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MINIREVIEWS

Legacy of neuropsychiatric symptoms associated with past COVID-19 infection: A cause of concern

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Abstract

Although primarily affecting the respiratory system, growing attention is being paid to the neuropsychiatric consequences of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. Acute and sub-acute neuropsychiatric manifestations of coronavirus disease 2019 (COVID-19) disease and their mechanisms are better studied and understood currently than they had been when the pandemic began; however, many months or years will be necessary to fully comprehend how significant the consequences of such complications will be. In this editorial, we discuss the possible long-term sequelae of the COVID-19 pandemic, deriving our considerations on experiences drawn from past coronaviruses' outbreaks, such as the SARS and the middle east respiratory syndrome, and from the knowledge of the mechanisms of neurotropism and invasiveness of SARS-CoV-2. Acknowledging the global spread of COVID-19 and the vast number of people affected, to date amounting to many millions, the matter of this pandemic's neuropsychiatric legacy appears concerning. Public health monitoring strategies and early interventions seem to be necessary to manage the possible emergence of a severe wave of neuropsychiatric distress among the survivors.

Key Words: COVID-19; Neuropsychiatric symptoms; Neuropsychiatric sequelae; Mental health; Post-traumatic stress disorder; Depression

Core Tip: While acute neuropsychiatric manifestations of coronavirus disease 2019 (COVID-19) are the object of study, far less is known about long-term neuropsychiatric sequelae of COVID-19 infection. Much of the knowledge about this topic can be drawn from past coronaviruses outbreaks and from the study of the mechanisms through which severe acute respiratory syndrome coronavirus 2 harms the central nervous system. A relevant wave of both psychiatric (anxiety and depressive disorders, post-traumatic syndromes) and neurological symptoms could be expected. There will be a vital need for monitoring and early intervention to minimize this potential burden of neuropsychiatric distress.

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INTRODUCTION

Starting December 2019, several cases of pneumonia of unknown etiology were reported in Wuhan, China. A novel coronavirus was identified as the cause of such illnesses, and on January 12, China made public the gene sequence of the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) coronavirus[1]. On January 30, 2020, the World Health Organization (WHO) declared the outbreak of coronavirus disease 2019 (COVID-19) a Public Health Emergency of International Relevance, and on March 11, 2020, the same organization proclaimed the beginning of the COVID-19 pandemic[1]. It was the start of the global crisis we are still struggling with[2].

Coronaviruses are single-stranded RNA viruses; in the past, they have been responsible for two well-known epidemics: (1) The 2002 SARS, caused by SARS-CoV-1; and (2) The 2012 Middle East Respiratory Syndrome (MERS). Like other coronaviruses, the newly identified SARS-CoV-2 affects the respiratory tract, usually causing mild and self-limiting symptomatology similar to the common cold. In susceptible individuals, the virus can reach the lower respiratory tract causing pneumonia and severe acute respiratory syndrome[3].

However, COVID-19 does not only induce a respiratory syndrome, but it can elude the immune response and spread to distant apparatuses, as the renal and cardiovascular[4] ones. In particular, like SARS and MERS, COVID-19 has been shown to be neuro-invasive[6]. A growing body of literature shows that 27% to 41% of COVID-19 patients may present neuropsychiatric complications during the acute stage of the illness[7]. The most reported ones are anosmia, ageusia, headache, confusion, agitation, cerebrovascular events, encephalopathies, anxiety, depressed mood, impaired memory and insomnia[8-10].

On the contrary, far less is known about long-term neuropsychiatric sequelae of COVID-19 infections [11]. The delayed effect of this pandemic, particularly that on the population's mental health, will require many months, or even years, to be fully acknowledged. Considering that many millions of people have been affected by COVID-19, this becomes a matter of deep concern. Given the aforementioned observations, this editorial aims at discussing the possible long-term effects of the COVID-19 pandemic on neuropsychiatric health.

LONG-TERM NEUROPSYCHIATRIC SEQUELAE: A CAUSE OF CONCERN

Most of the hypotheses about COVID-19 long-term effects on the nervous system can be drawn from evidence on SARS-CoV-1 and MERS neuropsychiatric sequelae. As to SARS-CoV-1, high rates of depression (39%), pain disorders (36.4%), panic disorder (32.5%), and obsessive-compulsive disorder (15.6%) were reported among survivors. The mean time of onset of such complications ranged 31 mo to 50 mo post-infection[12]. According to another study, one year after the SARS-CoV-1 outbreak, 64% of the survivors showed some sign of psychiatric morbidity[13], while 30 mo after the outbreak, the prevalence of any psychiatric disorder was 33.3%[14]. A meta-analysis reported rates of neuropsychiatric sequelae in SARS-CoV-1 and MERS survivors raging 10% to 20%; the symptomology most often displayed was insomnia, anxiety, depression, fatigue, and memory impairment[7].

Moreover, an examination of the literature's data about the relationship between other non-epidemic coronaviruses and neuropsychiatric consequences can be helpful. Human coronavirus HCoV-NL63 infection was associated with mood disorders and suicide attempts[15]. Furthermore, exposure to viral infections, both in utero and during child development, has been linked to an increased risk for schizophrenia[16,17]. In this regard, when compared to controls, an increase in antibodies for four human coronavirus strains was found in patients with a recent psychotic onset[18]. In light of this, such data suggest a possible relation between coronavirus infection and psychosis that could emerge in the long

run from SARS-CoV-2.

Given the insight drawn from other coronaviruses and considering the mechanisms through which COVID-19 invades and damages the central nervous system (CNS), we can speculate on the long-term neuropsychiatric symptoms this virus may cause. Coronaviruses can spread to the CNS *via* retrograde axonal transport, from the olfactory nerve, or *via* the hematogenous route[19] (see Figure 1).

Once in the CNS, the latent virus can be hosted by both neural and immune cells, contributing to the onset of delayed neuropsychiatric complications. There are different pathways through which coronaviruses can affect the CNS, including damages through direct infections, immune or hypoxic damage, and direct binding to the ACE2 enzyme, which is highly expressed by neurons and glia[20]. These pathways were detected both in patients and in experimental animals affected by SARS-CoV-1 [21]. Several reports on SARS-CoV-1 and MERS discussing sub-acute demyelinating complications and neuromuscular and neurodegenerative diseases have been published[19,22,23]. Considering the neurotropism of all coronaviruses, we can imagine similar mechanisms and consequences also in COVID-19 patients.

However, SARS-CoV-2 has also shown different mechanisms of neuroinvasiveness. Besides from ACE-2, the neuropilin-1 protein was identified as an additional mediator, facilitating the virus entering the cells[24,25]. This protein is highly expressed in the brain, representing an element of concern, particularly for long-term cognitive sequelae of COVID-19 infections[26]. Early studies showed that cognitive impairment, frequently reported during acute infection, could also persist after recovery. A paper examining patients at a median of 85 d after acute illness showed that 78% of the group reported sustained cognitive difficulties. These deficits did not correlate with depressed mood, fatigue, hospitalization, type of treatment received, acute inflammation, or viremia. If these effects were to extend over time, the impact of SARS-CoV-2 on cognitive functioning might be of great concern[27]. Studies to shed light on SARS-CoV-2 specific neurotropism and its possible neurological consequences are still active [28].

The emergence of post-traumatic stress disorder (PTSD) associated with a prior COVID-19 infection should also be considered. This is because the experience of a potentially severe disease, such as COVID-19, is considered a traumatic event[29]. On the one hand, the infection can lead to brain vulnerabilities that could increase the risk of developing clinically relevant psychological distress. On the other hand, profound stressors linked to the infection, such as medical interventions or isolation, could play a critical role in the development of PTSD as seen for other diseases[30]. This was also demonstrated after the SARS-CoV-1 epidemic, with a 55% rate of PTSD detected among survivors[12]. There are many reports about the emergence of PTSD after a COVID-19 acute infection, and many more are probably yet to come[31,32].

CONCLUSION

As said, long-term neuropsychiatric complications of COVID-19 infection will remain covert for several months or possibly even several years. Given the global spread of the COVID-19 infection, even if only a small part of the affected people will develop delayed neuropsychiatric sequelae the public health burden generated by these complications will be significant. Thus, we could expect a "crashing wave" [33] of COVID-19 neuropsychiatric consequences, with a plausible relevant impact on countries healthcare resources and on healthcare workers[34] as well. These consequences might be even more severe for those who were already suffering from a psychiatric or neurological disorder[35]. These consequences, hence, might be both psychiatric and neurological. Psychiatric long-term consequences could be observed in the form of an escalation in PTSD, depression and depressive symptoms, anxiety disorders, and perhaps even more severe mental illnesses such as psychosis. A variety of neurological sequelae have also been hypothesized.

This editorial will hopefully encourage many future considerations. Firstly, clinicians should be aware of the distant burden of neuropsychiatric distress that is potentially linked to COVID-19 infections. Careful attention should be given to survivors, in order to prevent or anticipate possible complications. It might be essential to mention an eventual wave of suicidality as the endpoint of unrecognized depressive syndromes or other severe mental distress. A patient's cognitive examination should also be included in long-term monitoring, exploring executive functions, memory, attention, and information processing.

