoubtedly bring new challenges to people's mental health. How to make rational use of multimedia or the internet to improve the psychological state of the population during the COVID-19 blockade is a research direction worthy of attention for future researchers.

CONCLUSION

Overall our findings suggest that social support was inversely associated with anxiety symptoms during COVID-19 pandemic lockdown. Thus providing social support may reduce the prevalence of anxiety in the population.

ARTICLE HIGHLIGHTS

Research background

Due to the massive spread and high infectivity of coronavirus disease 2019 (COVID-19), most countries have adopted various lockdown measures to control the epidemic. Changes in social distance and daily life activities during the blockade can affect personal well-being, mental health, and increase the risk of mental illness. Anxiety disorder is one of the most common mental disorders.

Research motivation

It is not clear whether social support is equally protective of anxiety disorders in the context of the unique features of the first wave of COVID-19 pandemic in Israel in particular during lockdown. This study used data from an interim study on the lockdown enforced during the first wave of the COVID-19 pandemic in Israel to clarify the potential associations between social support and anxiety disorders.

Research objectives
The purpose of this study was to study the relationship between social support and anxiety in Israelis during the first COVID-19 epidemic.

Research methods
Data for this cross-sectional study were retrieved from an online survey. Linear regression, logistic regression and restricted cubic spline models were conducted to test for associations between social support and anxiety.

Research results
A total of 655 individuals took part in the present study. In the univariate linear regression model, there is a negative correlation between the Generalized Anxiety Disorder-7 score (GAD-7) and the Multidimensional Perceived Social Support Scale (MSPSS) score. For MSPSS score, the multivariable adjusted regression coefficient and 95% confidence interval (CI) of GAD-7 score were -0.779 (-1.063 to -0.496). In the univariate logistic regression model, there was a negative correlation between anxiety (GAD-7 ≥ 9) and MSPSS score, and there was still a negative correlation in multivariate logical regression analysis. The odds ratios and 95%CI were 0.709 (0.563-0.894).

Research conclusions
Social support was inversely correlated with anxiety during COVID-19 in an Israeli sample.

Research perspectives
Our findings suggest that social support was inversely associated with anxiety symptoms during COVID-19 pandemic lockdown. Thus providing social support may reduce the prevalence of anxiety in the population.

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FOOTNOTES

Author contributions: Xi Y, Elkana O and Jiao WE contributed to the work equally. Y Xi, Li D, and Jiao WE contributed to the data analysis and interpretation; Elkana O and Jiao WE involved in data acquisition; Tao ZZ contributed to the study conception and design final approval of the manuscript for submission.

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SYSTEMATIC REVIEWS

Psychotic symptoms in bipolar disorder and their impact on the illness: A systematic review

Subho Chakrabarti, Navdeep Singh

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Abstract

BACKGROUND

Lifetime psychotic symptoms are present in over half of the patients with bipolar disorder (BD) and can have an adverse effect on its course, outcome, and treatment. However, despite a considerable amount of research, the impact of psychotic symptoms on BD remains unclear, and there are very few systematic reviews on the subject.

AIM

To examine the extent of psychotic symptoms in BD and their impact on several aspects of the illness.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines were followed. An electronic literature search of six English-language databases and a manual search was undertaken to identify published articles on psychotic symptoms in BD from January 1940 to December 2021. Combinations of the relevant Medical Subject Headings terms were used to search for these studies. Articles were selected after a screening phase, followed by a review of the full texts of the articles. Assessment of the methodological quality of the studies and the risk of bias was conducted using standard tools.

RESULTS

This systematic review included 339 studies of patients with BD. Lifetime psychosis was found in more than a half to two-thirds of the patients, while current psychosis was found in a little less than half of them. Delusions were more common than hallucinations in all phases of BD. About a third of the patients reported first-rank symptoms or mood-incongruent psychotic symptoms, particularly during manic episodes. Psychotic symptoms were more frequent in bipolar type I compared to bipolar type II disorder and in mania or mixed episodes compared to bipolar depression. Although psychotic symptoms were not more severe in BD, the severity of the illness in psychotic BD was consistently greater.

Psychosis was usually associated with poor insight and a higher frequency of agitation, anxiety, and hostility but not with psychiatric comorbidity. Psychosis was consistently linked with increased rates and the duration of hospitalizations, switching among patients with depression, and poorer outcomes with mood-incongruent symptoms. In contrast, psychosis was less likely to be accompanied by a rapid-cycling course, longer illness duration, and heightened suicidal risk. There was no significant impact of psychosis on the other parameters of course and outcome.

CONCLUSION

Though psychotic symptoms are very common in BD, they are not always associated with an adverse impact on BD and its course and outcome.

Key Words: Psychotic symptoms; Bipolar disorder; Extent; Impact

Core Tip: This systematic review examined the extent and impact of psychosis in 339 studies of bipolar disorder (BD). The results endorsed the high rates of all types of psychotic symptoms in BD. However, psychosis was associated with an adverse impact only in a few domains of the illness including the severity of BD, the rate/duration of hospitalizations, switches to BD, and poorer outcomes with mood-incongruent symptoms. No consistent associations were found in other areas, suggesting that psychosis is not always associated with a negative impact on BD. This finding conformed to the current consensus in the literature on psychotic BD.

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INTRODUCTION

Psychosis in bipolar disorder (BD) is characterized by the presence of either delusions or hallucinations or both[1]. It is well known that over half of the patients with BD develop psychotic symptoms during their lifetimes[2,3]. Psychotic symptoms are more frequent in bipolar than in unipolar depression[3-5]. Rates of psychotic symptoms in BD may be comparable to schizophrenia, and there appears to be no qualitative distinction in psychotic symptoms found in BD or schizophrenia[6-8]. Psychotic symptoms are much more frequent during manic than depressive episodes[3,5,8]. Their rates are so high in mania that it is often indistinguishable from primary psychotic disorders[9]. All kinds of psychotic symptoms may occur among patients with BD, though grandiose, persecutory, and referential delusions, auditory verbal hallucinations or hearing voices, and visual hallucinations are particularly common[2,8,10]. Both mood-congruent and mood-incongruent psychotic symptoms as well as Schneiderian first-rank symptoms (FRS) also occur in BD[2,3,6,8].

Given their ubiquity, psychotic symptoms in BD have the potential to adversely affect its course, outcome, and response to treatment. Somewhat surprisingly, the impact of psychosis on the course and outcome of BD remains unclear despite extensive research on the subject. While some reviews regarding the impact of psychosis on BD have indicated that psychotic BD represents a more severe form of the illness with an adverse course and outcome[9,11,12], the majority of the others have not been able to find an association between psychotic symptoms and outcome in BD[2,3,5,8,13]. Nevertheless, the presence of psychotic symptoms in BD may be of some significance in determining its current nosology [12-14]. Moreover, the similarity of psychotic BD with schizophrenia on genetic, neurobiological, and cognitive aspects indicates common etiological underpinnings of these disorders[14-16]. In both aspects, BD seems to lie in an intermediate position between psychotic and non-psychotic disorders, leading to the hypothesis of a continuum of psychosis stretching from major depressive disorders with psychosis to psychotic BD and schizophrenia[15-18]. Finally, from the clinical perspective, psychotic symptoms have a considerable influence on the way BD is diagnosed and treated. The high prevalence of psychotic symptoms in BD often results in a mistaken diagnosis of schizophrenia. This can lead to inappropriate treatment and can have negative social and economic consequences for those with BD[2,6,8,19]. Moreover, the best way to manage psychotic BD is not clear. Though guidelines emphasize the role of antipsychotics or electroconvulsive therapy, research on adjunctive psychosocial interventions for psychotic symptoms is limited[8,14].

Over the years there have been many reviews of psychotic symptoms in BD including the seminal ones by Goodwin and Jamison[3,5] and by other authors[2,6,9,14,20]. However, there have been very few systematic reviews on the subject. Only three such systematic reviews could be identified. Two of them were primarily focused on hallucinations in BD, unipolar depression, or other disorders[10,21]. Only one systematic review had examined the phenomenology of auditory verbal hallucinations and delusions along with their clinical and cognitive correlates in 32 studies of BD[8].

Aims and objectives of the current systematic review

The current systematic review was specifically intended to address the gaps in the literature regarding psychotic symptoms and their impact on BD. It attempted to comprehensively examine the extent of psychotic symptoms in BD with a particular emphasis on the associations of psychotic symptoms with the course and outcome of BD. For this purpose, it focused on four groups of studies including those of BD [type I (BP I) and type II (BP II) disorders], studies of mania, bipolar depression, and mixed episodes. Four types of psychotic symptoms were examined including delusions, hallucinations, mood-congruent and mood-incongruent symptoms, and FRS. Mood-congruent and incongruent symptoms and FRS were examined separately because these symptoms usually indicate a more severe form of BD and may have a greater impact on its outcome. The impact of psychotic symptoms was determined by exploring the demographic correlates of psychotic symptoms, their clinical correlates, and the influence of psychotic symptoms on different parameters of the course and outcome of BD.

MATERIALS AND METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[22]. Supplementary Table 1 includes the PRISMA 2009 Checklist.

Search strategy

The search for the studies was carried out in 2021. A comprehensive literature search was undertaken using six English-language databases, MEDLINE, PubMed, PsycINFO, EMBASE, Cochrane, and Google, to identify published articles on psychotic symptoms in BD from January 1940 to December 2021. The *Reference Citation Analysis* (https://www.referencecitationanalysis.com/) was also used to search these databases. The year 1940 was chosen as the inception point because the initial search revealed that very few studies of psychotic symptoms in BD had been conducted before that year. Only two studies from 1931 identified by the manual search were included in the final list of studies.

The following Medical Subject Headings search terms or combinations of these terms were used to search for the relevant studies: BD, mania, depression, psychosis, psychotic, delusions, hallucinations, FRS, mood-congruent symptoms, mood-incongruent symptoms, prevalence, course, and outcome. Supplementary Table 1 includes a list of the search strings used and the results retrieved from the PubMed search.

Selection of studies

During the screening phase, all relevant original research articles were identified based on their titles and abstracts. At this stage, articles with no relevant information on the subject, those not in English, reviews, case reports/series, conference abstracts, editorials, and viewpoints were excluded. Full texts of the articles derived from the screening phase were reviewed to determine whether they met the selection criteria. These full texts were also searched manually to identify additional studies.

Inclusion criteria: Studies were included if they: (1) Had examined psychotic symptoms in BD; psychosis was defined as the presence of delusions and/or hallucinations; (2) Had a patient sample that included adult subjects (> 18 years of age); and (3) Had provided information on the relevant aspects of psychotic symptoms in BD including the rates and types of psychotic symptoms, clinical and demographic correlates, or the association with different parameters of outcome.

Exclusion criteria: The following were excluded: (1) Studies providing only qualitative data; (2) Studies where data on psychotic symptoms were not provided separately for BD; (3) Studies of child and adolescent subjects with BD; (4) Studies conducted exclusively among subjects with schizophrenia, schizoaffective disorder, and unipolar depression; and (5) Studies exclusively reporting neurocognitive outcomes of psychosis in BD (these studies were excluded because there are already several systematic reviews and meta-analyses on the subject).

Data extraction

The following data were extracted for each study included in the final list: Authors, year of study, sample size, assessment procedures, results related to the areas of interest, and any indices that estimated the strength of associations, *e.g.*, odds or hazard ratios. The mean, median, and range were estimated for the rates of psychosis and different types of psychotic symptoms. The relationship of psychotic symptoms with the clinical and demographic correlates and outcome parameters was

determined based on studies reporting either positive or negative associations. Other aspects, such as the difference between BP I and BP II disorders or between mania, mixed episodes, and depression were also examined.

Assessment of the quality of studies and risk of bias from the review

The STROBE Checklist for cohort, case-control, and cross-sectional studies (combined) was used to rate the quality of studies included in this review[23]. Additional considerations included a sample size of 200 patients (determined by power calculations based on the included studies), the use of standardized interviews to ascertain the diagnosis, the use of validated operational criteria, and the use of validated scales to measure outcomes. Based on these criteria, the studies included in the review were judged to be of good, moderate, or poor quality. The Risk of Bias in Systematic Reviews tool was used to ascertain the risk of bias arising from the quality of included studies, or the methods of this review[24].

To reduce the selection bias arising from included studies as well as the bias in rating the quality of studies, these procedures were initially carried out independently by the two authors. Any discrepancies were resolved by joint consensus following the independent evaluations.

RESULTS

Studies included for the review

The final list of this review included 339 studies. (These have been cited from reference number 25 to 363[25-363]). Figure 1 shows how these studies were eventually selected. Supplementary Table 2 includes the complete list of these studies with their methodological details. The largest number of studies provided data on patients with current episodes of mania (n = 121), followed by the studies on lifetime psychosis among patients with BD (n = 113), current psychosis in patients with BD (n = 66), bipolar depression (n = 57), and mixed episodes (n = 43). Comparatively fewer studies had provided lifetime data among patients with mania (n = 29), bipolar depression (n = 21), and mixed episodes (n = 8).

Ratings of study quality and risk of bias

Supplementary Table 2 also includes the quality ratings for individual studies. According to these ratings, 97 studies were of good quality, 168 were of moderate quality, and 74 were poor quality studies. Since the majority of studies were of moderate quality, the risk of bias from studies included in this review was moderate to high.

Prevalence of psychosis in BD

The lifetime and current rates of psychosis for BD, and manic, depressive, and mixed episodes are shown in Table 1. Supplementary Table 3 includes the complete details of these studies.

More than half of the patients with BD and about two-thirds of those with BP I disorder had psychotic symptoms during their lifetimes. The lifetime rates of psychosis were about 40%-60% in mania and mixed episodes but only about 20% in the episodes of bipolar depression. The current rates of psychosis were somewhat lower but still in the range of 40%-60% for BD, BP I disorder, mania, and mixed episodes. The current rates of psychosis were less than 20% for bipolar depression. Both the lifetime and current rates of psychosis were about two to three times higher in BP I compared to BP II disorder; this difference was more marked for mixed episodes where the current rates of psychosis in BP I disorder were about five times that of BP II disorder. Lifetime rates of psychosis were about twice as common in mania than in bipolar depression, while the current rates of psychosis were about three times higher in mania compared to bipolar depression. On the other hand, both the lifetime and current rates of psychosis were similar in mania and mixed episodes. Finally, about 60 studies had compared the rates of psychosis in bipolar and unipolar depression. In all but 12 of them, the rates of psychosis were higher in BD than in unipolar disorder. In contrast, 18 of the 20 studies that had compared BD with schizophrenia found much higher rates among patients with schizophrenia. An obvious problem in obtaining an accurate picture of the rates of psychosis was that the average rates tended to get skewed as the number of available studies declined. Though relying on median rates and excluding outliers resolved the problem to an extent, this did not completely correct the imbalance. Thus, the only reliable rates were those for BD, BP I disorder, and the current rates of psychosis in mania.

Rates of different psychotic symptoms in BD

The lifetime and current rates of the different psychotic symptoms for BD, mania, bipolar depression, and mixed episodes are shown in Table 2. Supplementary Table 4 includes the complete details of these studies.

Predictably, there was greater variability in the rates of the four types of psychotic symptoms. The number of studies from which these rates were derived was also smaller, ranging from 1 to 25. However, certain consistent trends could still be made out.

Table 1 Prevalence of psychosis in bipolar disorder

Study groups	Lifetime rates	Current rates
BD	*n* = 40, mean 57%; Median 56%; Range: 17%-93%	*n* = 32, mean 46%; Median 44%; Range: 11%-99%
BD I	*n* = 32, mean 61%; Median 64%; Range: 30%-90%	*n* = 10, mean 43%; Median 40%; Range: 12%-75%
BD II	*n* = 12, mean 22%; Median 20%; Range: 1%-49%	*n* = 6, mean 19%; Median 18%; Range: 9%-29%
Mania	BD-*n* = 5, mean 43%; Median 48%; Range: 19%-63%	BD-*n* = 20[1], mean 60%; Median 58%; Range: 25%-90%
	BP I-*n* = 4, mean 60%; Median 56%; Range: 44%-86%	BP I-*n* = 51, mean 56%; Median 56%; Range: 8%-91%
Bipolar depression	BD-*n* = 10, mean 21%; Median 19%; Range: 8%-42%	BD-*n* = 24[2], mean 24%; Median 19%; Range: 10%-80%
	BP I-*n* = 11, mean 27%; Median 27%; Range: 6%-55%	BP I-*n* = 12, mean 18%; Median 19%; Range: 3%-28%
	BP II-*n* = 6, mean 15%; Median 10%; Range: 7%-30%	BP II-*n* = 11, mean 11%; Median 8%; Range: 5%-28%
Mixed episodes	BD-*n* = 2, mean 50%; Median 50%; Range: 34%-66%	BD-*n* = 14, mean 47%; Median 40%; Range: 8%-97%
	BP I-*n* = 3, mean 43%; Median 33%; Range: 10%-86%	BP I-*n* = 14[3], mean 52%; Median 50%; Range: 15%-89%
		BP II-*n* = 2, mean 11%; Median 11%; Range: 7%-15%

[1]After excluding outliers, mean and median = 51%.
[2]After excluding outliers, mean = 19% and median = 18%.
[3]After excluding outliers, mean = 41% and median = 40%.
Complete details in Supplementary Table 3. BD: Bipolar disorder; BP I: Bipolar disorder type I; BP II: Bipolar disorder type II.