As possible strategies of intervention against this wave, implementation of telehealth and digital medicine should be cited. Although these are promising and effective ways to deliver health assistance, mainly if applied for mental health purposes, they are still underused in many countries[36]. Research carried out during the pandemic's acute outbreak shows promising results in this field[37].

In the event of the likely impact of neuropsychiatric sequelae on the health system, it would be crucial to focus our efforts on strong-effectiveness interventions. Depression, anxiety, PTSD, and other emerging issues should be addressed with evidence-based and easy-delivered treatments. Besides from telehealth platforms, group interventions should also be implemented in response to the expected increase in psychological needs.

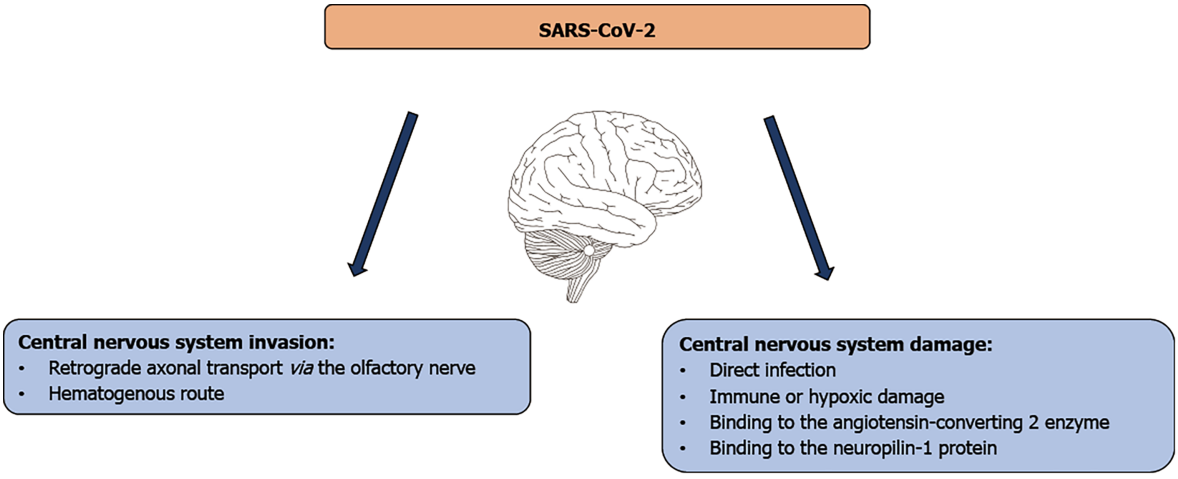

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Figure 1 Summary of severe acute respiratory syndrome coronavirus 2 mechanisms of neuroinvasiveness and damage.

As treatment approaches for COVID-19 neuropsychiatric consequences, we would imagine an important role for physical therapies and neuromodulation techniques, such as transcranial magnetic stimulation or transcranial direct current stimulation. Even if there is still no clear evidence, possible applications of neuromodulation techniques have been underlined[38]. Proposed pathways include regulating anti-inflammatory responses through dorsolateral prefrontal cortex stimulation and improving cognitive outcomes and fatigue. Moreover, the body of literature on the effectiveness of those techniques in many neuropsychiatric disorders has been growing, projecting a promising role for the management of long-term COVID-19 psychiatric sequelae[39,40].

In conclusion, all these considerations underline the need for a watchful follow-up on neuropsychiatric symptoms related to COVID-19 in order to understand the trajectories of possible neuropsychiatric outcomes in the future. Careful research, based mainly on longitudinal and prospective studies will be vital in this field, both for clinical and scientific purposes.

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MINIREVIEWS

Role of high mobility group box protein 1 in depression: A mechanistic and therapeutic perspective

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Abstract

As a common and serious psychiatric disorder, depression significantly affects psychosocial functioning and quality of life. However, the mechanism of depression is still enigmatic and perplexing, which limits its precise and effective therapeutic methods. Recent studies demonstrated that neuroinflammation activation plays an important role in the pathophysiology of depression. In this respect, high mobility group box 1 (HMGB1) may be a possible signaling inducer of neuroinflammation and can be a potential mechanistic and therapeutic target for depression. Herein, we review recent studies on the mechanistic and therapeutic targets of HMGB1 in depression and propose potential perspectives on this topic.

Key Words: Neuroinflammation; Depression; High mobility group box 1; Mechanism; Review; Perspective

Core Tip: Limited reviews in the literature contributed to the high mobility group box 1 (HMGB1) in depression. This review provides a comprehensive mechanistic and therapeutic perspective on this topic and proposed that the future perspectives of HMGB1 in depression should be understanding the full signaling pathway of HMGB1 in depression, deeply investigating potential HMGB1 related therapeutic targets, and exploring the role of HMGB1 in depression and combined disease.

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INTRODUCTION

Depression is one of the most common, serious, and costly psychiatric disorders that affect psychosocial functioning and quality of life[1]. The aggregate point, one-year, and lifetime prevalence of depression in the community is about 12.9%, 7.2%, and 10.8%, respectively[2]. Crucially, the number of people suffering from depression worldwide has increased from 172 million in 1990 to 258 million in 2017, with an increase of 49.86%[3,4]. The stress of the outbreak of coronavirus disease 2019 and interpersonal isolation makes it even more people suffer depression recently[5-7]. However, the mechanism of depression is still enigmatic and perplexing, which limits its precise and effective therapeutic methods [8,9]. Recent studies demonstrated that the activation of neuroinflammation might play an important role in the pathophysiology of depression[10]. High mobility group box 1 (HMGB1), a chromosomal protein, has been found to perform an essential job in the neuroinflammation of several central nervous system diseases, which might also be a potential therapeutic target[11-15]. Rana *et al*[11] proposed that HMGB1-mediated neuroinflammation in depression could have insights into the pathogenesis understanding and therapeutic promise. Herein, with recent studies concerning this topic, we review the role of HMGB1 in depression and propose several potential key mechanistic and future therapeutic perspectives.

RESEARCH PROGRESS OF HMGB1 IN DEPRESSION

HMGB1: a potential mechanistic direction in depression

HMGB1 is the most researched protein in the HMGB family for inflammation as innate immune responses[16]. Expressed in nearly all eukaryotic cells, HMGB1 is a kind of chromatin-binding molecule to function in chromatin remodeling in the nucleus under normal physiological situations[13]. Whereas in stressful situations or pathological situations, caused by immune and other cells or cell injury and death, HMGB1 secretes or translates from nuclei to the cytoplasm and eventually excretes or releases to the extracellular milieu, acting as a mediator of inflammation extracellularly[17]. Placing on extracellular milieu, HMGB1 is acknowledged by plenty of binding receptors, mainly including Toll-like receptors (TLRs) and receptors for advanced glycation end products (RAGE), resulting in the expression of proinflammatory response elements and eventually in the inflammatory cascade[18]. The TLRs and RAGE are transmembrane proteins, which are located in the membrane of several cells such as monocytes, macrophages, dendritic cells, and neural cells[12]. For the HMGB1-TLRs pathway (mainly including TLR2 and TLR4), MyD88 dependent and independent pathways were activated, resulting in the simulation of NF-κB and induction of pro-inflammatory response[19]. For MyD88-dependent pathway, MyD88 serves as a domain-containing adaptor for the cytoplasmic Toll/ interleukin (IL)-1 receptor[20]. Stimulated by ligands, MyD88 recruits IL-1 receptor-associated kinase-4 (IRAK-4) to TLRs; and IRAK-1 is phosphorylated and then associates with TRAF6, thereby activating the IKK complex and leading to activation of MAP kinases (JNK, p38 MAPK) and NF-κB[21,22]. The MyD88-independent pathway also mediates the immune response *via* TRIF and TRAF3, leading to recruitment of IKKε/TBK1, phosphorylation of IRF3, and expression of interferon-β[23,24]. A recent study also indicated that the HMGB1-TLR4 pathway could activate Nod-like receptor protein 3 (NLRP3) inflammasome and then enhanced the production of IL-1β[25]. For the HMGB1-RAGE pathway, the downstream signaling is propagated by the Akt, MAPK, ERK, JAK-STAT1, and Rac pathways, ultimately promoting the activation of NF-κB and expression of the proinflammatory cytokines and chemokines, which contributes in the immune cells' maturation and migration and surface receptors' expression[26,27]. Fully reduced HMGB1 (fr-HMGB1), which is a kind of three redox states (fr-HMGB1, disulfide HMGB1, and sulfonyl HMGB1), can act as a chemoattractant through connections with RAGE [28]. Furthermore, binding with C-X-C motif chemokine receptor 4, promotes chemotactic activity

(stimulates leukocyte recruitment)[29]. It should be noted that such inflammation activation can lead to inflammatory responses and cell injury and death, which promotes the further release of HMGB1 and upgrade of its receptors[30]. This may contribute to the aggravation and drug-resistance of HMGB1 related disease[15].

More recently, neuroinflammation has been proposed to play a significant role in several diseases including depression, epilepsy, stroke, traumatic brain injury, Parkinson's disease, and Alzheimer's disease[11-15]. HMGB1 is considered as an essential neuroinflammatory facilitator, which is released by glial cells and neurons upon inflammasome activation and acts as a pro-inflammatory cytokine[15]. Neurons are considered as a primary and necessary driver of neuroinflammation through release of HMGB1, with the subsequent amplification *via* recruitment of immunocompetent cells, including microglia and astrocytes[31]. HMGB1 has been proved that it releases from neurons in many central nervous system (CNS) diseases and then triggeres neuroinflammation as an upstream inflammatory mediator[15,32]. Activated by HMGB1, microglia functions as key contributor of the inflammatory processes sequentially influences neural cells, following by the activation of microglial NF-κB pathway and production of pro-inflammatory cytokines[33]. The study of Gao *et al*[34] using a Parkinson's disease model revealed that HMGB1 released from inflamed microglia and/or degenerating neurons, bound to microglial Mac1 and activated NF-κB pathway and nicotinamide adenine dinucleotide phosphate oxidase to stimulate production of multiple inflammatory and neurotoxic factors. Astrocytes are also a population of CNS cells with distinctive morphology and functions. Xiao *et al*[35] suggested that HMGB1 promoted the release of sonic hedgehog from astrocytes through signal pathway JNK, p38 and stat3 mediated by receptor RAGE in an animal model of multiple sclerosis, suggesting the important role of HMGB1-astrocytes medicated neuroinflammation. Also, some types of reactive astrocytes can also be induced by activated neuroinflammatory microglia and take parts in various human neurodegenerative diseases, formulating a complex immune network[36].

Depression is also found to closely link with neuroinflammation, which is mainly characterized by the increased mediators of inflammation and neurodegeneration[37]. Depressed patients have been found to have higher levels of proinflammatory cytokines, acute phase proteins, chemokines and cellular adhesion molecules, including IL-1β, IL-6, TNF-α and CRP[38,39]. Preclinical study based on animals also exhibited the activation of microglia together with enhanced inflammatory mediators. In a chronic mild stress (CMS) mouse model of depression, NLRP3-inflammasome/caspase-1/IL-1β axis microglia-mediated neuroinflammation was found being activated[40]. Another study suggested rats exposed to CMS exhibited a significant increase in inflammatory mediators, including TNF-α and IL-1β, activation of NF-κB signaling pathway in the hippocampus. Icariin, a flavonoid inhibiting neuroinflammation, could negatively regulated the activation of the NLRP3 inflammasome/caspase-1/IL-1β[41]. Chronic treatment with corticosterone and intraperitoneally administration of lipopolysaccharide depressed models also showed a higher expression level of pro-inflammatory phenotype characterized by IL-1β, IL-6, TNF-α and IκB-α[42,43]. These findings provide a powerful connection of neuroinflammation and depression.

Concerning HMGB1 medicates depression, recent studies suggested that HMGB1 might be a probable inducer of stress-mediated neuroinflammation in depression[11]. It has been proven that HMGB1 could activate neuroinflammatory reactions by inducing TNF-α to exhibit anhedonia-like behavior[44]. Based on the inescapable tail shock rats' model, Weber *et al*[45] indicated that HMGB1 in the brain is a probable inducer of stress-mediated microglial priming by acting on the NLRP3 inflammasome and pro-inflammatory cytokines. Based on recent studies, stress-mediated depression-like behaviors were found to be induced by HMGB1 and glycogen synthase kinase-3 dependent TLR4 signaling, resulting in the activation of NF-κB and NLRP3 inflammasome; and the HMGB1 was additionally promoted in mice[46]. This stress-induced neuroinflammation can further make it more susceptible to depression[47]. Based on rats' chronic unpredictable stress (CUS)-induced behavioral deficits, Franklin *et al*[48] discovered that CUS caused consistent upregulation of HMGB1 mRNA and RAGE mRNA in hippocampal microglia. They also found that HMGB1 infusion into the hippocampus caused anhedonic behavior and suggested that HMGB1-RAGE increased vulnerability to depressive-like behaviors long[10,48]. In addition, HMGB1 could also induce depressive behaviors by limiting the kynurenine pathway *via* suppression of activated enzymes[37]. Furthermore, based on preclinical studies, neuroinflammation induced by HMGB1 can mediate depressive behaviors such as reduction of locomotor activity and sucrose preference, which are analogs to the motivational deficits in depression [49,50].

HMGB1: a potential therapeutic target in depression

Current studies proposed that interventions in the HMGB1 and related molecular in its neuroinflammation pathways have the potential to be a therapeutic target in several diseases like depression, epilepsy, cancers, stroke, and other local and systemic neuroinflammatory diseases[4,13,15]. The main potential therapeutic targets include anti-HMGB1 monoclonal antibody (mAb), HMGB1 inhibitors, and HMGB1 receptors and its related molecular in neuroinflammation pathway[15].

For depression, although several studies provided evidence on mediating HMGB1, this topic is still needing more effort. Traditionally commonly used anti-depression drugs based on the theory of serotonin-like selective serotonin reuptake inhibitors (SSRIs) as well as serotonin and norepinephrine

reuptake inhibitors may be complicated to treat motivational deficits symptoms, suggesting additional neurotransmitters like dopamine dysfunction might be involved[51,52]. Also, recent studies suggested the anti-inflammatory and anti-oxidative effects may be one of the potential mechanisms of these anti-depression drugs[53]. Only limited studies are based on animal models concerning the therapeutic target of HMGB1 in anti-depression. Liu *et al*[50] and Fu *et al*[54] indicated that the anti-depressive-like behavior compound Hesperidin and Baicalin reduced the CUS-induced model by inhibition of neuroinflammatory actions *via* HMGB1-TLR4-NF-κB pathway or HMGB1-RAGE-NF-κB pathway. The anti-HMGB1 mAb is highly specific for HMGB1, which shows the value of target validation but also has potential for the treatment of neuroinflammation diseases, including depression[14]. Hisaoka-Nakashima *et al*[55] used the model of partial sciatic nerve ligation to introduce neuropathic pain and anxiodepressive-like behaviors in mice. They observed increased HMGB1 and microglia activation in the frontal cortex. Anti-HMGB1 mAb and glycyrrhizic acid (HMGB1 inhibitor) can reduce microglia activation and anxiodepressive-like behavior[55]. HMGB1 inhibitors can be another possible anti-HMGB1 strategy. Based on the CUS-induced model both *in vivo* and *in vitro*, glycyrrhizic acid, the inhibitor of HMGB1, may restrain HMGB1 thus improving depressive-like behaviors through regulating the kynurenine pathway[47,56]. Encouragingly, a recent clinical trial found that depressive symptoms are relieved more in SSRI+ glycyrrhizic acid than SSRI+ placebo, proving anti-inflammatory agents is effective in clinical use[57]. The HMGB1 receptors and their related molecular in neuroinflammation pathway can also be a therapeutic target. Cheng *et al*[46] based on an inescapable tail shock model suggested that TLR4 knockout mice were resistant to learned helplessness and GSK3 (a TLR4 signaling dependent kinase) inhibitor TDZD-8 reduced the stress-induced increases of hippocampal cytokines and chemokines.

HMGB1: summarize of HMGB1 in depression

Based on current studies, HMGB1 may be a possible signaling inducer of stress-mediated depression behaviors *via* HMGB1-TLRs signaling and HMGB1-RAGE signaling, followed by the activation of NF-κB and expression of the proinflammatory cytokines and chemokines, resulting in the neuroinflammation procedure[10]. This pathway suggests a possible mechanistic direction for depression. HMGB1 can also be a potential therapeutic target in depression by playing an important role in neurotransmitter-related anti-depression drugs, anti-HMGB1 mAb, HMGB1 inhibitors, and HMGB1 receptors[11]. However, there are still many challenges in further exploring HMGB1 as a potential mechanistic and therapeutic direction. The mechanistic illustration of HMGB1 in depression is provided as Figure 1.

PERSPECTIVES OF HMGB1 IN DEPRESSION

Focus on the complete signal pathway mechanism

As a multifunctional protein, HMGB1 has been extensively researched. Encouragingly, cell stresses and plenty of disease processes are found related to this important inflammation facilitator[58]. HMGB1 needs to translate from nuclei to the cytoplasm and eventually release to the extracellular milieu for its inflammatory function[16]. Thus, location and translocation are the keys to function[59]. The potential mechanism of HMGB1 translocation, however, is still not clear and requires further exploration in depression. Furthermore, most current studies only focus on the release of HMGB1 in neuroglial cells (especially neuroimmune cells), which requires more studies on the role of other neuronal cells[11]. Another potential perspective is about HMGB1 receptors. The different functions, distribution, and potential relationship among various HMGB1 receptors emerge as a research focus in inflammation[60,61]. For depression, the mechanism of neurotransmitters and neuroinflammation may make this question more interesting and meaningful[53,62]. It has to be admitted that only limited studies explored some parts of the HMGB1 as a mechanism in depression. There still is a long way to understand the full signaling pathway of HMGB1 and the complete mechanism of depression introduced by the neuroinflammation.

A potential therapeutic target needs more evidence

Although several studies indicated potential therapeutic targets as neurotransmitter-related anti-depression drugs, anti-HMGB1 mAb, HMGB1 inhibitors, and HMGB1 receptors, current researches are far from enough to provide evidence for potential therapy or clinical application[11]. The potential anti-inflammatory mechanisms and collaboration of neurotransmitter-related anti-depression drugs might be a clinically translational direction[53]. Furthermore, some anti-inflammatory and antiapoptotic compounds [such as (–)-Epigallocatechin-3-gallate and different microRNAs] can inhibit the HMGB1-NF-κB signaling pathway, which showed great potential in therapy of other HMGB1 related diseases [15]. These may also show effects in depression, which deserves further researches. The future need of the research is to deeply investigate potential HMGB1 related therapeutic targets using different animal models[63]. The ultimate goal is for contribution to human clinical applications, while the clinical study on glycyrrhizic acid (HMGB1 inhibitor) as an adjunctive treatment for depression is a meaningful attempt[57].