The average rates of delusions ranged from 44%-87% (median: 43%-87%) with the highest rates being obtained for a lifetime and current psychosis in BD, BP I disorder, mania, and mixed episodes. The average rates of delusions in bipolar depression were much less, ranging from 12%-20% in a lifetime and current episodes. In contrast, hallucinations were reported only in about a third of the patients, except for those with lifetime episodes of mania and mixed states where rates ranged from 55%-100%. However, the high rates in these two groups were probably because of the small number of studies involved. The number of studies was also small for bipolar depression, and the average rates were about 22% (median: 19%), with greater variability across individual studies. The lifetime rates of delusions and hallucinations in patients with BP I disorder far exceeded the rates among those with BP II disorder.

The rates of FRS were high, particularly for the studies of lifetime mania (mean and median: 45%, range up to 59%), current mania (mean: 28%, median: 32%, range up to 48%), and current mixed episodes (mean and median: 32%, range up to 49%). About a fifth of the patients with BD and BP I disorder also reported FRS during psychotic episodes, whereas the average rates in bipolar depression were somewhat lower. None of the studies of patients with BP II disorder reported FRS. However, apart from the current mania group, the number of studies was too small in the other groups to obtain an accurate estimate of the rates.

Mood-congruent psychotic symptoms were far more frequent and were present in about a third to half of the patients. Though some groups such as patients with current BP I disorder, lifetime depression, and lifetime mixed episodes reported very high rates of mood congruence, the number of studies was too small for these rates to be reliable. Mood-incongruent psychotic symptoms were usually reported by about a third of the patients (mean: 33%; median: 37%) apart from two exceptions. Rates were very high (72%-74%) for the lifetime mania and mixed groups, but these were based only on one or two studies. On the other hand, the rates in six studies of current bipolar depression were less than 10%. No studies of BP II disorder reported mood-congruent or incongruent symptoms. Finally, the difficulties of ascertaining mood congruence were reflected by the fact that nine studies had found that about 14% of the patients (range 2%-55%) had both types of symptoms simultaneously.

Types of delusions, hallucinations, and FRS in BD

The different types of delusions, hallucinations, and FRS found in BD are shown in Tables 3-5. Supplementary Tables 5-7 include the complete details of these studies.

The number of studies from which these rates were derived was generally small, apart from certain exceptions such as those reporting grandiose and persecutory delusions and auditory and visual hallucinations. Very few studies had examined the different types of FRS.

Nevertheless, it appeared that both grandiose and referential delusions were equally common in BD, particularly among patients with mania. Persecutory delusions were present in about a third of the patients with BD and were almost equally common in the groups with mania, depression, or mixed episodes. Other common delusions included religious and erotomanic delusions; both were more common in mania and mixed episodes. Somatic delusions, delusional jealousy, and depressive

Table 2 Rates of different psychotic symptoms in bipolar disorder

Study groups	Delusions	Hallucinations	First-rank symptoms	Mood congruent symptoms	Mood incongruent symptoms
Lifetime BD (*n* = 6-16)	Mean = 69%; Median = 71%; Range: 29%-100%	Mean = 37%; Median = 32%; Range: 13%-100%	Mean = 17%; Median = 11%; Range: 4%-44%	Mean = 49%; Median = 47%; Range: 18%-90%	Mean = 37%; Median = 40%; Range: 3%-76%
Lifetime BP I (*n* = 4-8)	Mean = 55%; Median = 71%; Range: 25%-82%	Mean = 32%; Median = 32%; Range: 23%-43%	Mean = 22%; Median = 25%; Range: 1%-38%	Mean = 37%; Median = 34%; Range: 11%-70%	Mean = 36%; Median = 30%; Range: 19%-66%
Lifetime BP II (*n* = 0-1)	Mean = 4%; Median = 4%; Range: 4%	Mean = 1%; Median = 1%; Range: 1%	-	-	-
Current BD (*n* = 2-13)	Mean = 54%; Median = 49%; Range: 16%-99%	Mean = 26%; Median = 19%; Range: 10%-58%	Mean = 26%; Median = 24%; Range: 5%-49%	Mean = 39%; Median = 39% Range: 24%-35%	Mean = 42%; Median = 46%; Range: 8%-75%
Current BP I (*n* = 1)	-	-	-	Mean = 68%; Median = 68%; Range: 68%	Mean = 32%; Median = 32%; Range: 32%
Current BP II	-	-	-	-	-
Lifetime mania (*n* = 1-5)	BD and BP I Mean = 77%; Median = 77%; Range: 33%-98%	BD and BP I Mean = 83%; Median = 83%; Range: 55%-100%	Only BP I Mean = 45%; Median = 45%; Range: 34%-59%	Only BD Mean = 87%; Median = 87%; Range: 87%	Only BP I Mean = 74%; Median = 74% Range: 74%
Current mania (*n* = 8-25)	BD and BP I Mean = 57%; Median = 62%; Range: 11%-87%	BD and BP I Mean = 35%; Median = 41%; Range: 10%-55%	BD and BP I Mean = 28%; Median = 32%; Range: 6%-48%	BD and BP I Mean = 41%; Median = 36%; Range: 20%-87%	BD and BP I Mean = 34%; Median = 36%; Range: 9%-64%
Lifetime bipolar depression (*n* = 1-3)	BD and BP I Mean = 16%; Median = 16%; Range: 10%-20%	BD and BP I Mean = 25%; Median = 25%; Range: 4%-73%	Only BP I Mean = 18%; Median = 18%; Range: 18%	Only BD Mean = 100%; Median = 100%; Range: 100%	-
Current bipolar depression (*n* = 2-13)[1]	BD and BP I Mean = 28%; Median = 22%; Range: 6%-97%	BD and BP I Mean = 14%; Median = 9%; Range: 7%-73%	Only BD Mean = 14%; Median = 14%; Range: 8%-20%	BD and BP I Mean = 54%; Median = 54%; Range: 7%-100%	BD and BP I Mean = 7%; Median = 6%; Range: 0-32%
Lifetime mixed episodes (*n* = 0-3)	Only BD Mean = 66%; Median = 66%; Range: 33%-100%	Only BD Mean = 55%; Median = 55%; Range: 10%-100%	-	BD and BP I Mean = 64%; Median = 64%; Range: 28%-100%	Only BP I Mean = 72%; Median = 72%; Range: 72%
Current mixed episodes (*n* = 2- 8)	BD and BP I Mean = 55%; Median = 53%; Range: 19%-90%	BD and BP I Mean = 38%; Median = 38%; Range: 23%-67%	Only BP I Mean = 32%; Median = 32%; Range: 16%-49%	BD and BP I Mean = 27%; Median = 28%; Range: 14%-37%	BD and BP I Mean = 41%; Median = 39%; Range: 22%-63%

[1]Lifetime rates of hallucinations in bipolar disorder type II: Mean = 17%, median = 17%, range: 13%-21%. Complete details in Supplementary Table 4. BD: Bipolar disorder; BP I: Bipolar disorder type I; BP II: Bipolar disorder type II.

delusions, particularly delusions of guilt were found in all phases. Auditory hallucinations, especially auditory verbal hallucinations, were the most frequent types of hallucinations reported in BD and were equally common across all the groups. Visual hallucinations were much less common and found more frequently in mania. Other types of hallucinations were rare including somatic, tactile, olfactory, and gustatory hallucinations. Among the FRS, passivity delusions were the most common, followed by delusional perception, "running commentary" type of hallucinations, "voices conversing," thought echo, thought broadcast, thought insertion, somatic passivity, and thought withdrawal. As expected, the rates of all FRS were more common in mania, BD, and BP I disorders.

Demographic correlates of psychosis in BD

Demographic correlates of psychosis in BD are included in Table 6. Supplementary Table 8 includes the complete details of these studies. The results showed that there were very few consistent associations of psychotic symptoms with sociodemographic variables in BD. Many studies (*n* = 27) had not found significant relationships between psychotic BD and any of the demographic characteristics. Moreover, when significant associations were found with demographic parameters in some of the studies, an equal number of studies usually reported contrary results. Finally, the number of studies that had failed to find significant associations of psychosis with individual demographic parameters far outweighed the studies that had found positive associations.

Clinical correlates of psychosis in BD

Clinical correlates of psychosis in BD are also shown in Table 6. Supplementary Table 9 includes the complete details of these studies.

(1) The severity of psychosis and severity of illness in psychotic BD. Whether psychotic BD represents a more severe form of the illness has been examined by three groups of studies. The first group examined the severity of psychosis in BD relative to schizophrenia and unipolar depression. The

Table 3 Types of delusions in bipolar disorder

Delusions	Grandiose	Referential	Persecutory	Erotomanic	Jealousy	Somatic	Depressive	Religious
Lifetime BD and BP I (*n* = 11)	Mean (*n* = 7) 52%; Median 61%; Range: 24%-69%	Mean (*n* = 3) 59%; Median 61%; Range: 54%-62%	Mean (*n* = 9) 40%; Median 40%; Range: 16%-56%	-	Mean (*n* = 2) 8%; Median 8%; Range: 3%-13%	-	Mean (*n* = 2) 13%; Median 13%; Range: 12%-15%	Mean (*n* = 1) 35%; Median 35%; Range: 35%
Current BD (*n* = 9)	Mean (*n* = 9) 36%; Median 39%; Range: 4%-75%	Mean (*n* = 3) 42%; Median 5%; Range: 5%-75%	Mean (*n* = 8) 35%; Median 30%; Range: 7%-71%	Mean (*n* = 2) 4%; Median 4%; Range: 4%	-	Mean (*n* = 3) 16%; Median 11%; Range: 7%-31%	Mean (*n* = 7) 9%; Median 6%; Range: 3%-36%	Mean (*n* = 2) 5%; Median 5%; Range: 5%
Lifetime mania (N = 3)	Mean (*n* = 3) 66%; Median 69%; Range: 41%-88%	-	Mean (*n* = 3) 21%; Median 21%; Range: 12%-30%	-	Mean (*n* = 1) 2%; Median 2%; Range: 2%	Mean (*n* = 2) 16%; Median 16%; Range: 16%	Mean (*n* = 2) 10%; Median 7%; Range: 7%-13%	Mean (*n* =1) 3%; Median 3%; Range: 3%
Current mania (*n* = 23)	Mean (*n* = 17) 57%; Median 59%; Range: 20%-80%	Mean (*n* = 7) 43%; Median 41%; Range: 14%-69%	Mean (*n* = 20) 46%; Median 47%; Range: 8%-90%	Mean (*n* = 4) 29%; Median 24%; Range: 9%-61%	Mean (*n* = 1) 3%; Median 3%; Range: 3%	Mean (*n* = 5) 15%; Median 13%; Range: 1%-35%	Mean (*n* = 3) 10%; Median 10%; Range: 6%-14%	Mean (*n* = 7) 27%; Median 27%; Range: 22%-31%
Lifetime depression (*n* = 2)	-	-	Mean (*n* = 2) 17%; Median 17%; Range: 15%-20	-	-	-	-	-
Current depression (*n* = 5)	-	Mean (*n* = 2) 32%; Median 32%; Range: 32%-33%	Mean (*n* = 4) 37%; Median 39%; Range: 1%-7%	-	Mean (*n* = 1) 20%; Median 20%; Range: 20%	Mean (*n* = 1) 17%; Median 17%; Range: 17%	Mean (*n* = 3) 12%; Median 7%; Range: 3%-30%	-
Lifetime mixed (*n* = 1)	-	-	Mean (*n* = 1) 33%; Median 33%; Range: 33%	-	Mean (*n* = 1) 33%; Median 33%; Range: 33%	-	-	-
Current mixed (*n* = 4)	Mean (*n* = 3) 42%; Median 41%; Range: 19%-66%	Mean (*n* = 2) 71%; Median 71%; Range: 56%-86%	Mean (*n* = 4) 46%; Median 31%; Range: 16%-90%	-	-	Mean (*n* = 3) 7%; Median 10%; Range: 7%-13%	Mean (*n* = 2) 19%; Median 19%; Range: 6%-33%	-
Overall rates	Mean (*n* = 39) 51%; Median 54%; Range: 4%-88%	Mean (*n* = 17) 49%; Median 42%; Range: 5%-86%	Mean (*n* = 52) 34%; Median 32%; Range: 1%-90%	Mean (*n* = 6) 16%; Median 14%; Range: 4%-61%	Mean (*n* = 6) 13%; Median 13%; Range: 3%-33%	Mean (*n* = 14) 14%; Median 13%; Range: 1%-35%	Mean (*n* = 19) 12%; Median 10%; Range: 3%-36%	Mean (*n* = 11)18%; Median 17%; Range: 3%-42%

Complete details in Supplementary Table 5. BD: Bipolar disorder; BP I: Bipolar disorder type I; BP II: Bipolar disorder type II.

number of studies showing that psychotic symptoms were either less or more severe in BD was exactly equal suggesting that the severity of psychotic symptoms in BD was no different from the other patient groups with psychosis. The second group of studies focused on the association between psychotic symptoms and the overall severity of BD or the severity of manic and depressive symptoms. Here, the number of studies showing that the severity of illness or mood symptoms was greater in psychotic BD outnumbered those that did not find a difference. This indicated that the overall severity of the illness and severity of acute episodes was greater in psychotic BD. However, about a third of these studies had found this to be true only for the severity of manic symptoms. Therefore, the association between severe mood symptoms and psychotic BD was largely applicable to patients with current manic episodes. The third group of studies had examined the severity of BD with psychosis in terms of its impact on the course and outcome of the disorder. These are discussed later.

(2) Other indicators of severity. There was some evidence that psychotic BD was associated with poorer insight and a higher frequency of symptoms of agitation, aggression, and anxiety. Then again, this finding was also derived from the studies of mania, where agitation, violence, lack of insight, and psychosis often co-occurred. On the other hand, the rates of psychiatric comorbidity did not appear to be greater in those with psychotic BD.

Impact of psychotic symptoms on the course and outcome of BD

The impact of psychosis on the different aspects of the course and outcome of BD is summarized in Table 7. Supplementary Table 10 includes the complete details of these studies.

The overall conclusion from these studies was that psychotic BD was not inevitably associated with a more adverse course and poorer outcome of BD. While several studies had found psychosis was associated with a poorer overall outcome, the number of those that had failed to find such an association

Table 4 Types of hallucinations in bipolar disorder

Hallucinations	Auditory/AVH	Visual	Tactile	Olfactory	Gustatory	Somatic	Others
Lifetime BD and BP I (n = 13)	Mean (n = 13) 26%; Median 24%; Range: 3%-52%	Mean (n = 10) 23%; Median 23%; Range: 9%-47%	Mean (n = 1) 16%; Median 16%; Range: 16%	-	-	-	Mean (n = 3) Median 12%; 9%; Range: 3%-13%
Current BD (n = 3)	Mean (n = 3) 17%; Median 17%; Range: 8%-17%	Mean (n = 2) 6%; Median 6%; Range: 3%-9%	Mean (n = 1) 0.3%; Median 0.3%; Range: 0.3%	Mean (n = 2) 1%; Median 1%; Range: 1%	Mean (n = 2) 1%; Median 1%; Range: 1%	Mean (n = 2) 2%; Median 2%; Range: 0.4%-3%	-
Lifetime mania (n = 3)	Mean (n = 3) 40%; Median 39%; Range: 22%-52%	Mean (n = 1) 25%; Median 25%; Range: 25%	-	-	-	Mean (n = 1) 11%; Median 11%; Range: 11%	-
Current mania (n = 18)	Mean (n = 17) 33%; Median 41%; Range: 12%-57%	Mean (n = 8) 20%; Median 17%; Range: 2%-61%	Mean (n =2) 4%; Median 4%; Range: 3%-5%	Mean (n = 2) 8%; Median 8%; Range: 6%-13%	-	Mean (n = 2) 11%; Median 11%; Range: 1%-21%	Mean (n = 5) 27%; Median 28%; Range: 7%-46%
Lifetime depression (n = 2)	Mean (n = 2) 40%; Median 40%; Range: 13%-67%	Mean (n = 1) 7%; Median 7%; Range: 7%	-	-	-	-	Mean (n = 2) 18%; Median 18%; Range: 4%-33%
Current depression (n = 6)	Mean (n = 6) 16%; Median 9%; Range: 4%-50%	Mean (n = 3) 5%; Median 3%; Range: 1%-11%	-	Mean (n = 1) 0.5%; Median 0.5%; Range: 0.5%	Mean (n = 1) 0.5%; Median 0.5%; Range: 0.5%	-	Mean (n = 1) 2%; Median 2%; Range: 2%
Lifetime mixed (n = 1)	Mean (n = 1) 33%; Median 33%; Range: 33%	-	-	-	-	-	-
Current mixed (n = 3)	Mean (n = 3) 37%; Median 41%; Range: 4%-67%	Mean (n = 3) 13%; Median 18%; Range: 2%-20%	Mean (n = 1) 5%; Median 5%; Range: 5%	-	Mean (n = 1) 0.5%; Median 0.5%; Range: 0.5%	Mean (n = 1) 2%; Median 2%; Range: 2%	Mean (n = 1) 6%; Median 6%; Range: 6%
Overall rates	Mean (n = 48) 30%; Median 30%; Range: 3%-67%	Mean (n = 28) 14%; Median 13%; Range: 3%-47%	Mean (n = 1) 6%; Median 6%; Range: 0.3%- 16%	Mean (n = 5) 3%; Median 3%; Range: 1%- 16%	Mean (n = 4) 1%; Median 1%; Range: 0.5%-1%	Mean (n = 5) 8%; Median 8%; Range: 0.4%-47%	Mean (n = 10) 12%; Median 1%; Range: 1%-46%

Complete details in Supplementary Table 6. AVH: Auditory verbal hallucinations or hearing voices; BD: Bipolar disorder; BP I: Bipolar disorder type I; BP II: Bipolar disorder type II.

was almost the same or even more. This trend also appeared to be true for several individual measures of outcome including earlier age of onset, a persistent or chronic course of the illness, lack of remission or recovery, more frequent relapses or recurrences, a greater number of lifetime mood episodes, poor functioning, poor quality of life, and poor functional outcome. Since a large number of studies with reasonable methodological quality had examined these outcome parameters, this lent further support to the notion that psychosis was not always associated with poor outcomes in BD. Moreover, studies that had estimated odds or hazard ratios also showed that psychotic symptoms were not associated with earlier age of onset, poorer functional, or poorer overall outcomes[51,159,256,313,355]. Though some of the studies based on similar estimations of risk had found adverse outcomes in psychotic BD[103,104,137,157], the positive association of psychosis with poor outcomes in these studies was usually found only in a few outcome measures and not in others[64,250,288,342].