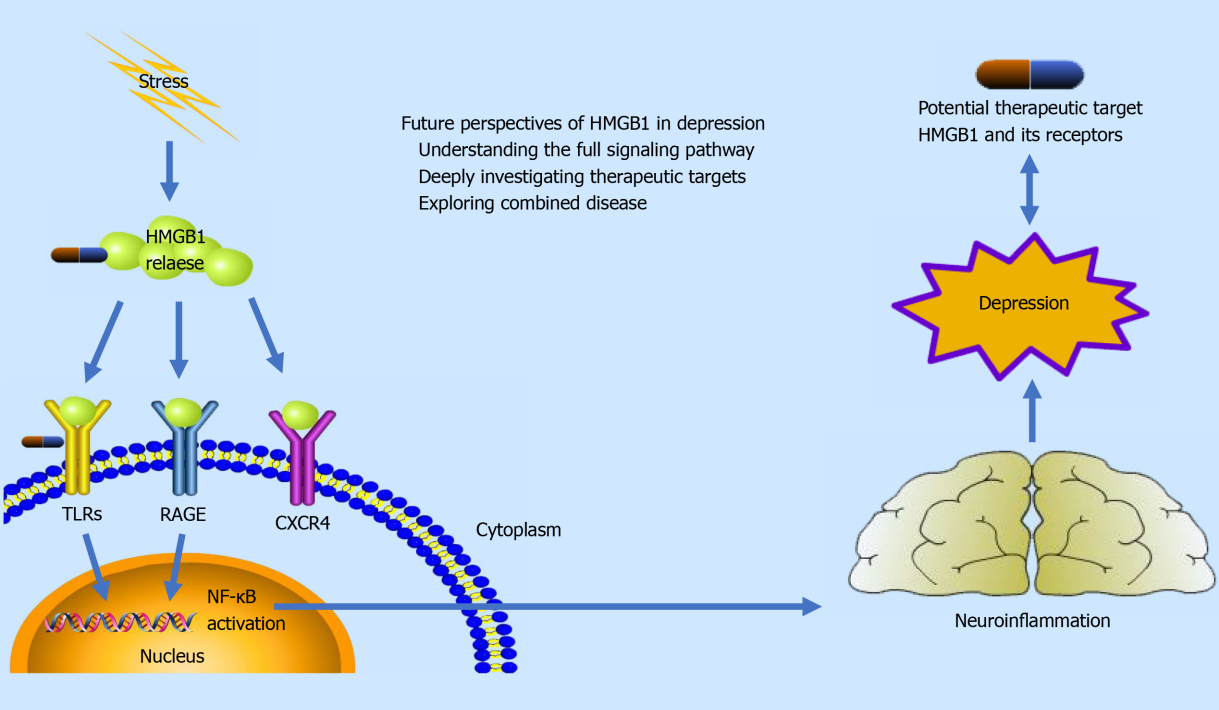

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Figure 1 Illustration of mechanistic and therapeutic perspective of high mobility group box 1 in depression. HMGB1: High mobility group box 1; TLRs: Toll-like receptors; RAGE: Receptors for advanced glycation end products; CXCR4: C-X-C motif chemokine receptor 4.

Combined disease: a future perspective

It is commonly observed in clinical practice that depression may combine with other diseases, such as epilepsy, stroke, and heart disease[64-66]. HMGB1 is found widely participating in different inflammation-related diseases on the nervous system, circulatory system, and others[13]. Thus, HMGB1 may be at the crossroads of depression and other combined diseases. These diseases may have consistent or similar pathogenesis as HMGB1 and response to the same therapeutic target on HMGB1. The researches and discussion of HMGB1 as a potential common mechanistic and therapeutic direction in depression and combined inflammation-related disease may be meaningful and beneficial. Figure 1 shows an illustration of mechanistic and therapeutic perspective of HMGB1 in depression.

CONCLUSION

Neuroinflammation activation plays an important role in the pathophysiology of depression. Playing an important role in neuroinflammation activation, HMGB1 may be a possible signaling inducer of depression. HMGB1 can also be a potential therapeutic target in depression by playing an important role in neurotransmitter-related anti-depression drugs, anti-HMGB1 mAb, HMGB1 inhibitors, and HMGB1 receptors. However, there are still many challenges in further exploring HMGB1 as a potential mechanistic and therapeutic direction. The future perspectives of HMGB1 in depression are understanding the full signaling pathway of HMGB1 in depression, deeply investigating potential HMGB1 related therapeutic targets, and exploring the role of HMGB1 in depression and combined disease.

FOOTNOTES

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Generalized structural equation modeling: Symptom heterogeneity in attention-deficit/hyperactivity disorder leading to poor treatment efficacy

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Abstract

BACKGROUND

Treatment efficacy for attention-deficit/hyperactivity disorder (ADHD) is reported to be poor, possibly due to heterogeneity of ADHD symptoms. Little is known about poor treatment efficacy owing to ADHD heterogeneity.

AIM

To use generalized structural equation modeling (GSEM) to show how the heterogeneous nature of hyperactivity/impulsivity (H/I) symptoms in ADHD, irritable oppositional defiant disorder (ODD), and the presentation of aggression in children interferes with treatment responses in ADHD.

METHODS

A total of 231 children and adolescents completed ADHD inattention and H/I tests. ODD scores from the Swanson, Nolan, and Pelham, version IV scale were obtained. The child behavior checklist (CBCL) and parent's satisfaction questionnaire were completed. The relationships were analyzed by GSEM.

RESULTS

GSEM revealed that the chance of ADHD remission was lower in children with a combination of H/I symptoms of ADHD, ODD symptoms, and childhood aggressive behavior. ODD directly mediated ADHD symptom severity. The chance of reaching remission based on H/I symptoms of ADHD was reduced by

13.494% [= exp (2.602)] in children with comorbid ADHD and ODD [odds ratio (OR) = 2.602, 95% confidence interval (CI): 1.832-3.373, P = 0.000] after adjusting for the effects of other factors. Childhood aggression mediated ODD symptom severity. The chance of reaching remission based on ODD symptoms was lowered by 11.000% [= 1 - exp (-0.117)] in children with more severe baseline symptoms of aggression based on the CBCL score at study entry [OR = -0.117, 95%CI: (-0.190)-(-0.044), P = 0.002].

CONCLUSION

Mediation through ODD symptoms and aggression may influence treatment effects in ADHD after adjusting for the effects of baseline ADHD symptom severity. More attention could be directed to the early recognition of risks leading to ineffective ADHD treatment, *e.g.*, symptoms of ODD and the presentation of aggressive or delinquent behaviors and thought problems in children with ADHD.

Key Words: Attention-deficit/hyperactivity disorder; Oppositional defiant disorder; Aggression; Remission; Generalized structural equation modeling

Core Tip: It is important to understand the factors that influence treatment outcomes for those with attention-deficit/hyperactivity disorder (ADHD). This generalized structural equation modeling pathway analysis studied heterogeneity in ADHD. We found that higher irritable oppositional defiant disorder (ODD) symptom levels mediated the treatment outcomes in children with ADHD. Treating children with ADHD is not only a matter of treating inattentive symptoms alone. Earlier recognition of risky hyperactivity/impulsivity ADHD symptoms + irritable ODD + childhood aggression as a particular subgroup and earlier provision of a more intensive combination of pharmacotherapy and cognitive behavior therapy modalities are essential.

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder among children and adolescents, with a high prevalence ranging from 5.00% to 12.76%[1], and definitely needs early treatment. Although we know quite well the importance of early treatment of ADHD, approximately 25% to 30% of treated ADHD patients remain nonresponsive to treatment[2]. ADHD is a heterogeneous disorder in clinical presentation. The heterogeneity of ADHD in terms of clinical symptom profiles in children with co-occurring ADHD and oppositional defiant disorder (ODD) involves differentially higher levels of behavioral and emotional difficulties. ADHD comorbid with ODD is common and presents clinically in more than half of children with ADHD[3].

Another commonly seen clinical phenomenon is childhood aggression, which plays an essential role in the heterogeneity of ADHD. Clinically, childhood aggression commonly co-occurs in children with ADHD and ODD. As a result, these combinations of ADHD and other symptom comorbidities might further increase the highest levels of behavioral and emotional difficulties in children[4,5]. Furthermore, the treatment efficacy for ADHD in children with the commonly seen irritable subtype of ADHD presenting with childhood aggression remains ineffective. Indeed, many parents seek help from mental health experts due to irritability in children with ADHD, but they do not obtain proper treatment efficacy owing to undertreated emotional dysregulation problems associated with ADHD[6].

Prior studies

In the real world, up to 80% of children with ADHD report an irritable subtype of ADHD[7]; here, we examined the heterogeneity of ADHD comorbid with ODD and aggression. As we reviewed studies on ODD, comorbidities between ADHD and ODD in children ranged from at least 40.6% to 60.0%[8,9]. Children with ADHD comorbid with ODD may have inattentive or hyperactivity/impulsivity (H/I) symptoms of ADHD and frequently have temper tantrums, excessive arguments with family, and uncooperative, deliberately annoying, or mean and spiteful behavior when younger[10], but the ODD

comorbidity problems in children with ADHD remain underdiagnosed[11]. The more irritable ODD symptoms noticed in children with ADHD, the more increased the risk of behavioral and emotional difficulties in these children with ADHD[12,13]. Clinically, there is more parental concern about this irritable mood associated with ADHD than inattentive symptoms of ADHD. Thus, ODD symptoms in ADHD may play mediating roles that impede treatment effects for ADHD, but little is known about these associations.

Additionally, when seeing the heterogeneity of ADHD from a childhood aggression perspective, child aggression is commonly seen in children with ADHD comorbid with ODD who have increased symptoms of irritable emotional difficulties associated with ODD[14-16]. Recently, childhood aggressive behavior was found to be closely associated with symptoms of ODD[17]. However, there is a gap in the study of childhood aggression in children with irritable ADHD because ODD commonly coexists with conduct disorder (CD)[18]. An earlier study focused more on childhood CD comorbid with ADHD. We know that any kind of childhood aggression may be a small part of the symptomatology of CD. However, in the real world, children with CD are not generally noticed in the clinic as more likely to have any kind of aggressive behavior. For example, the presentation of any kind of aggressive behavior was noticed to be as high as in 58% of preschool children[19]. A higher proportion of children with ADHD will present aggressiveness without meeting the full diagnostic criteria for CD[3]. Therefore, ODD plus aggression in children can be a bad predictor for children's future criminal behavior, social problems, and internalizing problems[20]. There is a lack of studies examining heterogeneity across symptom dimensions of ADHD + ODD + aggression. Here, we suggest that current child ADHD expertise should use updated latent class and factor analysis to account for all related levels of heterogeneity in ADHD.

Goal of this study

To provide an evidence-based understanding of the heterogeneity of ADHD to optimally reflect real-world variation among children with ADHD, multiple symptoms should be simultaneously evaluated. Structural equation modeling (SEM) is necessary to show the theoretical relationships among symptom heterogeneity in ADHD and poor treatment outcomes with quite different implications. Because treatment responses are usually expressed as binary data (yes/no), the traditional SEM method is not appropriate to explore the pathway of how ODD and aggression interfere with treatment efficacy for ADHD. A new pathway analysis, called generalized SEM (GSEM), can use more normally distributed observed variables by adding the logistic regression model into the SEM (StataCorp., 2013). By using GSEM pathway analysis, we can fit logistic, probit, poisson, multinomial logistic, ordered logit, ordered probit, and other models. In other words, the observed variables used in GSEM can be continuous, binary, countable, categorical, and ordered variables. GSEM can detail the pathways by which ODD mutually increases the symptom severity of ADHD (expressed by inattentive and H/I symptoms) and problematic aggressiveness. Furthermore, using GSEM pathway analysis can be a good way to detail how ODD and aggressive behavior possibly interfere with the treatment efficacy for ADHD due to their interacting joint influence on ADHD symptom severity[21].

In this study, we hypothesized that when children and adolescents with ADHD and ODD also present with any kind of aggression, treatment efficacy is poor. Regarding inattention, H/I, and ODD symptom severity and any kind of aggression at study entry, it is expected that all these risks may affect the pathways influencing treatment efficacy for ADHD. Indirectly, we hypothesized that ODD with various aggressive symptoms in children might play a mediating role in treatment efficacy for ADHD.

We used GSEM to test the hypothesis that ODD is essentially an intermediate mediator of treatment effectiveness for ADHD (in terms of odds of reaching remission or the chance of remission) by direct and indirect pathway analysis. We hope that mental health professionals can regard the combination of ODD and aggression in children with ADHD as a warning risk for difficulty achieving remission in treating the ADHD and taking earlier steps to properly manage the symptoms of ODD and the presentation of any kind of aggressive behavior.

MATERIALS AND METHODS

Participants and data collection

Patients for this study were children recruited from the outpatient unit of Mackay Memorial Hospital, a major medical center in Taipei, Taiwan. The hospital's institutional review board approved the design of the study (Institutional Review Board No: MMH-I-S-489; name of project: Exploring the symptomatology on children with internet addiction and attention deficit hyperactivity disorder and their parent). After receiving a complete description of the study, potential participants (children and their parents) provided written informed consent in line with the institutional review board's guidelines. A total of 231 children (mean age ± standard deviation = 10.17 ± 2.59) with a clinical diagnosis of ADHD based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) were enrolled in this study. An experienced child and adolescent psychiatrist confirmed the clinical diagnosis of ADHD based on the DSM-IV criteria.

Measurements

ADHD and ODD symptoms: The primary measures in this study reflected the core symptoms of ADHD (18 items) and ODD (8 items) as defined in the DSM-IV and included the inattention subscale, H/I subscale, and the ODD subscale of the Swanson, Nolan, and Pelham, version IV scale (SNAP-IV) [22]. Each item was scored by severity based on a 4-point scale (0-3 points, where 0: Not at all, 1: Just a little, 2: Quite a bit, and 3: Very much). The intraclass correlation coefficients for the three subscales of the Chinese-language SNAP-IV (SNAP-IV-C) ranged from 0.59 to 0.72 for the parent form and from 0.60 to 0.84 for the teacher form. All subscales of both the parent and teacher forms showed excellent internal consistency with Cronbach's α greater than 0.88[23].

Remission rate measurements: The remission criteria on the SNAP were defined as 0 (no) or equal to 1 (yes) for each of the symptoms or a total score that was < 9 (not at all-0 or just a little-1 for the ADHD symptoms) on the SNAP after treatment. More specifically, a patient was in remission with regard to inattention, hyperactivity, and ODD if after 6 wk of treatment, the three subscales of the SNAP-IV were ≤ 9, ≤ 9, and ≤ 8, respectively. Parents and investigators rated ADHD symptoms using the SNAP-IV-C at every follow-up session to measure remission after treatment.

Aggressive behavior: The child behavior checklist (CBCL) was designed to determine competencies and behavioral problems of children aged 4-18 years. The questionnaires, completed by the parents, contain 118 items to assess specific behavioral and emotional problems. The CBCL was translated into Chinese *via* a two-stage translation process[24]. The internal consistency and 1-mo test-retest reliability (all α values and reliabilities > 0.6, except for thought problems) of the Chinese version were satisfactory for Taiwanese patients[25]. The present study analyzed the following 6 scales: Aggressive behaviors (tpagbeh), attention problems (tpattpr), anxiety/depression (tpandep), social problems (tpsocpr), delinquent behaviors (tpdebeh), and somatic complaints (tpsoma).

Caregiver satisfaction: To assess the medication adherence of children with ADHD, parents/caregivers completed the caregiver's satisfaction form, which included the frequency of adverse events and the mean dose of methylphenidate (MPH), to understand the noncompliance risk. Parent/caregiver satisfaction with the current ADHD treatment was measured on a 5-point Likert scale as follows: (1) Completely dissatisfied; (2) Somewhat dissatisfied; (3) Neutral; (4) Somewhat satisfied; and (5) Completely satisfied. The only treatment was MPH (long- or short-acting formulations).

Statistical analyses

In this study, we wanted to simultaneously explore the potential relationships among the remission odds (based on inattention, H/I, and ODD symptoms) and the aforementioned measurements. We used a typical multiple-indicators and multiple-causes model. The GSEM method was used to include the logistic regression model in the SEM first with Stata 13 for Windows to test the mediation model that specified the relationships between inattention, H/I, and ODD symptom severity, any kind of aggression, and remission (StataCorp., 2013). First, we used multiple logistic regression models using GSEM notations to understand the odds of remission based on each measure. The goodness-of-fit indices in this part were *P* values of the fitted coefficients, deviance, and McFadden's pseudo R^2. The second part was the (combined) mediation model, which combined those three multiple logistic regression models in the first part presented by GSEM notations. All statistical analyses were performed using STATA v.13.0 (StataCorp., 2013). Statistical significance was defined as a $P < 0.05$.

RESULTS

Overall, 231 eligible patients with ADHD were enrolled. In terms of patient characteristics, 158 ADHD patients had a combined subtype (68.7%). The comorbidity rate was 73.0%. The remission rates with regard to inattention, H/I, and ODD symptoms were 30.7%, 53.7%, and 49.4%, respectively (Table 1).

As shown in Table 2, the results of the logistic regression showed that the chance of reaching remission based on inattentive symptoms of ADHD was significantly reduced by 22.7% [= 1 - exp (-0.258)] in those with more severe inattentive symptoms [odds ratio (OR) = -0.258, 95% confidence interval (CI): (-0.350)-(-0.167), $P < 0.001$] after adjusting for the effects of other factors. This means that the more severe the inattention problem at study entry, the poorer the ADHD treatment response. The chance of reaching remission was significantly reduced by 10.6% [= 1 - exp (-0.112)] in those with higher baseline CBCL aggression scores [OR = -0.112, 95%CI: (-0.186)-(-0.038), $P = 0.003$] after adjusting for the effects of other factors. The results of deviance, D (226) = 214.144 ($P = 0.704$), and McFadden's pseudo R^2 = 0.2485 indicated a very good model fit (Table 2, Figure 1).