Additionally, negative associations between psychosis and outcome were reported in other domains such as the manic polarity of BD, a seasonal pattern of the illness, the response to lithium treatment, and a poorer outcome with FRS. However, these findings were uncertain because of the small number of studies involved.

Finally, psychosis appeared to be linked to better outcomes in three other areas including a lower proportion of rapid cycling, a shorter duration of illness, and a lowered suicidal risk. The negative association with suicidal behavior appeared to be particularly strong based on the number of studies and estimations of risk[40,57,105,306].

Nevertheless, psychosis appeared to be more consistently linked with adverse outcomes in some of the other areas. The rate and the duration of hospitalizations were consistently higher among patients with psychotic BD. Some studies had found the risk of hospitalization to be about one and a half times in psychotic BD[209]. Patients with depression were more likely to switch to BD if they had psychotic

Table 5 Types of first rank symptoms in bipolar disorder

Study groups	Passivity/control	Delusional perception	Somatic passivity	Thought broadcast	Thought insertion	Thought withdrawal	Running commentary	Two or more voices conversing	Thought echo
Lifetime BD and BP I (*n* = 9)	Mean (*n* = 4) 10%; Median 11%; Range: 4%-16%	Mean (*n* = 1) 20%; Median 20%; Range: 20%	-	Mean (*n* = 3) 11%; Median 14%; Range: 3%-17%	Mean (*n* = 1) 20%; Median 20%; Range: 20%	Mean (*n* = 1) 4%; Median 4%; Range: 4%	Mean (*n* = 4) 17%; Median 17%; Range: 10%-27%	Mean (*n* = 4) 16%; Median 17%; Range: 5%-27%	Mean (*n* = 1) 13%; Median 13%; Range: 13%
Current BD (*n* = 4)	Mean (*n* = 2) 36%; Median 36%; Range: 18%-49%	Mean (*n* = 2) 6%; Median 6%; Range: 2%-10%	Mean (*n* = 1) 7%; Median 7%; Range: 7%	Mean (*n* = 3) 14%; Median 5%; Range: 5%-18%	Mean (*n* = 1) 5%; Median 5%; Range: 5%	Mean (*n* = 1) 2%; Median 2%; Range: 2%	Mean (*n* = 2) 20%; Median 20%; Range: 4%-37%	Mean (*n* = 2)12%; Median 12%; Range: 4%-20%	Mean (*n* = 1) 4%; Median 4%; Range: 4%
Lifetime mania (*n* = 2)	Mean (*n* = 2) 27%; Median 27%; Range: 3%-52%	-	-	Mean (*n* = 1) 6%; Median 6%; Range: 6%	Mean (*n* = 1) 4%; Median 4%; Range: 4%	Mean (*n* = 1) 3%; Median 3%; Range: 3%	Mean (*n* = 1) 1%; Median 1%; Range: 1%	Mean (*n* = 1) 1%; Median 1%; Range: 1%	Mean (*n* = 2) 14%; Median 14%; Range: 14%-15%
Current mania (*n* = 8)	Mean (*n* = 8) 23%; Median 20%; Range: 5%-48%	-	-	Mean (*n* = 5) 12%; Median 14%; Range: 2%-21%	Mean (*n* = 3) 9%; Median 7%; Range: 1%-18%	Mean (*n* = 3) 9%; Median 3%; Range: 3%-13%	Mean (*n* = 3) 9%; Median 3%; Range: 2%-14%	Mean (*n* = 3) 5%; Median 3%; Range: 2%-6%	Mean (*n* = 3) 5%; Median 2%; Range: 1%-12%
Lifetime depression (*n* = 1)	Mean (*n* = 1) 1%; Median 1%; Range: 1%	-	-	Mean (*n* = 1) 1%; Median 1%; Range: 1%	Mean (*n* = 1) 1%; Median 1%; Range: 1%	Mean (*n* = 1) 4%; Median 4%; Range: 4%	-	-	Mean (*n* = 1) 10%; Median 10%; Range: 10%
Current depression (*n* = 1)	-	-	-	-	-	-	-	Mean (*n* = 1) 17%; Median 17%	-
Current mixed (*n* = 1)	Mean (*n* = 1) 49%; Median 49%; Range: 49%	-		-	-	-	-	-	-
Overall rates	Mean (*n* = 18) 24%; Median 24%; Range: 1%-49%	Mean (*n* = 3) 13%; Median 13%; Range: 2%-20%	Mean (*n* = 1) 7%; Median 7%; Range: 7%	Mean (*n* = 17) 9%; Median 8%; Range: 1%-18%	Mean (*n* = 7) 8%; Median 7%; Range: 1%-20%	Mean (*n* = 7) 4%; Median 3%; Range: 2%-13%	Mean (*n* = 10) 12%; Median 10%; Range: 1%-20%	Mean (*n* = 11) 10%; Median 10%; Range: 1%-27%	Mean (*n* = 8) 9%; Median 9%; Range: 4%-15%

Complete details in Supplementary Table 7. BD: Bipolar disorder; BP I: Bipolar disorder type I; BP II: Bipolar disorder type II.

symptoms. Though this finding was based on only ten studies, some of them had estimated the risk to be between one and a half to two times based on odds ratios[186,216,222]. Lastly, the number of studies that found mood-incongruent psychotic symptoms to be associated with a poorer outcome was considerably more than those that had not found such an association.

DISCUSSION

The current systematic review examined the extent of psychotic symptoms in BD and their impact on the course and outcome of BD based on the 339 studies that were selected. Before focusing on its findings, it is imperative to understand the strengths and weaknesses of the studies included in this review.

Methodological considerations

This review showed that there is no dearth of studies on the subject of psychotic symptoms in BD. Moreover, almost every aspect such as the prevalence of psychotic symptoms, their correlates, and the impact of psychosis on the course and outcome of BD have been systematically assessed by a number of these studies. However, the existing literature has several methodological shortcomings that often make it difficult to reach firm conclusions.

Table 6 Demographic and clinical correlates of psychosis in bipolar disorder

Correlates	Studies showing positive association with psychosis	Studies showing inverse association or no association with psychosis[1]
Younger age	*n* = 14	*n* = 48
Female sex	*n* = 16	*n* = 51
Single status	*n* = 11	*n* = 14
Lower educational levels	*n* = 9	*n* = 26
Low income or unemployment	*n* = 6	*n* = 14
Ethnic minority status	*n* = 4	*n* = 10
Severity of psychotic symptoms in bipolar disorder		
Studies showing that psychotic symptoms are less severe in bipolar disorder	Studies showing that psychotic symptoms are more severe in bipolar disorder	
n = 20	*n* = 20	
Severity of illness/mood symptoms in psychotic bipolar disorder		
Studies showing that the illness/mood symptoms are not more severe in psychotic bipolar disorder	Studies showing that severity of illness/mood symptoms is greater in psychotic bipolar disorder	
n = 16	*n* = 34	
Insight and psychotic symptoms in bipolar disorder		
Studies showing that psychosis is associated with lack of insight in bipolar disorder	Studies showing that psychosis is not associated with lack of insight in bipolar disorder	
n = 15	*n* = 9	
Agitation, aggression and anxiety in psychotic bipolar disorder		
Studies showing that agitation, aggression and anxiety are associated with psychosis in bipolar disorder	Studies showing that agitation, aggression and anxiety are not associated with psychosis in bipolar disorder	
n = 13	*n* = 2	
Comorbidity and psychotic symptoms in bipolar disorder		
Studies showing that psychosis associated with greater comorbidity in bipolar disorder	Studies showing that psychosis is not associated with greater comorbidity in bipolar disorder	
n = 21	*n* = 27	

[1]Twenty-seven studies found no significant relationships between psychotic bipolar disorder and any of the demographic characteristics. Complete details in Supplementary Tables 8 and 9.

The studies covered a period from 1940 to 2021, during which the definition of BD has undergone many changes. Thus, there may be some difficulty in equating labels such as manic-depressive psychoses and BD. However, there were only minor differences between the definitions in older studies and the current definitions of the disorder. Moreover, leaving out studies conducted before the 1980s would have resulted in a significant loss of data. Psychosis has usually been defined as the presence of delusions and/or hallucinations by most studies. Though this definition fits the current standards and is easily established by using structured interviews[364], a few studies have included formal thought disorder as a part of the definition[142]. This complicates matters since thought disorder is relatively non-specific and more difficult to ascertain. Nevertheless, the broader definition seems to be commonly used[365], while the narrower one has its critics[366]. The method of assessment also had a bearing on the results of the studies. Although the majority of the studies had used structured interviews and validated scales to assess psychotic symptoms, some especially the older ones had not. However, rather than the assessment method, the inadequate sample size of most of the studies compromised their methodological adequacy. Moreover, almost all studies included hospital-based patients. The lack of community studies hinders the generalization of these findings to patients with BD in real-world settings. These lacunae in the quality of most of the studies included in the review raise the possibility of a moderate to high risk of bias in the findings of this review. The variability in results could also result from the lack of control for potential confounders such as age[159,321], sex[357,367], mood state[8], comorbidity[162], and chronicity of the illness[46]. Although multivariate statistics have been used in many studies to control for these factors, risk estimates are only offered by a few of them, and the estimation of the strength of associations by calculating effect sizes is rare. Finally, there was a lack of

Table 7 Impact of psychotic symptoms on the course and outcome of bipolar disorder

Outcome measure	Studies with positive association with psychosis in bipolar disorder	Studies with negative or no association with psychosis in bipolar disorder
Poor overall outcome	*n* = 38	*n* = 39
Earlier age of onset	*n* = 30	*n* = 36
Persistent or chronic course of illness	*n* = 23	*n* = 18
Lack of remission or lack of recovery	*n* = 12	*n* = 15
More frequent relapses or recurrences	*n* =5	*n* = 5
Greater number of mood episodes	*n* = 13	*n* = 19
Lower proportion with rapid cycling	*n* = 6	*n* = 6
Longer duration of illness	*n* = 5	*n* = 23
Manic polarity of illness	*n* = 9	*n* = 6
Seasonal pattern of illness	*n* = 2	*n* = 2
More frequent hospitalizations or longer hospital stays	*n* =26	*n* = 15
Poor functioning, poor quality of life, or poor functional outcome	*n* = 45	*n* = 46
More frequent suicidal attempts or heightened suicidal behavior	*n* = 14	*n* = 35
Good response to lithium treatment	*n* = 5	*n* = 10
Switch to diagnosis of bipolar disorder	*n* = 10	-
Poorer outcome with mood-incongruent psychotic symptoms	*n* = 21	*n* = 13
Poorer outcome with first-rank symptoms	*n* = 3	*n* = 9

Complete details in Supplementary Table 10.

studies examining the descriptive and subjective aspects of psychotic symptoms in BD[8].

Principal findings of this review

As a consequence of the methodological variability across the studies, some of the findings of this review were more reliable than the others.

One of the more reliable findings was the very high rates of psychotic symptoms in BD. In keeping with the earlier reviews, more than half of the patients with BD, mania, or mixed episodes developed such symptoms during their lifetimes[2,3,5,14,89]. Current rates of psychosis were also high and found in a little less than half of these patients. In contrast, earlier reviews have reported that about a third of the patients have psychotic symptoms during their current episodes[6,368].

Like the earlier reports, psychosis was much more common in mania and mixed episodes than in bipolar depression[3,5,8]. Psychosis was about twice as common in BP I compared to BP II disorder. Despite the smaller number of studies of patients with BP II disorder, this has been a consistent finding in the existing literature[3]. This could be because psychosis can be present only during depressive episodes in BP II disorder according to the current definitions or because of the lower severity of illness in this subtype[44,62]. In agreement with the earlier reviews[3-5], a large number of studies found the rates of psychosis to be much higher in bipolar compared to unipolar depression. However, the rates of psychosis were usually lower than those found in schizophrenia[6-8].

The rates of different types of psychotic symptoms were somewhat less reliable, principally because of the smaller number of studies involved. Nevertheless, the trends were similar to the existing reports. Thus, delusions were far more frequent than hallucinations in all phases of BD[2,3,5,8,10]. The higher rates in mania compared to bipolar depression and BP I compared to BP II disorder were also in keeping with the previous reviews[3,8-10,368]. Though based on the smallest number of studies, about a third of the patients reported experiencing FRS, particularly during acute manic episodes. This was almost equal to the rates of FRS reported in the existing literature[2,3,8,10]. Similar to the earlier reports, mood-congruent psychotic symptoms were more common among patients with BD[2,3,6,8,10]. As found in these reviews, mood-incongruent symptoms were reported in about a third of the patients with BD, and the rates were highest for those with mania. However, because of the small number of studies and the

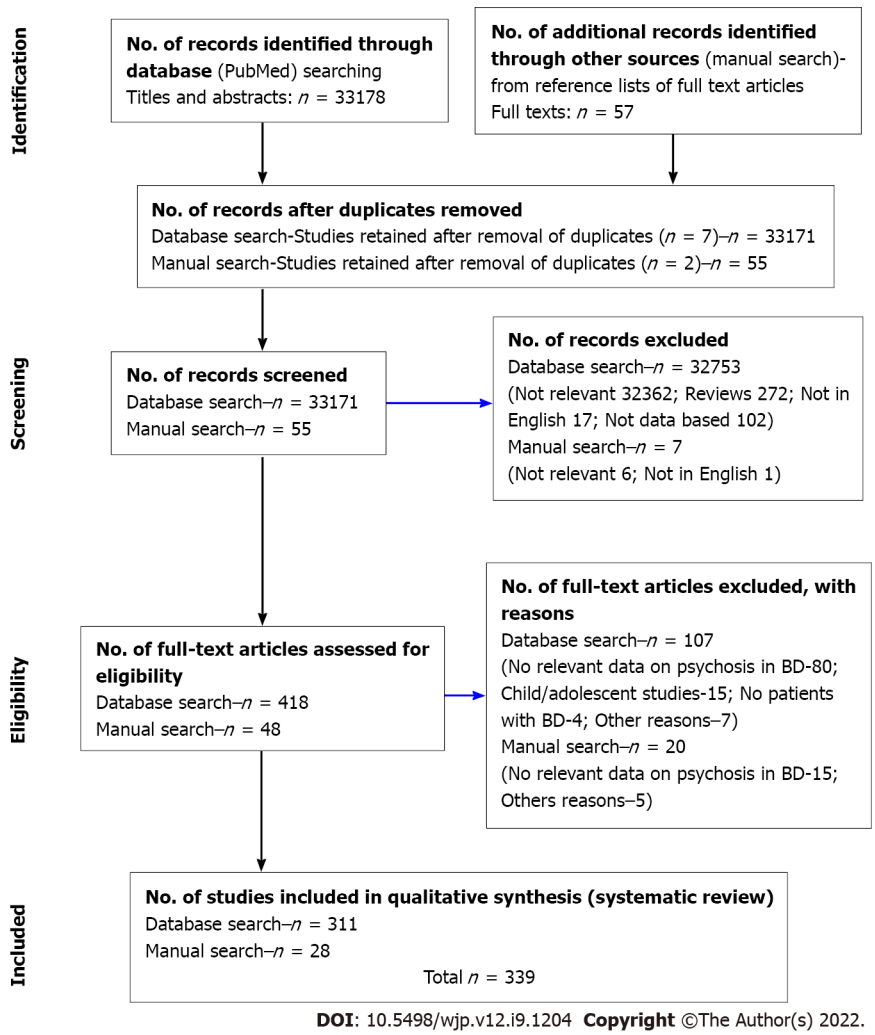

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Figure 1 PRISMA flow diagram of the PubMed and manual searches for the selection of articles included in the current review. BD: Bipolar disorder.

difficulties in ascertaining mood congruence, the validity of these findings is questionable. Similarly, the findings regarding the different types of delusions, hallucinations, and FRS were also based on very few studies but conformed to what has been reported earlier[3,5,8,10,89].

One of the principal objectives of this review was to examine the impact of psychosis on the course, outcome, clinical correlates, and demographic profile of BD. The findings of this aspect of the current review proved to be the most reliable since they were based on the largest number of studies, which were of moderate to good quality. Moreover, taken together these studies had carried out a comprehensive examination of different facets of BD that could be impacted by the presence of psychosis. The overall conclusion of this section of the review was that psychotic BD is not always associated with a negative impact on the illness. This reflected the continuing debate about the prognostic implications of psychosis in BD, with some reviews concluding that psychosis is associated with a poorer prognosis[9,11,12,89], whereas the majority have found an uncertain impact of psychosis on BD[2,3,5,8,46].

In line with the other reviews[3,8,10], the current one found few consistent associations of psychotic symptoms in BD with sociodemographic variables. Thus, the case for psychosis being associated with an adverse demographic profile[89] was not proven. The findings concerning the clinical correlates were more equivocal. As reported earlier[3,10,13], psychotic symptoms were not more severe in BD, particularly when compared to schizophrenia. On the other hand and in keeping with the existing evidence[2,3,12,89], the severity of the illness in psychotic BD appeared to be consistently greater. However, this finding was largely based on manic symptom severity, which tends to be inevitably higher than the other phases of BD[2]. Moreover, the genesis of psychotic symptoms is likely to be only partly mediated by clinical severity and partly by other factors such as early-onset, shorter duration of illness, comorbid conditions, and sex[8]. Psychosis was associated with a lack of insight, particularly during severe manic episodes. Then again, because most patients regain insight once mania resolves, the extent of impaired insight was less among patients with psychotic mania compared to those with schizophrenia[61,161]. Psychosis was also associated with a more frequent occurrence of agitation, anxiety, and hostility, but this association could be a consequence rather than the cause of psychosis in BD[8]. Finally, comorbid

disorders were less common in psychotic BD, which was in agreement with the other reviews[3].

There was greater uncertainty about the impact of psychosis on the other parameters of course and outcome. The number of studies reporting poorer overall outcomes in psychotic BD was no different from those that failed to find such a relationship. Moreover, there was no consistent association between psychotic symptoms and earlier age of onset, lack of remission and recovery, more frequent relapses and recurrences, the persistence of psychosis, poorer functional outcomes, and lithium response. Lastly, psychosis was less likely to be associated with a rapid-cycling course, longer duration of illness, and heightened suicidal behavior. This emulated the uncertainty in the existing literature regarding the associations of psychosis in BD with an earlier age of onset[2,89,369-371], a poorer long-term course[2,3,8,46,89], impaired functioning[88,367,372,373], more frequent suicide attempts[3,374,375], more frequent rapid-cycling course[46], predominant manic polarity[376], and lithium response[2,6,89,377]. The lack of impact on functioning was surprising but not unexpected. The existing literature suggests that though a significant proportion of the patients with BD have impaired functional and social outcomes, this does not appear to be mediated by the presence of psychotic symptoms[83,141].

Nevertheless, psychosis was associated with poor outcomes in three domains. Psychosis was associated with a higher risk of switching to BD, which is known to occur in about a fifth of the patients with depression[8]. Psychotic symptoms were also associated with more frequent hospitalizations and longer hospital stays, which has been noted by other reviews[9]. Finally, mood-incongruent symptoms appeared to be associated with poorer overall outcomes. Most of the earlier reviews have reported both positive and negative associations of mood-congruent symptoms with outcome[2,3,6,46,250]. However, the most comprehensive review on the subject found that though mood-incongruent symptoms were associated with poor outcomes, the differences between psychotic and non-psychotic BD were small and rarely significant[378]. Moreover, in line with the existing evidence, the current review also found that psychotic BD had a better outcome than schizophrenia[7,11].

CONCLUSION

The current systematic review has shown that there is no paucity of evidence on the subject of psychotic symptoms in BD. However, because of methodological shortcomings of the evidence, there are few consistent and reliable findings. One of them was the high prevalence of psychotic symptoms and the other was the lack of an adverse impact of psychosis on several domains of BD, including its course and outcome. These findings together with the genetic, neurobiological, and neurocognitive evidence suggest that psychotic BD lies on a continuum between non-psychotic forms of the disorder and schizophrenia[379-382]. Mood-incongruent psychotic BD, which is a severe form of BD overlaps with schizophrenia, whereas non-psychotic BD is similar to unipolar disorders[17,18,79,383]. The evidence from this review thus supports the current classification of BD as lying in an intermediate position between unipolar depression and schizophrenia[1]. Finally, from the clinicians' perspective, this review suggests that greater awareness and understanding of this subject is needed so that psychotic BD can be properly diagnosed and adequately treated in routine practice.

ARTICLE HIGHLIGHTS

Research background

Psychotic symptoms are very common in bipolar disorder (BD) and have the potential to adversely affect its course, outcome, and treatment. However, despite the considerable amount of research and several reviews on the subject, the impact of psychotic symptoms on the course and outcome of BD remains unclear. Moreover, there are very few systematic reviews on the impact of psychosis in BD.

Research motivation

The lack of information about the impact of psychotic symptoms in BD in existing literature prompted the current systematic review. Moreover, it was prompted by the possibility that the presence of such symptoms in BD and their impact on the illness may have significant etiological, nosological, and clinical implications.

Research objectives

The current systematic review was specifically intended to address the gaps in the literature regarding psychotic symptoms in BD. Therefore, it aimed to examine psychotic symptoms in BD and their impact on several domains of BD. This review focused on four groups of studies and four types of psychotic symptoms. The impact of psychotic symptoms was determined by exploring demographic correlates of psychotic symptoms, their clinical correlates, and the influence of psychotic symptoms on different parameters of course and outcome of BD.

Research methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. It undertook an electronic search supplemented by a manual one. Articles were selected in two phases: Screening of abstracts and review of full texts. The methodological quality of the studies and the risk of bias were ascertained by standard tools.

Research results

This systematic review included 339 studies of BD. The results endorsed the high rates of all types of psychotic symptoms found in BD. More than a half to two-thirds of the patients experienced psychosis during their lifetimes. Current psychosis was found in a little less than half of these patients. Delusions were more common than hallucinations. About a third of the patients had first-rank symptoms or mood-incongruent psychotic symptoms. Psychotic symptoms were more frequent in bipolar type I disorder, and in mania or mixed episodes. However, psychosis was associated with an adverse impact only in a few domains of the illness including the severity of BD, lack of insight, more frequent occurrence of agitation, anxiety, and hostility, the rate of and the duration of hospitalizations, switch to BD among patients with depression, and poorer outcomes with mood-incongruent symptoms. No consistent associations were found in other areas, suggesting that psychosis is not always associated with a negative impact on BD. This finding conformed to the current consensus in the literature on psychotic BD.

Research conclusions

Though psychotic symptoms are very common in BD, they are not always associated with an adverse impact on BD and its course and outcome.

Research perspectives

The ongoing debate about the impact of psychosis in BD is yet to be resolved. Studies with more improved methodology are needed to ascertain the true impact of psychotic symptoms in several domains of BD.

FOOTNOTES

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SYSTEMATIC REVIEWS

Mental health impact on Black, Asian and Minority Ethnic populations with preterm birth: A systematic review and meta-analysis

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Abstract

BACKGROUND

Preterm birth (PTB) is one of the main causes of neonatal deaths globally, with approximately 15 million infants are born preterm. Women from the Black, Asian, and Minority Ethnic (BAME) populations maybe at higher risk of PTB, therefore, the mental health impact on mothers experiencing a PTB is particularly important, within the BAME populations.

AIM

To determine the prevalence of mental health conditions among BAME women with PTB as well as the methods of mental health assessments used to characterise the mental health outcomes.

METHODS

A systematic methodology was developed and published as a protocol in PROSPERO (CRD420-20210863). Multiple databases were used to extract relevant data. I^2 and Egger's tests were used to detect the heterogeneity and publication bias. A trim and fill method was used to demonstrate the influence of publication bias and the credibility of conclusions.

RESULTS

Thirty-nine studies met the eligibility criteria from a possible 3526. The prevalence rates of depression among PTB-BAME mothers were significantly higher than full-term mothers with a standardized mean difference of 1.5 and a 95% confidence interval (CI) 29%-74%. The subgroup analysis indicated depressive symptoms to be time sensitive. Women within the very PTB category demonstrated a significantly higher prevalence of depression than those categorised as non-very PTB. The prevalence rates of anxiety and stress among PTB-BAME mothers were significantly higher than in full-term mothers (odds ratio of 88% and 60% with a CI of 42%-149% and 24%-106%, respectively).

CONCLUSION

BAME women with PTB suffer with mental health conditions. Many studies did not report on specific mental health outcomes for BAME populations. Therefore, the impact of PTB is not accurately represented in this population, and thus could negatively influence the quality of maternity services they receive.

Key Words: Preterm labor; Preterm birth; Black, Asian, and Minority Ethnic; Mental health; Women's health; Wellbeing

Core Tip: Preterm birth is a multi-etiological condition and a leading cause of perinatal mortality and morbidity. This study demonstrates the mental health impact due to preterm birth among the Black, Asian and Ethnic minority women. There is minimal research available at present around this subject matter, and this important disease sequelae.

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INTRODUCTION

Preterm birth (PTB) is a multi-etiological condition and a leading cause of perinatal mortality and morbidity[1]. PTB can be categorized as per the World Health Organization classification methods as extreme preterm (gestational age < 28 wk), very preterm (gestational age of 28-32 wk) and moderately preterm (32-37 wk). Most preterm infants are at risk of developing respiratory and gastrointestinal complications[2]. The PTB rates are higher in most developed regions of the world, despite advances in medicine. PTB are at the highest level in the US for between 12%-15% and 5%-9% in Europe. In comparison, PTB rates in China range between 4.7%-18.9% (1987-2006) and Taiwan 8.2%-9.1%[3]. The prevalence of PTB increased from 9.8% in 2000 to 10.6% by 2014 and has become a global public health

issue[1]. However, the mental health impact associated with PTB is not extensively examined, despite it potentially may exacerbate the patient's experience of a distressing birth. Furthermore, clearly pronounced risk of PTB among Black women have been reported in studies from United States or United Kingdom[4,5], with limited data on the risk among other ethnic groups. While health disparities, social deprivation are recognised risk factors for PTB that are also frequently associated with Black, Asian, and Minority Ethnic (BAME) populations, the available data on ethnic disparities associated with PTB remains limited.

In the United Kingdom, health disparities within Caribbean and West African populations demonstrate a significant risk of very PTB in comparison to Caucasians. Similar risks within the South Asian community appear to be less consistent in comparison to Caucasian PTB women[11]. In the United Kingdom, National Health Service (NHS) England reports improvements to maternity services are a priority as part of the NHS 10-year plan[12]. As per the 2018 Public Health England report on maternity services, 1 in 4 of all births within Wales and England were to mothers born outside the United Kingdom[12]. Additionally, 13% of all infants born between 2013-2017 are from the BAME population[12]. Importantly, Black women were 5 times more at risk of death during parturition and Asian babies are 73% more likely to result in neonatal death compared to Caucasian women[12], therefore, the mental health impact experienced by PTB mothers is vital to evaluate particularly in the BAME population. A number of socio-economic, genetic and obstetric causes have been proposed to explain mental health disorders among PTB women, but these theories do not fully explain the aetiology. Furthermore, they also exclude the bidirectional relationship between PTB, and mental health conditions demonstrated by some studies[13,18,19].

This available evidence demonstrates a need to explore the mental health impact on BAME women with PTB. We believe that gathering this evidence would inform the forthcoming evidence-based women's health strategy in the United Kingdom to explore both the physical and mental health components, and to be inclusive using cultural adaptations where appropriate.

MATERIALS AND METHODS

An evidence synthesis methodology was developed using a systematic protocol that was developed and published on PROSPERO (CRD42020210863). The aims of the study were to determine the prevalence of mental health conditions among BAME women with PTB as well as the mental health assessments used to characterise the mental health outcomes.

Data searches

Multiple databases were used, including PubMed, EMBASE, Science direct, and The Cochrane Central Register of Controlled trials for the data extraction process. Searches were carried out using multiple keywords and MeSH terms such as "Depression", "Anxiety", "Mood disorders", "PTSD", "Psychological distress", "Psychological stress", "Psychosis", "Bipolar", "Mental Health", "Unipolar", "self-harm", "BAME", "Preterm birth", "Maternal wellbeing" and "Psychiatry disorders". These terms were then expanded using the 'snow-ball' method and the fully developed methods are in the supplementary section (Supplementary material).

Eligibility criteria and study selection

All eligible randomised controlled trials (RCTs) and non-RCTs published in English were included. The final dataset was reviewed independently. Multiple mental health variables were used alongside of the 2 primary variables of PTB and BAME.

Data extraction and analysis

The extraction and eligibility has been demonstrated using a PRISMA diagram. The data was collected using Endnote and Microsoft excel. Stata 16.1 was used as a way to complete the final statistical analysis. Standardized mean difference (SMD) and 95% confidence interval (CI) were extracted for analysis. Heterogeneity was assessed by way of funnel plots, χ^2-test (P value) and I^2. A sub-group analysis was conducted to determine the mental health symptomatologies identified and the geographical location.

Due to the unified use of mental health assessments, in order to standardize the mean differences reported within each study, the following mathematical method was used[25-27]:

$$\widehat{g_k} = (1 - \frac{3}{4n_k - 9}) \frac{\widehat{u_{ek}} - \widehat{u_{ck}}}{\sqrt{((n_{ek} - 1)s_{ek}^2 + (n_{ck} - 1)s_{ck}^2)/(n_k - 2)}}$$

$$\widehat{Var}(\widehat{g_k}) = \frac{n_k}{n_{ek} \cdot n_{ck}} + \frac{\widehat{g_k}^2}{2(n_k - 3.94)}$$

where, $n_k = n_{ek} + n_{ck}$, n_{ek}, $\widehat{u_{ek}}$, s_{ek} are the number, mean and standard variation of exposed group and n_{ck}, $\widehat{u_{ck}}$, s_{ck} are the number, mean and standard variation of control group. Then we can obtain the 95%

confidence interval by $\widehat{g_k} \pm 1.96 * S.E.(\widehat{g_k})$ where $S.E.(\widehat{g_k}) = \sqrt{\widehat{Var}(\widehat{g_k})}$.

Meta-regression and sub-group analysis

To eliminate heterogeneity, a meta-regression and sub-group analyses were conducted by mental health assessment timepoints and country.

Sensitivity analysis

To further analyse the heterogeneity of studies reporting depression and anxiety, a sensitivity analysis was conducted.

Risk of bias quality assessment

Studies included within this study were critically appraised individually using mental health variables. All studies appraised for methodological quality and risk of bias based on the Newcastle-Ottawa Scale (NOS), which is commonly used for cross-sectional and/or cohort studies as demonstrated by Wells *et al* [73]. These could be further modified using the adapted NOS version as reported by Modesti *et al*[74]. The NOS scale includes 8 items within 3 specific quality parameters of selection, outcome and comparability. The quality of these studies was reported as good, fair or poor based on the details below: Good quality score of 3 or 4 stars were awarded in selection, 1 or 2 in comparability and 2 or 3 stars in outcomes; Fair quality score of 2 stars were awarded in selection, 1 or 2 stars in comparability and 2 or 3 stars in outcomes; Poor quality score was allocated 0 or 1 star in selection, 0 stars in comparability and 0 or 1 star in outcomes.

Outcomes

The following outcomes were included within the meta-analysis: Prevalence of anxiety and depressive symptoms, and parenting stress; Clinical significance of the data identified; Critical interpretive synthesis of common mental health reported outcomes.

Outcomes such as post-partum depression could not be synthesised for the meta-analysis. Therefore, these aspects have been included in the narrative analysis only.

Publication bias

Publication bias is a concern to the validity of conclusion of a meta-analysis. As a result, several methods could be used to assess this aspect. An egger's test was used to report on publication bias. Additionally, a trim and fill (TAF) method was used to analyze the influence of publication bias. TAF estimates any missing studies due to publication bias within the funnel plot to adjust the overall effect estimate.

Patient and public involvement

A representative from a patient-public focus group associated with a multi-morbid project investigating women's physical and mental health sequelae was invited to review the protocol and the resulting paper. This is a vital facet of developing and delivering an authentic evidence synthesis to reduce the gap between evidence production, development of solutions to address the identified gaps and the implementation of the solutions into practice as well as their acceptability by patients.