Similarly, as shown in Table 3, the chance of reaching remission based on H/I symptoms of ADHD was significantly reduced by 9.7% [= 1 - exp (-0.102)] for each increase in the baseline CBCL aggression score [OR = -0.102, 95%CI: (-0.170)-(-0.073), $P = 0.004$) after adjusting for the effects of other factors. Moreover, for each increase in the parental satisfaction level, the chance of reaching remission based on H/I symptoms was significantly increased by 57.4% [= exp (0.579) – 1]. The results of goodness-of-fit

Table 1 Sample characteristics and means and standard deviations of study measures

Characteristics	*N*	Mean, *n* (%)	SD
Age	231	10.17	2.59
Male (%)	231	175 (75.8)	
Comorbidity			
Yes	230	168 (73.0)	
No	230	62 (27.0)	
Subtype			
Combined	230	158 (68.7)	
Inattentive	230	72 (31.3)	
Education			
Elementary school	228	171 (75.0)	
Junior high school	228	54 (23.7)	
Senior high school	228	3 (1.3)	
ADHD			
Inattention	231	17.19	4.50
Hyperactivity	231	12.43	6.46
Disruptive child symptom			
Oppositional defiant disorder	231	12.25	5.82
Aggression	231	13.32	7.23
Remission			
Inattention	231	71 (30.7)	
Hyperactivity	231	124 (53.7)	
Disruptive child symptom			
Oppositional defiant disorder	231	114 (49.4)	
SCL			
Somatization	231	4.53	6.19
Obsessive compulsive	231	5.68	5.53
Interpersonal sensitivity	231	3.31	4.10
Depression	231	5.11	6.08
Anxiety	231	2.54	3.43

SCL: Symptom check list; ADHD: Attention-deficit/hyperactivity disorder; SD: Standard deviation.

indices, namely, deviance and McFadden's pseudo R^2, were D (224) = 242.862 (P = 0.184) and pseudo R^2 = 0.2386, respectively, which indicated a very good model fit. The corresponding multiple logistic regression model presented by GSEM is shown in Figure 2.

The chance of reaching remission based on ODD symptoms decreased by 11.0% [= 1 - exp (-0.117)] with each increase in the baseline CBCL aggression score [OR = -0.117, 95%CI: (-0.190)-(-0.044), P = 0.002] (Table 4). Again, the deviance and McFadden's pseudo R^2, D (226) = 255.740 (P = 0.085) and pseudo R^2 = 0.2013, indicated that the model fit was good. The corresponding multiple logistic regression model of remission based on ODD symptoms presented by GSEM is shown in Figure 3.

Regarding the combined (mediation) model (Table 5), we first noted that the chance of reaching remission based on H/I ADHD symptoms was reduced by 13.494% [= exp (2.602)] in the children with ODD (OR = 2.602, 95%CI: 1.832-3.373, P = 0.000) after adjusting for the effects of other factors. Moreover, the chance of reaching remission based on inattention ADHD symptoms was reduced by 29.785% [= exp (3.394)] in children with H/I ADHD symptoms (OR = 3.394, 95%CI: 1.862-4.927, P = 0.000) and reduced by 5.094% [= exp (1.628)] in children with ODD symptoms (OR = 1.628, 95%CI: 0.600-2.656, P = 0.002) after adjusting for the effects of other factors. The chance of reaching remission based on ODD

Table 2 Results of the multiple logistic regression model in pathway to the remission of inattention of attention-deficit/hyperactivity disorder

	Coef	SE	*z*	*P* value	95%CI
Remission I					
ADHD-I B	-0.258	0.047	-5.53	< 0.001	(-0.350)-(-0.167)
Aggression_B	-0.112	0.038	-2.96	0.003	(-0.186)-(-0.038)
Delinquent B	0.112	0.038	2.96	0.003	0.038-0.186
Satisfaction	0.402	0.147	2.74	0.006	0.114-0.689
_cons	3.065	0.834	3.68	< 0.001	1.431-4.699

Pseudo-R^2 statistics assessed the predictive strength of the logistic regression model. The deviance and McFadden's pseudo R^2 were D (226) = 214.144 (P = 0.704), pseudo R^2 = 0.2487, respectively. Remission I: Remission status of inattention; ADHD-I B: Attention-deficit/hyperactivity disorder baseline inattention; Aggression_B: Baseline aggressive behaviors; Delinquent B: Baseline delinquent behaviors; CI: Confidence interval; Coef: Coefficient; SE: Standard error.

Table 3 Results of the multiple logistic regression model in pathway to the remission of hyperactivity/impulsivity of attention-deficit/hyperactivity disorder

	Coef	SE	*z*	*P* value	95%CI
Remission H/I					
ADHD-H/I B	-0.132	0.030	-4.39	< 0.001	(-0.191)-(-0.073)
Aggression_B	-0.102	0.035	-2.92	0.004	(-0.170)-(-0.033)
Anx/dep B	0.075	0.046	1.64	0.101	(-0.015)-0.164
Social pro. B	-0.177	0.076	-2.34	0.019	(-0.325)-(-0.029)
Thought pro. B	0.204	0.070	2.92	0.004	0.067-0.340
Satisfaction	0.579	0.133	4.34	< 0.001	0.317-0.840
_cons	1.743	0.518	3.36	0.001	0.727-2.759

Pseudo-R^2 statistics assessed the predictive strength of the logistic regression model. The deviance and McFadden's pseudo R^2 were D (224) = 242.862 (P = 0.184), pseudo R^2 = 0.2386, respectively, which indicated that the model fit was good. Remission H/I: Remission status of hyperactivity/impulsivity of attention-deficit/hyperactivity disorder; ADHD-H/I B: Attention-deficit/hyperactivity disorder baseline hyperactivity/impulsivity of attention-deficit/hyperactivity disorder; Aggression_B: Baseline aggressive behaviors; Anx/dep B: Baseline anxiety/depression; Social pro. B: Baseline social problems; Thought pro. B: Baseline thought problem; CI: Confidence interval; Coef: Coefficient; SE: Standard error.

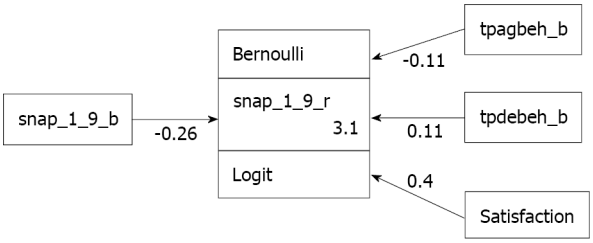

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Figure 1 Results of the multiple logistic regression model of remission of inattention of attention-deficit/hyperactivity disorder presented by generalized structural equation modeling. snap_1_9_b: Inattentive of attention-deficit/hyperactivity disorder baseline; snap _1_9_r: Inattentive of attention-deficit/hyperactivity disorder remission; tpagbeh_b: Aggressive behavior baseline; tpdebeh_b: Delinquent behavior baseline.

symptoms was lowered by 11.000% [= 1 - exp (-0.117)] in children with more severe baseline symptoms of aggression in the CBCL scores at study entry [OR = -0.117, 95%CI: (-0.190)-(-0.044), P = 0.002]. The corresponding combined (mediation) model presented by GSEM is shown in Figure 4.

Table 4 Results of the multiple logistic regression model in pathway to the remission of oppositional defiant disorder

	Coef	SE	*z*	*P* value	95%CI
Remission ODD					
ODD B	-0.130	0.033	-3.97	< 0.001	(-0.195)-(-0.066)
Aggression B	-0.117	0.037	-3.15	0.002	(-0.190)-(-0.044)
Delinquent B	0.117	0.037	3.15	0.002	0.044-0.190
Satisfaction	0.505	0.127	3.98	< 0.001	0.256-0.754
_cons	1.453	0.516	2.82	0.005	0.442-2.464

Pseudo-R^2 statistics assessed the predictive strength of the logistic regression model. The deviance and McFadden's pseudo R^2 were D (226) = 255.740 (P = 0.085) and pseudo R^2 = 0.2013, respectively, which indicated that the model fit was good. Remission ODD: Remission status of oppositional defiant disorder; ODD B: Baseline oppositional defiant disorder; Aggression_B: Baseline aggressive behaviors; Delinquent B: Baseline delinquent behaviors; CI: Confidence interval; Coef: Coefficient; SE: Standard error.

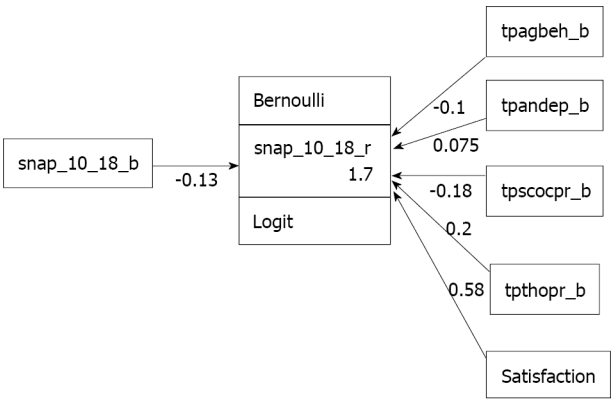

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Figure 2 Results of the multiple logistic regression model of remission of hyperactivity/impulsivity of attention-deficit/hyperactivity disorder presented by generalized structural equation modeling. Snap_10_18_b: Hyperactivity/impulsivity of attention-deficit/hyperactivity disorder baseline; snap_10_18_r: Hyperactivity/impulsivity of attention-deficit/hyperactivity disorder remission; tpagbeh_b: Aggressive behavior baseline; tpdebeh_b: Delinquent behavior baseline; tpscocpr_b: Social problem baseline; tpthorpr_b: Thought problem baseline.