RESULTS

Of the 3526 studies, 39 met the eligibility criteria. All 39 studies reported the mental health status of BAME women with PTB although it remained unclear if they reported mental health symptoms or clinical diagnoses. Figure 1 shows the PRISMA diagram. The mental health assessments and frequency of the data gathering varied across studies. The 39 studies primarily reported stress, anxiety and depression as indicated in Table 1 along with other characteristics. The quality assessment using the Newcastle Ottawa scale (NOS) and Risk of Bias identified within the pooled studies are shown in Tables 2 and 3 and Supplementary Table 1. Brief description of various scales used to assess depression, anxiety, and stress across studies is presented in the supplementary file on Mental Health Questionnaires.

Depression

Of the 39 studies, 36 primarily reported an association between the prevalence of depression and PTB. Fifteen studies only examined the differences of non-depressive symptoms as well other factors such as race, ethnicity, plurality across multiple assessment timepoints although, they were not compared to full-term birth mothers of BAME decent. The overall SMD was 0.4 and 95%CI of a range of 0.25-0.56, indicating the prevalence of depression in PTB mothers to be significantly higher than mothers who delivered at term. I^2 = 82.69% indicated high heterogeneity among the depression group.

Table 1 Key features of the studies included in the systematic review

ID	Ref.	Study type	Country	Symptoms			Outcome assessment[1]
1	Ballantyne *et al* [37]	Cross-sectional study	Canada	Depression		Stress	(1) CES-D; and (2) PSS: NICU
2	Baptista *et al*[48]	Cross-sectional study	Portugal	Psychological problem		Stress	(1) BSI; and (2) Daily hassles questionnaire
3	Barroso *et al*[38]	Cross sectional study	United States	Depression			EPD-S
4	Bener[60]	Hospital-based study (cross sectional study)	Qatar	Depression	Anxiety	Stress	(1) DASS-21; (2) DASS-21; and (3) DASS-21
5	Bouras *et al*[34]	Cross-sectional study	Greece	Depression	Anxiety		(1) BDI; and (2) STAI
6	Brandon *et al*[39]	Descriptive study	United States	Depression	Anxiety	Stress	(1) EPDS; (2) STAI-S; (3) PPQ; and (4) CHWS
7	Carson *et al*[49]	Cohort study	United Kingdom	Psychological problem			Modified RMI
8	Cheng *et al*[13]	Cohort study	United States	Depression			CES-D
9	Davis *et al*[57]	Cross-sectional study	Australia	Depression		Stress	(1) EPDS; and (2) DASS
10	Drewett *et al*[50]	Cross-sectional study	United Kingdom	Depression			EPDS
11	Edwards *et al*[58]	Cohort study	Australia	Depression		Parenting stress	(1) EPDS; and (2) PSI
12	Fabiyi *et al*[40]	Cross-sectional study	United States		(1) State anxiety; and (2) Trait anxiety		STAI
13	Gambina *et al*[33]	Case-control study	Italy	Depression	(1) State anxiety; and (2) Trait anxiety	Stress	(1) EPDS; (2) STAI-State and STAI-Trait; and (3) PSM
14	Gueron-Sela *et al* [30]	Cross-sectional study	Israel	Depression		Stress	(1) CES-D; and (2) PSS: NICU
15	Gulamani *et al* [24]	Cohort study	Pakistan	Depression			EPDS
16	Gungor *et al*[35]	Case-control study	Turkey	Depression	(1) State anxiety; (2) Trait anxiety		(1) BDI; and (2) STAI
17	Hagan *et al*[59]	Prospective, randomised, controlled study	Australia	Depression	Anxiety		(1) EPDS; and (2) BDI
18	Henderson *et al* [51]	Cross-sectional study	United Kingdom	Depression			EPDS
19	Holditch-Davis *et al*[44]	Cross-sectional study	United States	Depression	Anxiety	Stress	(1) CES-D; (2) STAI; and (3) PSS: NICU
20	Ionio *et al*[52]	Longitudinal study	Italy	Depression			Profile of mood states
21	Logsdon *et al*[41]	Descriptive study	United States	Depression			CES-D
22	Misund *et al*[53]	Longitudinal study	Norway	Psychological distress	Anxiety	Trauma-related stress	(1) GHQ likert sum and case sum; (2) STAI-X1; and (3) Impact of event scale (IES)
23	Misund *et al*[53]	Cohort study	Norway	Psychological distress	Anxiety	Trauma-related stress	(1) GHQ likert sum and case sum; (2) STAI-X1; and (3) IES
24	Pace *et al*[32]	Longitudinal, prospective, follow-up cohort study	Australia	Depression	Anxiety		(1) CES-D; and (2) Hospital anxiety and depression scale
25	Rogers *et al*[42]	Cohort study	United States	Depression	Anxiety		(1) EPDS; and (2) STAI
26	Sharan *et al*[61]	Cross-sectional study	Israel	Depression			EPDS
27	Shaw *et al*[43]	Cross-sectional study	United States	Depression	Anxiety	Stress	(1) BDI-II; (2) BAI; and (3) SASRQ

28	Trumello *et al*[54]	Longitudinal study	Italy	Depression	(1) State anxiety; and (2) Trait anxiety		(1) EPDS; and (2) STAI-State Y1 and Y2
29	Holditch-Davis *et al*[44]	Longitudinal study	United States	Depression	State anxiety	Stress	(1) CESD; (2) STAI; (3) PSS: NICU; and (4) PSS:PBC
30	Mautner *et al*[55]	Prospective, longitudinal study	Austria	Depression			EPDS
31	Gray *et al*[28]	Cross-sectional study	Australia	Depression		Parenting stress	(1) EPDS; and (2) PSI-SF
32	Gray *et al*[29]	Cross-sectional study	Australia	Depression		Parenting stress	(1) EPDS; and (2) PSI-SF
33	Howe *et al*[62]	Cross-sectional study	Taiwan			Parenting stress	PSI-Chinese version
34	Miles *et al*[45]	Longitudinal, descriptive study	United States	Depression			CES-D
35	Mew *et al*[46]	Correlational analysis	United States	Depression			CES-D
36	Madu and Roos [31]	Cross-sectional study	South Africa	Depression			EPDS
37	Suttora *et al*[36]	Descriptive study	Italy			(1) PTSD; and (2) Parenting stress	(1) PPQ-Modified version; and (2) PSI-SF
38	Korja *et al*[56]	Cross-sectional study	Finland	Depression			EPDS
39	Younger *et al*[47]	Descriptive correlational study	United States	Depression		Stress	(1) CES-D; and (2) MSI

[1]Outcome assessment scales: Edinburgh Postnatal Depression Scale; State-Trait Anxiety Inventory; Hospital Anxiety and Depression Scale; Centre for Epidemiological Studies Depression; Beck's Depression Inventory; Profile of Mood States; Parent Stress Index; Professional Personality Questionnaire; Perceived Stress Measure. EPDS: Edinburgh Postnatal Depression Scale; STAI: State-Trait Anxiety Inventory; HADS-A: Hospital Anxiety and Depression Scale; CES-D: Centre for Epidemiological Studies Depression; BDI: Beck's Depression Inventory; POMS: Profile of Mood States; PSI: Parent Stress Index; PPQ: Professional Personality Questionnaire; PSM: Perceived Stress Measure.

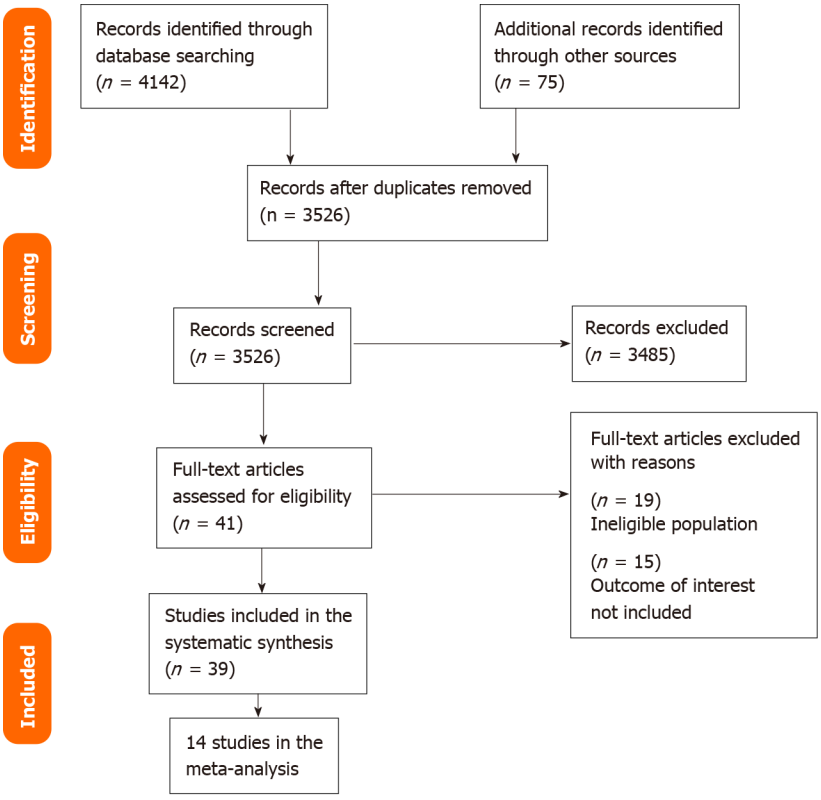

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Figure 1 PRISMA diagram.

Table 2 The quality assessment outcomes using the Newcastle-Ottawa Scale

ID	Ref.	Study type	Country	Symptoms			Outcome assessment	NOS score
1	Ballantyne *et al* [37]	Cross-sectional study	Canada	Depression		Stress	(1) CES-D; and (2) PSS: NICU	****** (6)
2	Baptista *et al* [48]	Cross-sectional study	Portugal	Psychological problem		Stress	(1) BSI; and (2) Daily hassles questionnaire	***** (5)
3	Barroso *et al* [38]	Cross sectional study	United States	Depression			EPD-S	****** (6)
4	Bener[60]	Hospital-based study (Cross sectional study)	Qatar	Depression	Anxiety	Stress	(1) DASS-21; (2) DASS-21; and (3) DASS-21	***** (5)
5	Bouras *et al*[34]	Cross-sectional study	Greece	Depression	Anxiety		(1) BDI; and (2) STAI	****** (6)
6	Brandon *et al* [39]	descriptive study	United States	Depression	Anxiety	Stress	(1) EPDS; (2) STAI-S; (3) PPQ; and (4) CHWS	******* (7)
7	Carson *et al* [49]	Cohort study	United Kingdom	Psychological problem			Modified RMI	***** (5)
8	Cheng *et al*[13]	Cohort study	United States	Depression			CES-D	***** (5)
9	Davis *et al*[57]	Cross-sectional study	Australia	Depression		Stress	(1) EPDS; and (2) DASS	***** (5)
10	Drewett *et al* [50]	Cross-sectional study	United Kingdom	Depression			EPDS	***** (5)
11	Edwards *et al* [58]	Cohort study	Australia	Depression		Parenting stress	(1) EPDS; and (2) PSI	***** (5)
12	Fabiyi *et al*[40]	Cross-sectional study	United States		(1) State anxiety; and (2) Trait anxiety		STAI	****** (6)
13	Gambina *et al* [33]	Case-control study	Italy	Depression	(1) State anxiety; and (2) Trait anxiety	Stress	(1) EPDS; (2) STAI-State and STAI-Trait; and (3) PSM	****** (6)
14	Gueron-Sela *et al*[30]	Cross-sectional study	Israel	Depression		Stress	(1) CES-D; and (2) PSS: NICU	******* (7)
15	Gulamani *et al* [24]	Cohort study	Pakistan	Depression			EPDS	**** (4)
16	Gungor *et al* [35]	Case-control study	Turkey	Depression	(1) State anxiety; (2) Trait anxiety		(1) BDI; and (2) STAI	****** (6)
17	Hagan *et al*[59]	Prospective,randomised, controlled study	Australia	Depression	Anxiety		(1) EPDS; and (2) BDI	****** (6)
18	Henderson *et al*[51]	Cross-sectional study	United Kingdom	Depression			EPDS	******* (7)
19	Holditch-Davis *et al*[44]	Cross-sectional study	United States	Depression	Anxiety	Stress	(1) CES-D; (2) STAI; and (3) PSS: NICU	****** (6)
20	Ionio *et al*[52]	Longitudinal study	Italy	Depression			Profile of mood states	***** (5)
21	Logsdon *et al* [41]	Descriptive study	United States	Depression			CES-D	****** (6)
22	Misund *et al* [53]	Longitudinal study	Norway	Psychological distress	Anxiety	Trauma-related stress	(1) GHQ likert sum and case sum; (2) STAI-X1; and (3) Impact of Event Scale (IES)	****** (6)
23	Misund *et al*	Cohort study	Norway	Psychological	Anxiety	Trauma-	(1) GHQ likert sum	***** (5)

	[53]			distress		related stress	and case sum; (2) STAI-X1; and (3) IES	
24	Pace *et al*[32]	Longitudinal, prospective, follow-up cohort study	Australia	Depression	Anxiety		(1) CES-D; and (2) Hospital anxiety and depression scale	****** (6)
25	Rogers *et al*[42]	Cohort study	US	Depression	Anxiety		(1) EPDS; and (2) STAI	***** (5)
26	Sharan *et al* [61]	Cross-sectional study	Israel	Depression			EPDS	****** (6)
27	Shaw *et al*[43]	Cross-sectional study	US	Depression	Anxiety	Stress	(1) BDI-II; (2) BAI; and (3) SASRQ	****** (6)
28	Trumello *et al* [54]	Longitudinal study	Italy	Depression	1) State anxiety2) Trait anxiety		(1) EPDS; and (2) STAI-State Y1 and Y2	******* (7)
29	Holditch-Davis *et al*[44]	Longitudinal study	US	Depression	1) State anxiety	Stress	(1) CESD; (2) STAI; (3) PSS: NICU; and (4) PSS:PBC	****** (6)
30	Mautner *et al* [55]	Prospective, longitudinal study	Austria	Depression			EPDS	****** (6)
31	Gray *et al*[28]	Cross-sectional study	Australia	Depression		Parenting stress	(1) EPDS; and (2) PSI-SF	****** (6)
32	Gray *et al*[29]	Cross-sectional study	Australia	Depression		Parenting stress	(1) EPDS; and (2) PSI-SF	****** (6)
33	Howe *et al*[62]	Cross-sectional study	Taiwan			Parenting stress	PSI-Chinese version	****** (6)
34	Miles *et al*[45]	Longitudial, descriptive study	United States	Depression			CES-D	***** (5)
35	Mew *et al*[46]	Correlational analysis	United States	Depression			CES-D	***** (5)
36	Madu and Roos[31]	Cross-sectional study	South Africa	Depression			EPDS	****** (6)
37	Suttora *et al* [36]	Decriptive study	Italy			(1) PTSD; and (2) Parenting stress	(1) PPQ-Modified version; and (2) PSI-SF	***** (5)
38	Korja *et al*[56]	Cross-sectional study	Finland	Depression			EPDS	****** (6)
39	Younger *et al* [47]	Decriptive correlational study	United States	Depression		Stress	(1) CES-D; and (2) MSI	****** (6)

*: Quality of the included cross-sectional studies was measured using the modified Newcastle-Ottawa Measurement Scale specific for Cross-sectional studies. We rated the quality of the studies (good, fair and poor) by allocating each domain with stars in this manner: A good quality score was awarded 3 or 4 stars in selection, 1 or 2 in comparability, and 2 or 3 stars in outcomes; A fair quality score was awarded 2 stars in selection, 1 or 2 stars in comparability, and 2 or 3 stars in outcomes; A poor quality score was allocated 0 or 1 star(s) in selection, 0 stars in comparability, and 0 or 1 star(s) in outcomes domain in line with the Newcastle-Ottawa Scale guidelines. NOS: Newcastle-Ottawa Scale; EPDS: Edinburgh Postnatal Depression Scale; STAI: State-Trait Anxiety Inventory; HADS-A: Hospital Anxiety and Depression Scale; CES-D: Centre for Epidemiological Studies Depression; BDI: Beck's Depression Inventory; POMS: Profile of Mood States; PSI: Parent Stress Index; PPQ: Professional Personality Questionnaire; PSM: Perceived Stress Measure.

Shaw *et al*[43] focused on the association between depression symptoms and the efficiency of Edinburgh Postnatal Depression Scale (EPDS), although the specificity of EPDS to the BAME population was not demonstrated. Since most of the studies reported mean and SD, we pooled mean differences and its 95%CI. Seven of the studies lacked information about mean score and SD, thus, were excluded from the meta-analysis. Gray *et al*[28,29] used the same dataset in two papers, therefore one of these was included into the meta-analysis. Therefore, a total of 12 studies were included in the meta-analysis as indicated by Table 4. Additionally, Gueron-Sela *et al*[30] studied two ethnicities, therefore it was used twice as reported in Table 4. Therefore, 13 items were reported in the meta-analysis for depression. The meta-analyses for anxiety and stress had 5 studies each, as demonstrated in Tables 5 and 6.

Anxiety

The 12 studies reporting anxiety utilised EDPS, the State-Trait Anxiety Inventory (STAI), Hospital

Table 3 Risk of Bias using the Newcastle-Ottawa Scale

	Selection (S)				Comparability (C)		Exposure/outcome E/O			Sub total assessment			Conclusion
	1	2	3	4	1a	1b	1	2	3	S[1]	C[2]	E/O[2]	
Ballantyne *et al*[37]	*	*	No	*	*	*	No	*	*	Good	Good	Good	Good
Baptista *et al*[48]	*	*	No	*	*	*	*	*	*	Good	Good	Good	Good
Barroso *et al*[38]	*	*	*	*	*	*	*	No	*	Good	Good	Good	Good
Bener[60]	*	No	*	*	*	*	*	*	*	Good	Good	Good	Good
Bouras *et al*[34]	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good
Brandon *et al*[39]	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good
Carson *et al*[49]	*	No	*	*	*	*	*	*	*	Good	Good	Good	Good
Cheng *et al*[13]	*	*	No	*	No	*	*	*	*	Good	Good	Good	Good
Davis *et al*[57]	*	*	No	No	*	*	*	*	*	Fair	Good	Good	Good
Drewett *et al*[50]	*	*	*	*	No	*	*	*	*	Good	Good	Good	Good
Edwards *et al*[58]	*	No	No	*	No	*	*	*	*	Fair	Good	Good	Fair
Fabiyi *et al*[40]	*	No	*	No	No	*	*	*	*	Fair	Fair	Good	Fair
Gambina *et al*[33]	*	No	*	*	*	*	*	*	*	Good	Good	Good	Good
Gueron-Sela *et al*[30]	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good
Gulamani *et al*[24]	*	No	*	*	*	*	*	*	*	Good	Good	Good	Good
Gungor *et al*[35]	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good
Hagan *et al*[59]	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good
Henderson *et al*[51]	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good
Holditch-Davis *et al*[44]	*	*	No	*	No	*	*	*	*	Good	Good	Good	Good
Ionio *et al*[52]	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good
Logsdon *et al*[41]	*	No	No	*	No	*	*	*	*	Fair	Fair	Good	Fair
Misund *et al*[53]	No	*	*	*	*	*	*	*	*	Good	Good	Good	Good
Misund *et al*[53]	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good
Pace *et al*[32]	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good
Rogers *et al*[42]	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good

Sharan *et al*[61]	No	*	*	*	*	*	*	*	*	Good	Good	Good	Good
Shaw *et al*[43]	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good
Trumello *et al*[54]	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good
Holditch-Davis *et al*[44]	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good
Mautner *et al*[55]	*	No	*	*	*	*	*	*	*	Good	Good	Good	Good
Gray *et al*[28]	*	*	No	*	No	*	*	*	*	Good	Good	Good	Good
Gray *et al*[29]	*	*	No	*	No	*	*	*	*	Good	Good	Good	Good
Howe *et al*[62]	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good
Miles *et al*[45]	*	No	No	*	No	*	*	*	*	Fair	Good	Good	Fair
Mew *et al*[46]	*	No	No	*	No	*	*	No	*	Fair	Fair	Good	Fair
Madu and Roos[31]	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good
Suttora *et al*[36]	*	*	*	*	*	*	*	*	*	Good	Good	Good	Good
Korja *et al*[56]	*	*	No	*	No	*	*	*	*	Good	Good	Good	Good
Younger *et al*[47]	*	No	No	*	No	*	*	*	*	Fair	Good	Good	Good

[1]Domain scored: 0-1 (Poor); 2 (Fair); 3+ (Good).
[2]Domain scored: 0 (Poor); 1 (Fair); 2+ (Good).
*: Domain acceptable.

Anxiety and Depression Scale (HADS-A), Centre for Epidemiological Studies Depression, Beck's Depression Inventory and Profile of Mood States as their assessment tool. The total scores of these scales are different, and the mean difference of the studies are not compatible. Four studies reported on anxiety using STAI and HADS-A as their mental health assessment of choice. The overall SMD of Anxiety was 0.63 with 95%CI of 0.35-0.91. I^2 = 86.83% also indicated high heterogeneity among anxiety group.

Stress and parent stress index

Studies reporting stress used the Parent Stress Index assessment on three separate timepoints along with the Professional Personality Questionnaire and the Perceived Stress Measure. The total scores of these scales in each meta-analysis are different, and the mean difference of the studies are not compatible. The overall SMD of Stress was 0.47 with 95%CI 0.22-0.72. I^2 =77.55% indicated high heterogeneity among stress group.

Posttraumatic stress disorder

Suttora *et al* [36] was the only study reporting on posttraumatic stress disorder (PTSD). The reported

Table 4 Characteristics of the 12 studies included within the meta-analysis for depression

ID	Ref.	Study type	Country	Sample size	Outcome assessment
1	Brandon *et al*[39]	Descriptive study	United States	60	EPDS
2	Bouras *et al*[34]	Cross-sectional study	Greece	200	BDI
3	Cheng *et al*[13]	Cohort study	United States	5350	CES-D
4	Drewett *et al*[50]	Cross-sectional study	United Kingdom	10838	EPDS
5	Gambina *et al*[33]	Case-control study	Italy	84	EPDS
6	Gray *et al*[28,29]	Cross-sectional study	Australia	217	EPDS
7	Gueron-Sela *et al*[30]	Cross-sectional study	Israel	103 (Bedouin); 230 (Jewish)	CES-D
8	Gungor *et al*[35]	Case-control study	Turkey	299	BDI
9	Ionio *et al*[52]	Longitudinal study	Italy	50	Profile of mood states
10	Madu and Roos[31]	Cross-sectional study	South Africa	100	EPDS
11	Mautner *et al*[55]	Prospective, longitudinal study	Australia	61	EPDS
12	Pace *et al*[32]	Longitudinal, prospective cohort study	Australia	230	CES-D

EPDS: Edinburgh Postnatal Depression Scale; BDI: Beck's Depression Inventory; CES-D: Centre for Epidemiological Studies Depression.

Table 5 Characteristics of the 5 studies included within the meta-analysis for anxiety

ID	Ref.	Study type	Country	Sample size	Outcome assessment
1	Brandon *et al*[39]	Descriptive study	United States	60	STAI-S
2	Bouras *et al*[34]	Cross-sectional study	Greece	200	STAI-T; STAI-S
3	Gambina *et al*[33]	Case-control study	Italy	84	STAI-T; STAI-S
4	Gungor *et al*[35]	Case-control study	Turkey	299	STAI-T; STAI-S
5	Pace *et al*[32]	Longitudinal, prospective cohort study	Australia	230	HADS-A

STAI: State-Trait Anxiety Inventory.

Table 6 Characteristics of the 5 studies included within the meta-analysis for stress

ID	Ref.	Study type	Country	Sample size	Outcome assessment
1	Brandon *et al*[39]	Descriptive study	United States	60	PPQ
2	Gambina *et al*[33]	Case-control study	Italy	84	PSM
3	Gray *et al*[28,29]	Cross-sectional study	Australia	217	PSI-SF
4	Howe *et al*[62]	Cross-sectional study	Taiwan	420	PSI-Chinese version
5	Suttora *et al*[36]	Descriptive study	Italy	243	PSI-SF

PPQ: Professional Personality Questionnaire; PSM: Perceived Stress Measure; PSI: Parent Stress Index.

mean and SD of the symptoms of PTSD were transformed to SMD. The SMD was 1.12 with a 95%CI of 0.84-1.40 indicated significantly high PTSD symptoms among BAME PTB women than the term mothers.

Assessment of mental health at differing time-points for depression, anxiety and stress were evaluated between full term and PTB mothers. Different mean scores and SD values were reported across the included studies. The dataset was unified with converting the mean difference to the SMD and demonstrated in the forest plots (Figures 2-4).

This meta-analysis identified depression to be a primary mental health outcome among PTB mothers and significantly higher prevalence rates of depression was reported in PTB mothers compared with full-term mothers.

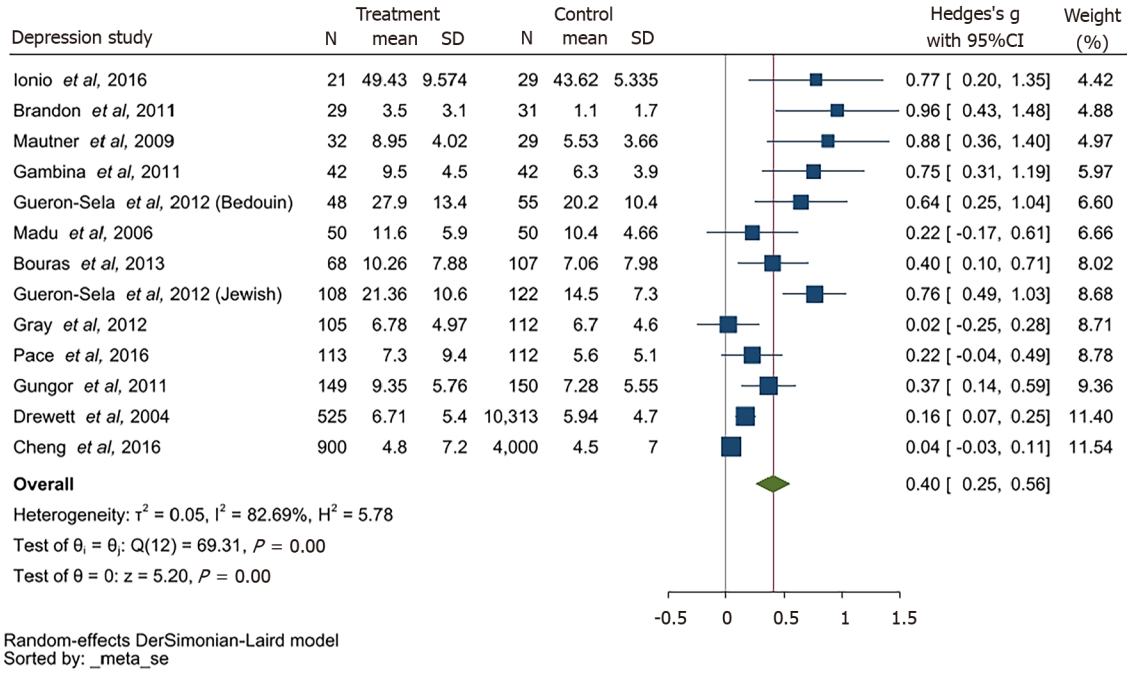

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Figure 2 Forest plot for depression (full term *vs* preterm birth). CI: Confidence interval.

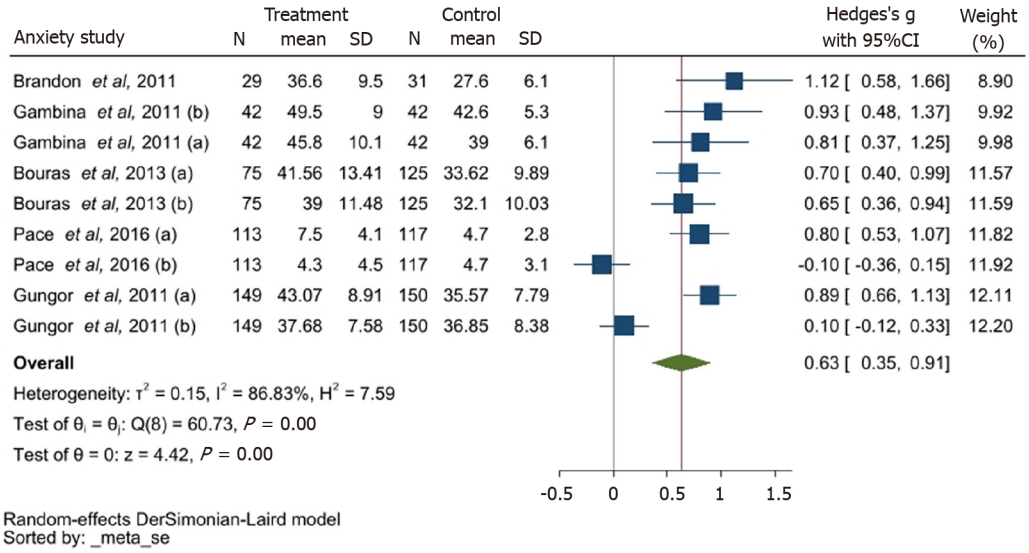

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Figure 3 Forest plot for anxiety (full term *vs* preterm birth). CI: Confidence interval.

Meta-regression analysis

Of the 16 studies included within the meta-regression analysis for depression, 5 reported mean scores and SD of the mental health questionnaires used at parturition. Four studies recorded the mean and SD at 1-mo post-delivery, while another four studies reported the same at 1 mo to 8 mo post-delivery. To eliminate the heterogeneity, these studies were adjusted by timepoints (Figure 5).

The estimated intercept for depression is 0.629 with a 95%CI of 0.455-0.804. This indicates the mental health assessment scores within the PTB group were significantly higher than full-term group at the birth. The coefficient of the covariate time was -0.061 with a 95%CI of -0.094, -0.028 indicating that the coefficients of time were significantly lower than 0. This is indicative of a reduction depression symptoms post-delivery. Heterogeneity decreased from 82.69% to 79.82%, and the differences of assessment time points could explain the 31.75% of the heterogeneity identified.

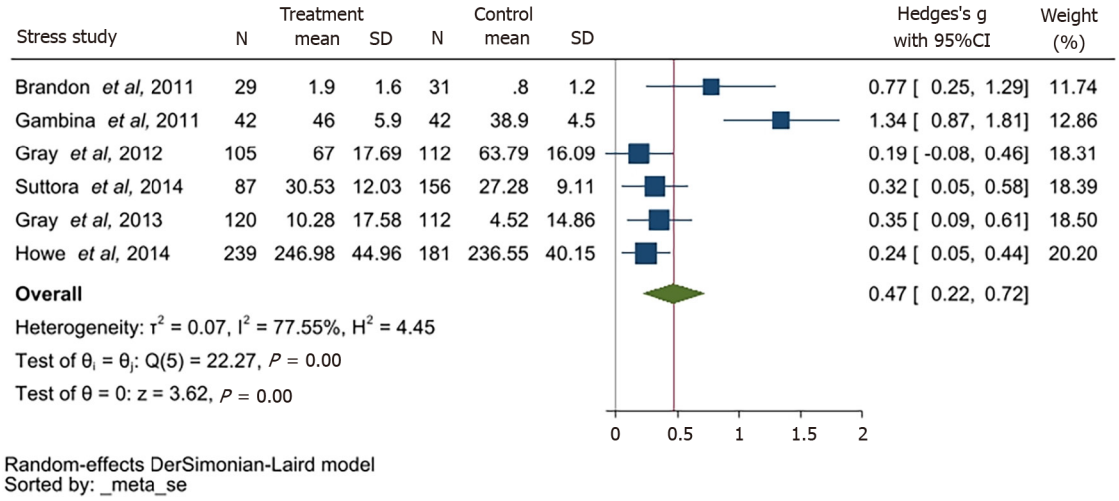

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Figure 4 Forest plot for stress (full term *vs* preterm birth). CI: Confidence interval.

```
Random-effects meta-regression                  Number of obs   =        16
Method: DerSimonian-Laird                       Residual heterogeneity:
                                                          tau2 =  0.04072
                                                       I2 (%)  =    79.82
                                                          H2   =     4.96
                                                R-squared (%)  =    31.75
                                                Wald chi2(1)   =    13.41
                                                Prob > chi2    =   0.0002
------------------------------------------------------------------------------
     _meta_es |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       tvalue |  -0.0609896   0.0166533    -3.66   0.000    -0.0936296   -0.0283497
        _cons |   0.6294887   0.0889261     7.08   0.000     0.4551968    0.8037807
------------------------------------------------------------------------------
Test of residual homogeneity: Q_res = chi2(14) = 69.38   Prob > Q_res = 0.0000
```

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Figure 5 Meta regression conducted by time for depression.

Nine studies that reported anxiety were included in the meta-regression (Figure 6). The estimated intercept was 0.772 with a 95%CI of 0.500-1.045 which indicates the mental health assessment scores of the PTB group are significantly higher than the scores of full-term group. The coefficient of the covariate time is -0.136 with 95%CI of -0.262, -0.010 indicating that the symptoms of anxiety gradually disappeared among PTB group following birth. Heterogeneity reduced from 86.83% to 80.29%. The differing time points in administering the mental health assessment could explain 34.91% of the heterogeneity (Figure 6).

Following the reduction of heterogeneity by way of the meta-regression method, the statistical conclusions demonstrate a statistical significance where the prevalence of depression among BAME women with PTB was higher in comparison to BAME women who delivered at full-term. The I^2 was almost 80% which indicates a high heterogeneity.

The pooled SMD within the studies using PTB mothers from United States was 0.46 with a 95%CI of -0.43 – 1.35. The pooled SMD within Australia was 0.44 with a 95%CI of 0.07-0.81. I^2 of these two subgroups indicated a high heterogeneity: 91.14% and 87.79% respectively. The assessment timepoints of these two groups have a significant difference, which could be the source of the high heterogeneity. As there were only 2 studies, a meta-regression of the timepoints could not be completed.