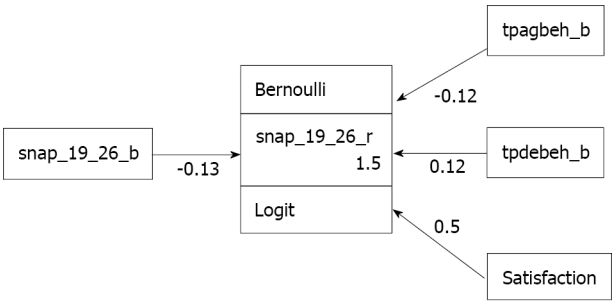

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Figure 3 Results of the multiple logistic regression model of remission of oppositional defiant disorder presented by generalized structural equation modeling. snap_19_26_b: Oppositional defiant disorder baseline; snap_19_26_r: Oppositional defiant disorder remission; tpagbeh_b: Aggressive behavior baseline; tpdebeh_b: Delinquent behavior baseline.

DISCUSSION

This study examined the structure of ADHD symptoms in child adolescent samples using GSEM. This GSEM pathway analysis first supported that poor treatment outcomes in ADHD can be predicted as irritable ODD subtype of ADHD with aggressive behavior. This pathway analysis indicated higher ODD symptom levels mediated treatment outcomes for ADHD through enhancing inattentive and H/I

Table 5 Results of the combined (mediation) model presented by the generalized structural equation modeling

	Coef	SE	z	*P* value	95%CI
Remission I					
Remission H/I	3.394	0.782	4.340	0.000	1.862-4.927
Remission ODD	1.628	0.524	3.100	0.002	0.600-2.656
ADHD-I B	-0.234	0.058	-4.050	0.000	(-0.348)-(-0.121)
Aggression_B	-0.019	0.043	-0.440	0.661	(-0.104)-0.066
Delinquent_B	0.019	0.043	0.440	0.660	-0.066-0.104
Satisfaction	0.216	0.173	1.250	0.212	(-0.124)-0.556
_cons	-1.433	1.196	-1.200	0.231	(-3.777)-0.910
Remission H/I					
Remission ODD	2.602	0.393	6.620	0.000	1.832-3.373
ADHD-H/I B	-0.148	0.036	-4.150	0.000	(-0.218)-(-0.078)
Aggression_B	-0.050	0.039	-1.270	0.205	(-0.127)-0.027
Anx/dep B	0.093	0.054	1.710	0.087	(-0.014)-0.200
Social pro. B	-0.203	0.086	-2.380	0.017	(-0.371)-(-0.036)
Thought pro. B	0.160	0.078	2.050	0.040	0.007-0.313
Satisfaction	0.431	0.153	2.810	0.005	0.130-0.731
_cons	0.567	0.607	0.930	0.350	(-0.622)-1.756
Remission ODD					
ODD B	-0.130	0.033	-3.970	0.000	(-0.195)-(-0.066)
Aggression_B	-0.117	0.037	-3.150	0.002	(-0.190)-(-0.044)
Delinquent B	0.117	0.037	3.150	0.002	0.044-0.190
Satisfaction	0.505	0.127	3.980	0.000	0.256-0.754
_cons	1.453	0.516	2.820	0.005	0.442-2.464

Remission I: Remission status of inattention; ADHD-I B: Baseline inattention; Aggression_B: Baseline aggressive behaviors; Delinquent B: Baseline delinquent behaviors; Remission H/I: Remission status of hyperactivity/impulsivity of attention-deficit/hyperactivity disorder; ADHD-H/I B: Baseline hyperactivity/impulsivity of attention-deficit/hyperactivity disorder; Anx/dep B: Baseline anxiety/depression; Social pro. B: Baseline social problems; Thought pro. B: Baseline thought problem; Remission ODD: Remission status of oppositional defiant disorder; ODD B: Baseline oppositional defiant disorder; CI: Confidence interval; Coef: Coefficient; SE: Standard error.

symptoms. Treating children with ADHD is not only a matter of treating inattentive symptoms alone, but there is also a need to recognize and manage symptoms of ODD and the presented aggressive behavior, delinquent behavior, and thought problems in children with ADHD to improve ADHD treatment outcomes.

Comparison with prior work

Hinshaw *et al*[26] suggested that only detailed pathway analysis can further assist clinicians in understanding the internal joint relationships among aggressive behavior, symptoms of ODD, and symptom severity of ADHD. Such pathway analysis might remind clinicians to recognize earlier risky irritable symptoms of ADHD + ODD + childhood aggression as a special subgroup and provide more effective therapeutic treatment modalities earlier.

Aggression in children and adolescents with irritable ADHD is a serious clinical and public health problem. Especially in the recent internet age, many children and adolescents present inattentive symptoms, externalizing behavior, or risk-taking behavior after excessive use of the internet[27,28]. We know that this unrecognized aggression in early childhood becomes more aggressive or violent behavior later in these irritable children[5,29]. Alternatively, the results of this study indicated that children with the irritable ODD subtype of ADHD characterized by symptoms of irritable ODD and aggressive behavior is harder to treat well. However, previous studies have focused more on conduct behavior (CD)[30,31] instead of any kind of aggression in children with ODD, which warrants more attention. Therefore, the implication of this study is that we suggest using a CBCL scale to identify

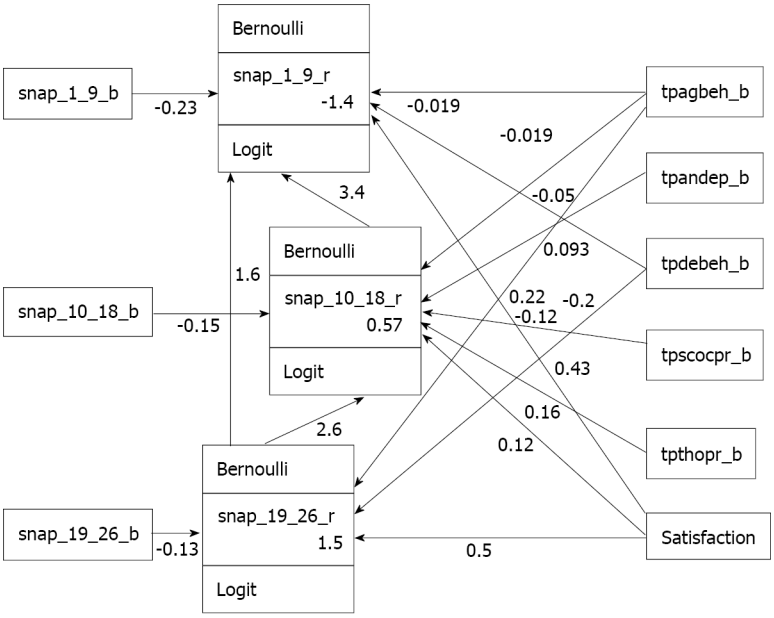

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Figure 4 Results of the combined (mediation) model presented by generalized structural equation modeling. snap_1_9_b: Inattentive of attention-deficit/hyperactivity disorder (ADHD) baseline; snap _1_9_r: Inattentive of ADHD remission; snap_10_18_b: Hyperactivity/impulsivity of ADHD baseline; snap_10_18 r: Hyperactivity/impulsivity of ADHD remission; snap_19_26_b: Oppositional defiant disorder baseline; snap_19_26_r: Oppositional defiant disorder remission; tpagbeh_b: Aggressive behavior baseline; tpdebeh_b: Delinquent behavior baseline; tpscocpr_b: Social problem baseline; tpthorpr_b: Thought problem baseline.

aggressive children and adolescents in child and adolescent clinics or internet gaming disorder clinics in the future. The presented aggressive behavior we derived from CBCL included relational aggression (argues a lot, bragging, boasting, demands much attention), disobedience at home, disobedience at school, easily jealous, screams a lot, showing off or clowning, stubborn, sullen or irritable, sudden changes in mood or feelings, talks too much, teases a lot, temper tantrums or hot temper, direct aggression (cruelty, bullying or meanness to others, destroys his or her own things, destroys things belonging to his or her family or others), and gets in many fights (physically attacks people, threatens other people), which can all be regarded as early recognition of any kind of aggression in children with ADHD and ODD. Earlier and effective treatment inventions for children with particular heterogeneous subtypes of ADHD should be provided by ADHD experts in these days with digital technology.