Subgroup analysis

A subgroup analysis of depression and anxiety was completed using geographical location as demonstrated in Supplementary Figures 1-3. For depression, the pooled SMD within Greece, Italy, Israel and Turkey was 0.57 with a 95%CI of 0.4-0.74. The pooled SMD within United Kingdom was 0.12 with a 95%CI of 0.03-0.21. I^2 was denoted to be indicating a lack of heterogeneity as demonstrated in Supplementary Figure 1.

```
Random-effects meta-regression                  Number of obs  =         9
Method: DerSimonian-Laird                       Residual heterogeneity:
                                                          tau2 =    0.1002
                                                       I2 (%)  =     80.29
                                                          H2   =      5.07
                                                  R-squared (%) =    34.91
                                                Wald chi2(1)    =      4.50
                                                Prob > chi2     =    0.0338
------------------------------------------------------------------------------
     _meta_es |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       tvalue |  -0.1359486   0.0640626    -2.12   0.034    -0.261509  -0.0103882
        _cons |   0.7723931   0.1391725     5.55   0.000     0.4996201    1.045166
------------------------------------------------------------------------------
Test of residual homogeneity: Q_res = chi2(7) = 35.51    Prob > Q_res = 0.0000
```

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Figure 6 Meta regression conducted by time for anxiety.

Although a meta-regression was not conducted for the pooled SMD within the studies with PTB mothers from United States, a subgroup analysis demonstrated that the high heterogeneity could be attributed to the differences of time points of the mental health assessments.

Of the 39 studies included in the systematic review, thirteen studies were from North America[1,3,6,8,12,19,21,25,27,29,34,35,39], thirteen from Europe[2,5,7,10,13,18,20,22,23,28,30,37,38], six studies from Australia[9,11,17,24,31,32], three from Asia[15,16,33], three from the Middle East[4,14,26] and one from South Africa[36]. These have been demonstrated in Table 1. Depression was the most frequently reported theme across all the studies, followed by anxiety and stress (Table 7). A variety of diagnostic tools were used across the studies, which reflects the diverse clinical practices across different countries.

Based on the identified data, PTB women from the Mediterranean region (Greece, Italy, Turkey and Israel) may be more prone to depressive symptoms in comparison to BAME women with PTB in Australia and the United States. The pooled odds ratio (OR) and its respective 95%CIs appear credible for PTB BAME women experiencing a significantly higher prevalence of depression post-parturition, although the mental health symptoms appear to reduce over time.

The pooled SMD of anxiety within United States was 1.12 with 95%CI of 0.58-1.66 whilst the pooled SMD of the Mediterranean region (Greece, Italy, Turkey) was 0.66 with a 95%CI of 0.37-0.95. The pooled SMD of Australia was 0.35 with a 95%CI of -0.54 -1.23 (Supplementary Figure 2). BAME women with PTB from Australia appear to have less symptoms of anxiety and the main source of the high heterogeneity in subgroup was still from the time points.

In relation to assessing stress, Gray *et al*[28,29] conducted mental health assessments at months 4 and 12, post-parturition. Whilst this appears to be useful follow-up data to evaluate, the outcome measures were analysing 2 different mental health variables of parenting stress and general stress. As shown in Supplementary Figure 4 four studies reported on parenting stress and 2 of them reported on the overall state of stress. The subgroup analysis conducted indicated a lack of heterogeneity between these studies. Mild heterogeneity was identified within the studies included in the stress group alone. The pooled SMD within the parenting group was 0.27 with a 95%CI of 0.15-0.39. In the stress group, the pooled SMD was 1.07 with a 95%CI of 0.51-1.62. Additionally, the symptoms of parenting stress were less severe within the PTB group (Table 7 and Supplementary Figures 4 and 5).

Sensitivity analysis

Studies reporting depression[32] demonstrated women with severe PTB indicated a high SMD at parturition indicating elevated levels of depressive symptoms (Supplementary Figure 6). A combination of worries about very premature babies and the trauma following parturition may further attribute to elevated depressive symptoms. Only Pace *et al*'s study conducted the assessment of questionnaires among the very PTB women group at the birth[32]. Women with a more severe PTB may indicate higher scores of depression, therefore this study was excluded from the sensitivity analysis. After removing Pace *et al*'s study, the heterogeneity in Australia reduced from an I^2 of 87.79% to 52.99%[32]. Therefore, conclusions were adjusted from a pooled SMD of 0.42 (with 95%CI: 0.28-0.56) to 0.34 (with 95%CI: 0.22-0.46). Despite this numerical change, an elevated level of depression among BAME PTB women were visible in comparison to those with a full-term pregnancy (Supplementary Figure 6).

Based on the anxiety studies, Gungor *et al*[35] in particular, reported extremely small OR and a sensitivity analysis was conducted excluding one possible outlier study, as indicated by Supplementary Figure 7. The heterogeneity identified without Gungor *et al*[35] was 0%. Therefore, this study in particular appears to have design and methodological issues limiting generalisability of the findings. As a result, conclusions were amended from an SMD of 0.63 (with 95%CI: 0.35-0.91) to 0.7 (with 95%CI: 0.42-0.98). Therefore, despite the amendment[35], a significantly high prevalence among BAME PTB

Table 7 The thematic synthesis

Themes	Population group
	Women who had a preterm birth
Depression	++++++++++++++++++++++++++++++++
Stress	++++++++++
Anxiety	++++++++++
Parenting stress	+++++
State anxiety	+++++
Trait anxiety	++++
Psychological distress	++
Trauma-related stress	++
Psychological problem	++
Post-traumatic stress disorder	+

women is observed (Supplementary Figure 7).

Publication bias

For studies with a small sample size, the pooled OR is significantly higher based on the funnel plots, therefore, these would be prone to publication bias. To assess this further, Egger's tests were conducted for all studies included within the meta-analysis.

Funnel plots developed within this sample intuitively revealed publication bias (Supplementary Figures 8-10. Egger's test of meta-analysis studies for depression (*P* value = 0.001), indicated the small sample sizes are a source of publication bias (Supplementary Figure 11). The pooled SMD 0.4 and associated CI (0.25-0.56) may have been overrated. Therefore, the TAF method was used to further improve the statistical conclusions (as indicated in Supplementary Figures 11 and 12). The asymmetry of the funnel plot demonstrates the studies could minimally impact publication bias.

Based on the findings demonstrated in Supplementary Figures 11, 3 further studies were imputed to correct the effect size of small studies. The small study effect was eliminated with using the imputation method, and publication bias was corrected (demonstrated in Supplementary Figure 12). The Hedge's g (Supplementary Figure 12) was significantly higher than 0 among the meta-analysis based and imputed studies. After imputing the 3 new studies and removing the publication bias, the statistical conclusion was adjusted from a SMD of 0.4 with 95%CI of 0.25-0.56 to 0.32 (95%CI of 0.18-0.47). Despite the adjustments of publication bias, there was significant evidence that the prevalence of depression among BAME PTB women were higher than those who gave birth at full-term (Supplementary Figures 12 and 13).

Egger's test *P* value for anxiety was 0.198, indicating no publication bias exists (demonstrated in Supplementary Figure 14). Egger's test *P* value for stress was 0.036, indicating a slight publication bias among the studies (demonstrated in Supplementary Figure 15).

Ascertainment bias was considered within the context of the meta-analysis. Due to the lack of required details such as the proportion of different ethnic groups and mental health assessments, it was not possible to assess this numerically. However, within the context of all the studies included in the systematic review portion of the study, it is evident, there could be ascertainment bias as the sampling methods used in the studies comprise of patients who may or may not have a higher or lower probability of reporting mental health symptomatologies. These studies may be subjected to selection bias due to the lack of consistency around frequency of administering the relevant mental health instruments. In essence, studies should have had samples with all ethnicities and races (including Caucasians) to better evaluate the true mental health impact due to PTB. Furthermore, the sample population should have received a standardised set of mental health assessments to determine anxiety, depression, PTSD and other mental illnesses at specific time points during the pre and post-natal period since it is common to have undiagnosed mental health conditions. In addition to this, some studies have had attempted to evaluate the mental health impact after birth at 8 mo although this lacks scientific justification and thereby, epidemiologically insignificant. Furthermore, due to the lack of consistency in assessing and reporting mental health outcomes post-natally, attrition bias may be present. However, a definitive conclusion could not be attained numerically due to limitations in the sample sizes reported.

DISCUSSION

In this meta-analysis, the prevalence rate of depression among PTB BAME mothers was identified to be significantly higher than in full-term mothers with an OR of 1.50 and 95%CI of 29%-74%. Depressive symptoms in mothers and fathers of premature infants were frequently reported in the post-natal period[13]. There may be many causes for this including the social support. Cheng *et al*[13] reported that mothers with non-resident fathers experienced higher rates of depressive symptoms, as did the non-resident fathers included in this study. Lack of social support is likely to be further exacerbated by prolonged hospitalisation of preterm infants and the unique challenges faced by infants the premature following hospital discharge. Additionally, mothers may be admitted to hospital prior to delivery, in some cases for weeks, due to conditions like severe preeclampsia or PROM associated with PTB and hence they may be more isolated than mothers of term infants.

This study defined three sub-groups; assessment timepoint < 1 mo, 1-8 mo and > 8 mo, and indicated that shorter the time after giving birth, the more significant was the depression. Therefore, the provision of mental health support following the immediate post-partum period would benefit patients. Within the first month after delivery, depressive symptoms were significant among PTB mothers; however, by 8 mo and after 8 mo, the increased prevalence of depression was only slightly significant among PTB mothers (OR of 1.17 with 95%CI of 8%-27%; OR of 1.06 with a CI of 1%-12%).

Separation of the infant and the mother is an important and frequent occurrence in PTB, which may explain why mothers of preterm infants are at increased risk of depression. Furthermore, maternal co-morbidities including preeclampsia or recovery from an obstetrics intervention such as a caesarean section may also impact on a mother's ability to bond with her new-born, who maybe in a neonatal intensive care unit (NICU) or special care unit. One study from South Africa[31] demonstrated a high prevalence of depression in mothers of both full term and preterm infants from lower socioeconomic groups. Women from lower socioeconomic groups are likely exposed to greater stressors relevant to the scarcity of resources[31], affecting their mental health.

Adjusting to parenthood is important for all parents. In the case of PTB mothers may not have sufficient time to prepare, which may lead to maternal stress[47]. Familiarity with the situation, possibly by having had a previous preterm infant, and predictability of birth outcome have been found to reduce stress and anxiety[47]. Medically indicated preterm delivery may have been planned, for example, in multiple pregnancies or mothers with diabetes and thus, predictable. Therefore, it is possible that those mothers experience less stress than those who give birth following an acute spontaneous onset preterm labor. In addition to mental preparation, the former group of parents of preterm infants may have had time to visit the NICU and speak with neonatologists to gain further information and this may reduce anxiety following birth.

Parenting stress is found to be higher in mothers of preterm infants at one year[29]. This relationship may by predicted by maternal depression as well as impaired parent and infant interactions[29]. Interestingly, parenting stress is not significantly different in mothers of preterm or full-term infants in early infancy[28], suggesting all mothers require support in the immediate post-partum period to reduce parental mental health but prolonged provision of such support is important in managing PTB mothers.

Increased and unexpected medical interventions associated with PTB, including painful corticosteroid injections or the use of magnesium sulphate. Mothers may have additional intimate examinations and the need for emergency procedures such as caesarean sections, which may negatively impact a mother's physical and mental health. These may exacerbate the underlying stress faced by a PTB mother and her partner; their feelings of anxiety and stress are compounded in some circumstances by the lack of preparedness and loss of control. Together, these experiences may explain why mothers and fathers of preterm infants have greater levels of stress[29] and depression[13].

Cheng *et al*[13] conducted the comparison between fathers and mothers suffering as a result of PTB among Hispanic, Non-Hispanic White, Non-Hispanic Black and Non-Hispanic as well as other races. Gueron-Sela *et al*[30] on the other hand focused on depression and stress symptomatologies among Bedouin and Jewish women. Based on Gueron-Sela *et al*'s findings, Bedouin women experienced the highest level of depression[30]. In comparison to these, Rogers *et al*[42] compared the Caucasian and African American PTB patients that indicated a lack of significant differences between the two groups. Ballantyne *et al*[37] conducted their study on Canadian PTB women which included immigrant women. However, immigrant's status had no contribution to the differences in mental health disorders or symptomatologies.

The mental health impact on those with PTB could be exacerbated due to understandable feelings of helplessness and hopelessness, and low mood is commonly reported by these women. On the contrary, Jotzo and Poets[14] demonstrated PTB could lead to traumatising effects on parents with 49% of mothers reporting traumatic reactions even after a year. Muller-Nix *et al*[15] demonstrated this correlation of traumatic stress and psychological distress between mother and child. Pierrehumbert *et al*[16] indicated post-traumatic stress symptoms after PTB was a predictor of a child's eating and sleeping problems. Similarly, Solhaug *et al*[17] found that parents, who had hospital stays following a PTB requiring NICU, demonstrated high levels of psychological reactions that required treatment.

Perinatal mental health around suicidality or suicidal ideation should be considered as a priority to be addressed among BAME women, which is vital in particular within the United Kingdom. BAME women are at a higher risk of suffering from mental health disorder in comparison to Caucasian women in the United Kingdom and they are less likely to access healthcare support. This is particularly true for women of Pakistani and Indian background. Additionally, Anderson *et al*[63] reported prevalence and risk of mental health disorders among migrant women. These factors should be considered by those treating clinical groups. In addition to the timepoint, we also considered the impact of population. It remains unclear whether the prevalence rate of depression varies after PTB in different ethnic groups. Gulamani *et al*[64] have found the depressive symptoms of women with PTB may be associated with race and culture, but further evidence is lacking. Due to the higher risk of mental health symptoms around the time of PTB, this data may help the health service providers to focus on delivering timely support to the BAME mothers with PTB.

Interestingly, alcohol consumption and substance abuse that are linked to worsening of mental health and poor pregnancy outcomes were not identified within the literature pertinent to BAME population in the scope of this study[65-70].

Similarly, substance abuse among pregnant women increases the risk of PTB and the association of mental illness among the BAME population[71,72]. Holden *et al*[72] demonstrated self-reported depressive symptoms associated with a group of 602 BAME and Caucasian pregnant women that had substance abuse and were subjected to intimate partner violence. This study used the EPDMS which demonstrated elevated levels of depressive illness that required clinical diagnoses and treatments at a mental health care facility. Additionally, women abuse screening tool was used to evaluate relationship issues and those needing appropriate support was referred to social services[71,72]. There is limited information available around substance abuse and partner violence associated with mental health among BAME women. Research conducted within this area appears to lack consistency and this makes systematic evaluation of cultural paradigms relevant to BAME women and the direct association with PTB and mental health difficult, given the complexity of these issues.

Limitations

Heterogeneity of studies gathered within this review challenged the evidence synthesis. Studies identified reported on mental health outcomes without a clear distinction mostly between mental health symptomatologies and psychiatric comorbidities. Timelines for administering mental health instruments and other tools such as talking therapies were not unified across all studies. Collectively, these are design and methodological flaws influencing heterogeneity. Studies were excluded if they discussed quality of life as this does not demonstrate the identification or reporting of mental health outcomes such as pre or postnatal depression, anxiety, psychosis and other mood disorders.

CONCLUSION

PTB has a significant association with depression, anxiety and stress symptoms in new mothers during the immediate postpartum period. The mental health symptoms are more significant in very preterm mothers than non-very preterm mothers. However, the effect of PTB on the incidence of depression and other mental health outcomes is unclear among different ethnic groups and therefore more studies are needed to explore this.

This study identified a methodological gap to evaluate disease sequelae between PTB and mental health among BAME populations. This important facet should be considered in future research studies, which requires the involvement of multidisciplinary teams. Most included studies did not indicate a publicly available protocol, and availability of such would have assisted in reducing potential biases during study selection in this systematic review to improve sampling techniques and the subsequent data analysis. Future PTB research will be benefited by Population Intervention (s) Comparator and Outcome (s) based reporting to address true mental health impact within BAME populations. The evidence gap that exists from multi-stakeholder needs to be filled to improving patient care. The development of a classification framework for healthcare systems to better assess BAME women at risk with PTB and mental health outcomes would be beneficial. Including cultural adaptation methods as well as training of healthcare professionals will help to manage patients' expectations with the required sensitivities. Similarly, cost-effectiveness and long-term sustainability should be considered when developing a suitable framework.

It is also vital to acknowledge health inequalities and avoidable disparities should be addressed as a matter of urgency. Maternal care should have integrated methods of working with mental health care professionals and a culturally adapted and sensitive specialist service to support BAME women after a PTB may improve the patient outcomes. It is important to improve quality of care received by vulnerable BAME women such as those who are refugees or migrants and do not speak English. Equally, mental health services should work more cohesively within the women's health in the community setting and training should be offered to all healthcare professionals to provide a personalised care.

ARTICLE HIGHLIGHTS

Research background

Preterm birth (PTB) is a complex clinical condition contributing to significant maternal morbidity and a leading cause of neonatal morbidity and mortality. Therefore, potential mental health impact of PTB on women is an important clinical and social sequel that requires further understanding.

Research motivation

Existing research primarily reports the mental health impact of women with PTB within the Caucasian population. There remains a paucity of research on the ethnic minority populations. Thus, we aimed to assess the current research gap relevant to ethnic minorities to inform future research that could aid with improving patient and clinical reported outcomes.

Research objectives

(1) We aimed to describe the prevalence of mental health conditions and/or symptoms reported by women with PTB experiences within the ethnic minorities; and (2) We also extended our study to report the commonly used methods of mental health assessments to charactertise the identified mental health conditions and/or symptoms with the pooled sample.

Research methods

A systematic methods protocol was developed, peer reviewed and published in PROSPERO (CRD42040210863). Multiple databases were used to extract relevant data for a meta-analysis. A trim and fill method was used to report publication bias in addition to an Egger's test. I^2 was used to report heterogeneity.

Research results

From a total of 3516 studies identified, we included 39 studies that met the inclusion criteria. Depression was the most commonly reported mental illness among PTB mothers in comparison to those who had a full-term pregnancy. The subgroup analysis demonstrated depression to be time-sensitive relative to the PTB. Stress and anxiety were also prevalent among PTB mothers as opposed to full-term mothers.

Research conclusions

There appears to be a mental health impact among PTB mothers from ethnic minorities. This is an important aspect to consider for maternity care services to improve the quality care provided to PTB women.

Research perspectives

Future researchers should consider inclusion of all ethnicities and races to ensure generalizability of any findings to all mothers that could truly improve maternity care services.

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FOOTNOTES

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LETTER TO THE EDITOR

Sodium selenite may be not the optimal speciation as an effective therapy for arsenic-induced anxiety-/depression-like behavior

Xiao-Hua Ren, Xiao-Xuan Wang, Lian-Ping He

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Abstract

Major depressive disorder is a serious and prevalent neuropsychiatric disorder, affecting more than 350 million people worldwide. Here, sodium selenite (SS) was selected as the selenite supplement to improve the behavior in a mouse model of depression induced by As. SS may be not the optimal speciation for selenite supplementation and the source of the SS used in the study was not disclosed. There are many mouse models of depression and anxiety; however, in the current study, a classical mouse model of depression was not used. Thus, several questions still need to be further discussed. Taken together, the results indicate that SS may be not the optimal speciation as an effective therapy for As-induced anxiety-/depression-like behavior.

Key Words: Depression; Arsenic; Major depressive disorder; Sodium selenite; Optimal speciation

Core Tip: Sodium selenite (SS) may be not the optimal speciation for selenite supplementation and the source of the SS used in the study was not disclosed. There are many mouse models of depression and anxiety; however, in the current study, a classical mouse model of depression was not used.

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TO THE EDITOR

Major depressive disorder is a highly disabling psychiatric syndrome associated with deficits of specific subpopulations of cortical GABA-ergic interneurons[1,2]. We were pleased to read the article by Samad *et al*[3]. Their work highlights that Se, as a dietary source and/or supplement, is an effective therapy for As poisoning and its associated disorders. Furthermore, this study provides important findings regarding the prevention and treatment of anxiety disorders and depression. However, we believe there are several issues with the research design that need to be addressed. First, the use of sodium selenite (SS) as the Se supplement to improve the behavior of depression-like behavior in mice induced by As. Second, the use of the mouse model of depression. There are many mouse models of depression and anxiety; however, the authors chose not to use a classical mouse model of depression. As a result, questions remain regarding the validity of the study.

The main weakness of the study is SS as a means of Se supplementation. In particular, Se biological activity is dependent on its metabolic disposition; for example, absorption and excretion. It was observed that selenomethionine (SeMet) in organic form is more rapidly and completely (98%) absorbed than SS (84%) in inorganic form, and that liver uptake occurs faster after intake of organically bound Se than that of inorganic Se (SS)[4,5]. Moreover, various excretion indices confirm that SeMet has lower excretion (4%) than SS (18%)[4]. SS was also reported to induce DNA damage, particularly DNA strand breaks and base damage[6]. Se nanoparticles can also be used as a means to supplement Se. A recent study found Se nanoparticles to be a Se species with novel biological activities, bioavailability, and low toxicity[7]. Therefore, SS may not be the optimal speciation for selenite supplementation and as the source of the SS used in the study was not disclosed, questions remain.

The failure to select a suitable mouse model for depression was another issue with the study. A chronic unpredictable mild stress (CUMS) mouse model of depression is widely used[8]. As-induced depressive-like behavior cannot be used as a model of depression. Whether dietary Se can alleviate symptoms of the CUMS mouse model of depression needs to be further determined. In addition, dietary Se supplementation for depression in large-scale clinical trials is also necessary. As-induced depression-like behavior in mice may be associated with a large number of inflammatory factors and neurotransmitter changes that were not explored in this study.

Conclusion

Overall, SS may be not the optimal speciation for selenite supplementation and the source of the SS used in the study was not disclosed. The failure to select a suitable mouse model for depression was another issue, which the authors need to address.

FOOTNOTES

Author contributions: Ren XH and He LP contributed to the conception of research; Ren XH and Wang XX wrote the letter; Wang XX and He LP contributed to the revision of the letter; all authors approved the final manuscript for submission.

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LETTER TO THE EDITOR

Beneficial for mental health, exercise more or less?

Wen-Jie Yan, Fan Zhang, Hui Ouyang, Chen-Qi Xing, Wei-Zhi Liu

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Abstract

Regular physical activity may improve mental health during the pandemic by reducing inflammatory responses. However, overtraining or prolonged exercise training may adversely affect mental health.

Key Words: Physical activity; Exercise; Mental health; Runner's high

Core Tip: Several empirical studies have provided evidence regarding coronavirus disease 2019 (COVID-19)'s deleterious effects on people's physical and mental well-being. Those who exercised frequently before the COVID-19 pandemic, such as professional athletes, may suffer from significant imbalance, which can be as uncomfortable as withdrawal symptoms. Further research should focus on groups with high physical activity levels.

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TO THE EDITOR

We recently reviewed the article "Physical activity and mental well-being during the coronavirus disease 2019 (COVID-19) pandemic," issued in Volume 11 No. 12 of *World J of Psychiatry*. The authors assert that the COVID-19 pandemic may have deleterious effects on physical and mental well-being, including a growing level of angiotensin-converting enzyme 2 (ACE-2), associated with highly inflammatory effects[1].

Furthermore, they highlighted the significance of regular physical activities that maintain individuals' mental health during the pandemic. The conclusion should be adequately considered. Additionally, several empirical studies have provided evidence supporting this opinion, along with our comments in this correspondence.

Previous studies have shown that quarantine during an epidemic can be detrimental to mental health. In particular, it may lead to an increased probability of depression, anxiety, or post-traumatic stress disorder symptoms[2,3]. Moreover, the pandemic presents an explicit threat of suicide risk for some individuals[4]. During the pandemic, Brazilian undergraduate students had a higher rate of suicide risk than they had in the past[5]. Notably, one of the most visible negative changes the pandemic forced upon the public owing to the isolation policy, is increased sedentary behavior and reduced physical activity[6]. According to a multi-country cross-sectional analysis involving 8424 adults[7], negative changes in exercise behavior were associated with worse mental health and low happiness during the early COVID-19 restrictions compared to pre-pandemic restrictions. Research has proved that even home-based physical activities, such as cleaning the floor, bathing pets, or singing with children, can meet the WHO's recommendations when it is necessary to stay at home[8].

Abdelbasset *et al*[1] concluded in the article that regular physical activities might improve mental health during the pandemic by reducing inflammatory responses. However, they also noted that overtraining or prolonged exercise may adversely induce mental disorders. The endorphin hypothesis is a part of the physiological mechanism that explains the effect of exercise on mental health. Athletes who endured prolonged stress and overtraining may experience a feeling of well-being under the impact of endorphin; this phenomenon was acknowledged as "runner's high"[9]. Recently, Pearce *et al*[10] conducted a meta-analysis to explore the dose-response association between physical activity and incident depression in adults. They noted an inverse curvilinear association, in which the benefits were maximized when the frequency of activity changed from none to some. Additionally, the differences in the risk of depression were most significant with low doses of physical activity. Those who exercised frequently before COVID-19, such as professional athletes, may suffer from more imbalance, which is as uncomfortable as withdrawal symptoms. We call for further research focusing on these groups, enriching the data available about populations with higher physical activity levels.

FOOTNOTES

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LETTER TO THE EDITOR

Magnesium may be an effective therapy for Alzheimer's disease

Dao-Yun Lei, Jie Sun

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Abstract

Magnesium deficiency in serum or the brain of Alzheimer's disease (AD) patients has been shown to be associated with AD. Current research suggests that supplementing or restoring magnesium may be a novel approach to AD treatment. However, the physiological properties of magnesium make such treatment difficult. It is undeniable that magnesium may be an effective therapy for AD.

Key Words: Alzheimer's disease; Magnesium; Therapy; Deficiency

Core Tip: Magnesium deficiency in serum or the brain of Alzheimer's disease (AD) patients has been shown to be associated with AD. However, the physiological properties of magnesium make such treatment difficult. Undeniably, magnesium may be an effective therapy for AD.

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TO THE EDITOR

Alzheimer's disease (AD) is the most common dementia characterized by the decline of cognitive function in the elderly. The accumulation of β-amyloid plaques and the existence of neurofibrillary tangles are the pathological bases for the dysfunction of various signaling pathways in the nervous system[1]. Since the pathogenic mechanism of AD is still not clear, its treatment approaches are unlikely to be meaningfully effective. Several approved drugs ameliorate some of the symptoms of AD, but no

current interventions can modify the underlying disease mechanisms[2,3]. We read the interesting article by Xiong *et al*[4], which was published in *World Journal of Psychiatry*. Their study found that magnesium L-threonate alleviated neuronal apoptosis by inhibiting oxidative stress, especially in the hippocampus. Although the research work revealed a potential scheme for the treatment of AD, we still believe that some views deserve further consideration and look forward to receiving the reply from the authors.

Admittedly, magnesium is one of the most abundant cations in the intracellular environment after potassium. Mg^{2+} is tightly regulated and kept at basal levels by normal Mg^{2+} intake, absorption, and metabolism under physiological conditions. Total magnesium levels in the hippocampus of AD patients decreased by 18% compared with that of normal subjects[5]. Although the presence of magnesium deficiency in patients with AD is notable, its severity may be underestimated. The concentration of serum Mg^{2+} in healthy people ranges from 0.70 mM to 1.05 mM[6]. Mg^{2+} deficiency is generally determined by measuring the total serum Mg^{2+} concentration, but it cannot accurately reflect the concentration of magnesium in the human body. Most Mg^{2+} is stored in bone, muscle, and soft tissue, and the proportion of serum Mg^{2+} is very low. Even if the human body is in a serious state of Mg^{2+} depletion, serum magnesium may also be in the normal range. Although the magnesium concentration in AD patients is reduced, the degree of deficiency cannot be accurately evaluated. It is not only difficult to evaluate magnesium deficiency, but also a reasonable supplement of magnesium. Slutsky *et al* found that following long-term magnesium supplementation, Mg^{2+} concentration in cerebrospinal fluid only increases by 15%[7]. On one hand, systemic magnesium is closely regulated by renal function. On the other hand, the blood-brain barrier separates the brain from the daily fluctuations of blood magnesium. Hippocampal synapses are very sensitive to small changes in extracellular Mg^{2+} concentration (increasing the concentration of magnesium by 15% can increase the synaptic density by 50%)[8]. Encouragingly, compared with other Mg^{2+} compounds (such as magnesium chloride, magnesium citrate, and magnesium gluconate), dietary intake of magnesium L-threonate could significantly increase Mg^{2+} levels in the brain[4]. Therefore, restoring brain magnesium may be a potential way to treat cognitive impairment in patients with AD.

Conclusion

In summary, magnesium may be a novel therapeutic strategy for AD-induced cognitive impairment. However, numerous clinical studies are still needed to confirm the clinical application of magnesium.

FOOTNOTES

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LETTER TO THE EDITOR

Why do we not reverse the path? Stress can cause depression, reduction of brain-derived neurotrophic factor and increased inflammation

Angelo Emilio Claro, Clelia Palanza, Marianna Mazza, Alessandro Rizzi, Linda Tartaglione, Giuseppe Marano, Giovanna Muti-Schuenemann, Marta Rigoni, Paola Muti, Alfredo Pontecorvi, Luigi Janiri, Gabriele Sani, Dario Pitocco

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Abstract

The aim of this paper is to describe the direction of the link between stress, depression, increased inflammation and brain-derived neurotrophic factor (BDNF) reduction. We hypothesize that severe stress or prolonged stress can be the driving factor that promote the onset of depression. Both stress and depression, if not resolved over time, activate the production of transcription factors that will switch on pro-inflammatory genes and translate them into cytokines. This cascade fosters systemic chronic inflammation and reduced

plasma BDNF levels. Since people with depression have a 60% increased risk of developing type 2 diabetes (T2D) and show high levels of inflammation and low levels of BDNF, we hypothesize possible reasons that might explain why T2D, depression and dementia are often associated in the same patient.

Key Words: Depression; Inflammation; Brain-derived neurotrophic factor; Type 2 diabetes mellitus; Dementia; Psychological stress

Core Tip: This paper proposes a distinct interpretation of the link that exists between increased inflammation and reduction of brain-derived neurotrophic factor (BDNF). We describe why most of the people with altered inflammatory status and low BDNF do not automatically have depression, and why some people become depressed without diverging from average serum levels of these markers. We also suggest a reason why the use of tumor necrosis factor-α inhibition has no effect as a therapy in patients with resistant depression and high inflammatory levels.

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TO THE EDITOR

We read with great interest the work of Porter and O'Connor[1] describing how brain-derived neurotrophic factor (BDNF) and inflammation are considered key players in the pathogenesis of depression.

We found the ideas of our colleagues very interesting and sharable. In this letter, we would like to suggest a different way to evaluate the link between BDNF, inflammation and depression. Following the "*social signal transduction theory of depression*"[2] we consider stress as the main cause of development of depressive symptoms; depression, in turn, is able to induce increased inflammation and reduced BDNF production.

It has been demonstrated that when a person lives in an environment characterized by numerous stressful situations (physical and social threat, or internal perceived stressors, like internal thoughts) that are severe or prolonged over time and he is not able to eliminate or psychically rework them, he displays a greater risk of developing depression[2,3].

Stress and depression, if not resolved over time, can activate brain regions connected with pain. These areas will project into lower regions that regulate inflammation *via* the hypothalamus–pituitary–adrenal axis and the sympathetic nervous system (SNS)[3]. The SNS, in the first stage of modulation, will set up the production of epinephrine and norepinephrine. These neurotransmitters will activate the production of transcription factors that will switch on pro-inflammatory genes and translate them into cytokines that will foster major inflammation or Systemic Chronic Inflammation (SCI)[2]. If this state is sustained for years, there is a high risk of developing inflammation-related disorders, quickened biological aging, infections, and premature mortality[4].

Moreover, stress and chronic inflammation are capable of inducing reduction of BDNF and indeed plasma BDNF levels are significantly lower in depressed patients compared with matched controls[5].

These considerations might explain why most of the people with altered inflammatory status and low BDNF do not automatically develop depression, and why some people become depressed without presenting the serum levels of either of the two markers far from the average[1]. It is neither the reduced BDNF nor the increased inflammation that induces depression, but rather it is stress itself that is able to promote the onset of depression. Moreover, if stress and depression last over time they can lead to increased inflammation and decreased BDNF[1]. Following this reasoning, it appears clearer why pharmacological intervention with tumor necrosis factor-α antagonist as an anti-depressant treatment in patients with resistant depression and high inflammation does not give positive results, while the same type of intervention is quite effective in treatment resistant patients with high inflammation and without depression[6,7]. That is because in patients with inflammatory diseases inflammation recognizes physical causes as an origin while in patients with depression it recognizes stress as the underlying

cause of inflammation. If patients are not able to eliminate the source of stress, this will continue to generate depression, inflammation and reduced BDNF.

The article by Porter and O'Connor[1] allowed us to move even further and to hypothesize a possible link between stress, depression, inflammation, development of type 2 diabetes (T2D), BDNF reduction, and dementia.

Patients suffering from depression have high levels of stress which lead them to overeating, in particular food rich in carbohydrates or snacks, because this high-calorie food acts as a self-medication and is able to increase serotonin levels[8,9]. These patients are accordingly more prone to develop overweight and obesity, the strongest risk factors for the onset of T2D[10-12]. It has been showed that people with depression have a 60% increased risk of developing T2D[13] and 25% of patients with T2D have depression[14]. Nevertheless, depression in T2D patients is frequently unrecognized and therefore not treated[15-17].

Thus depression, untreated for years, contributes to maintain T2D and both depression and T2D can lead to increased SCI and decreased BDNF. In this way, the reduction of neurogenesis and synaptogenesis, a reduction of the vascular bed and vascular support and neuroinflammation are determined, finally leading to an increasing risk of dementia onset. Low BDNF levels are present in dementia patients[18,19] and patients with T2D are approximately two to four times more likely to develop dementia than individuals without T2D. These associations might explain why T2D, depression and dementia are often associated in the same patient[20-23]. We are aware that these are hypotheses, but we can consider them as useful reflections inspired by the article by Porter and O'Connor[1] to be validated in future studies.

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FOOTNOTES

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