In the present study, the GSEM results found that ADHD symptom severity was determined by the joint effects between ODD, aggression, and delinquent behavior symptoms. With the under recognition and undertreatment of ODD and aggression in children with ADHD, there is always a significant risk that predicts poor treatment efficacy. Here, we suggest that children and psychiatrists should record a more extensive history of oppositional symptoms because one previous study indicated that there was an underdiagnosed ODD comorbidity problem in children with ADHD[11]. The treatment effects on ODD depend on how the underlying comorbid ADHD is treated. Usually, the core symptoms of ODD are not amenable to pharmacotherapy alone[32]. For children with ADHD with ODD, treatments with only pharmacotherapy for inattention alone always remains noneffective for these ODD symptoms[33,34]. The use of nonstimulant drugs such as atomoxetine was recently noticed to be effective in treating ODD symptoms in children with ADHD[35,36]. However, for children with ADHD with severe ODD and behavioral symptoms, there is still a need to use pharmacotherapy with stimulants (MPH), mood stabilizers such as sodium valproate (Depakin), and antipsychotics such as risperidone with concurrent behavioral therapy[37].

Cognitive behavior psychotherapy in children with ADHD is also essential to regulate emotion regulation circuitry by reducing reactive aggression[38]. Essentially, clinicians should provide effective combined pharmacotherapies with additional effective behavioral modification interventions, parenting programs, and cognitive behavioral therapy to improve treatment outcomes in this particular group of children with ADHD.

Based on the pathway analysis, both ODD and aggressive symptoms interacted as joint effects to exacerbate ADHD symptom severity, as a previous study had noticed[15,16]. We revealed the insight that aggression during childhood rarely occurs alone and is closely correlated with other symptoms of childhood psychopathology. Both ODD symptoms and aggression are important influences on the efficacy of ADHD treatment[39]. Clinicians should consider additional assessments to detect dimensional behavioral symptoms such as childhood aggressive or destructive behaviors to further provide effective treatment modalities to achieve remission of ADHD[40].

Regarding the childhood H/I symptoms of ADHD, previous findings showed that hyperactive ADHD symptoms had a role in predicting children becoming more socially immature, aggressive, and peer rejected[41]. Additionally, one recent meta-analysis indicated more severe symptoms of H/I, and children with ADHD were less likely to obtain better treatment outcomes[42]. In this GSEM, we found that childhood H/I symptoms resulted in a greater risk of increasing the inattention symptom severity, leading to subsequent poor treatment outcomes for ADHD. ODD symptoms and the presentation of aggressive behavior mediated an increase in inattentive and H/I symptom severity of ADHD. Nevertheless, children and adolescents need more attention regarding the diagnosing and managing of H/I symptoms of ADHD. ODD, aggression, and H/I symptoms of ADHD interactively increased the symptom severity of ADHD.

A previous study indicated that the coexistence of a diagnosis of ODD/CD, learning difficulties, anxiety, younger age, family dysfunction, and socioeconomic adversity were all risk factors for predicting poor treatment efficacy for ADHD[43]. This pathway analysis further focused on children with ADHD with ODD, and aggression led to poor treatment outcomes. ADHD is a heterogeneous disorder with complicated emotional and impulsivity deficits. From the Research Domain Criteria perspective, ADHD patients have deficits in the domains of cognition (specifically in working memory) and positive valence (in rewarding anticipation/delay/receipt)[44]. Emotional dysregulation defects may be highly associated with abnormal reward processing systems[45]. Therefore, for children with ADHD presenting symptoms of irritable ODD and aggression, our pathway analysis suggests that the children may have deficits in both cognition and reward domains. Thus, the children with symptoms of ADHD + ODD + aggression should be a clinically distinct emotional irritability subgroup, and clinicians should provide more specific treatment guidelines for these children with ADHD. Future DSM systems need to regard ODD as an essential risk for poor treatment effects for ADHD.

Limitations

This study has the following limitations. First, the construction of the subscale of the SNAP and CBCL, without a direct interview with the parents, seems to be arbitrary. Additionally, the fact that most of the scale is provided by a main caregiver, mainly mothers and teachers, may lead to sampling bias. Another limitation is the cross-sectional design of the study, which may not necessarily represent the longitudinal relationships among ADHD, ODD, aggression, and remission rate. As the main purpose of this study was to explore the association among disruptive symptoms in children and remission rates, aggression scores from the CBCL were used to represent disruptive child behaviors instead of CD measures. This was a naturalistic observational study performed in Taiwan. Most patients from the outpatient department at that time received psychopharmacologic treatment, including short-term or long-acting MPH, or long-acting drugs such as atomoxetine rather than parenting behavior therapy. However, the thrust of this study was to predict poor treatment efficacy in the children with co-occurring ADHD, ODD, and aggressive symptoms by special GSEM statistical analysis. Therefore, we did not show the detailed treatment response after different kinds of drugs or other psychosocial interventions. Finally, the definitions of direct, indirect, and total effects in SEM have not yet been established in the GSEM. Although three out of four requirements for the mediation model were satisfied in our GSEM, it might not be appropriate to call the results in Figure 4 a mediation model. Here, we only borrowed the concept and spirit of the mediation model to emphasize the relationships among remissions based on ODD, H/I, and inattention symptoms for treating children with ADHD.

CONCLUSION

Despite these limitations, to the best of our knowledge, this is the first study to determine mediators in reaching remission of ADHD. ODD is a categorical diagnosis, and aggressive behavior is a dimensional problem. Such interactive categorical and dimensional information provides an added dimension in the understanding of the etiology of heterogenicity of ADHD. This pathway study revealed additional insights into devising more efficacious pharmacotherapies and cognitive behavior therapies. Clinicians should regard ADHD + ODD + aggression comorbidity as a distinct entity that needs an early and combined intensive biopsychosocial model approach, as recent research demonstrated[46]. Future longitudinal and systemic research is needed to validate this as a potential obstacle, with the ODD symptoms dynamically interacting with childhood aggressive behavior symptoms.

Clinical significance

GSEM pathway analysis was used to demonstrate that disruptive childhood symptoms, including categorical diagnoses such as ODD and dimensional problems such as aggressive symptoms before treatment, apparently lower the remission rate for those with ADHD. This paper suggests that clinicians should directly examine the joint effects of ADHD, ODD, and aggression to assess the risk for poor treatment outcomes. An early and more intensive combined biopsychosocial model approach for ADHD should be warranted for these children.

ARTICLE HIGHLIGHTS

Research background

Many parents seek help from mental health experts due to irritability in children with attention-deficit/hyperactivity disorder (ADHD). But treatment efficacy for irritable and aggressive ADHD in children remains ineffective. Therefore, the heterogeneity to ADHD treatment should be proposed by a specific mathematical method.

Research motivation

Treating children with ADHD is not only a matter of treating inattentive symptoms alone. It is important to understand the factors that influence treatment outcomes for those with ADHD.

Research objectives

This study used the generalized structural equation modeling (GSEM) pathway analysis to analyze heterogeneity in ADHD.

Research methods

We used the GSEM to test the hypothesis that ODD is essentially an intermediate mediator of treatment effectiveness for ADHD (in terms of odds of reaching remission or the chance of remission) by direct and indirect pathway analysis.

Research results

Higher irritable oppositional defiant disorder (ODD) symptom levels mediated the treatment outcomes in children with ADHD. Earlier recognition of risky hyperactivity/impulsivity ADHD symptoms + irritable ODD + childhood aggression as a particular subgroup and earlier provision of a more intensive combination of pharmacotherapy and cognitive behavior therapy modalities are essential.

Research conclusions

Treating children with ADHD is not only a matter of treating inattentive symptoms alone, but there is also a need to recognize and manage symptoms of ODD and the presented aggressive behavior, delinquent behavior, and thought problems in children with ADHD to improve ADHD treatment outcomes.

Research perspectives

Poor treatment outcomes in ADHD can be predicted as irritable ODD subtype of ADHD with aggressive behavior. An early and more intensive combined biopsychosocial model approach for ADHD should be warranted for these children. This study revealed additional insights into devising more efficacious pharmacotherapies and cognitive behavior therapies.

FOOTNOTES

Author contributions: Tzang RF and Chang YC designed the study and wrote the protocol; Chang YC undertook the statistical analysis; and all authors contributed to and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the Mackay Memorial Hospital, Institutional Review Board (Approval No. MMH-I-S-489).

Informed consent statement: Patient were not required to give informed consent to the study because the analysis used the data of Institutional Review Board No: MMH-I-S-489; name of project: Exploring the symptomatology on children with internet addiction and attention deficit hyperactivity disorder and their parent that were obtained after each patient agreed the study by written consent.

Conflict-of-interest statement: All the authors have no potential conflicts of interest to disclose.

Data sharing statement: Participants gave informed consent for data sharing.

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ORIGINAL ARTICLE

Clinical Trials Study

Randomized trial estimating effects of hypnosis *versus* progressive muscle relaxation on medical students' test anxiety and attentional bias

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Abstract

BACKGROUND

Test anxiety is prevalent among medical students and leads to impaired academic performance. Test-related attentional bias has been identified as an important maintaining factor in test-anxious individuals.

AIM

To evaluate whether hypnosis and progressive muscle relaxation (PMR) could modify medical college students' test anxiety and attentional bias.

METHODS

A total of 598 medical students were screened. The participants were divided into higher and lower test anxiety groups according to their scores on the test anxiety scale (TAS). Ninety medical college students with high TAS score were randomly assigned to a hypnosis or PMR group. Another 45 students with low TAS score

were included, forming a baseline control group. The intervention was conducted weekly for 6 wk, and each session lasted approximately 30 min. The total intervention time and the number of intervention sessions for the hypnosis and PMR groups were equal. Data were collected at the pretest, posttest, and 2-mo follow-up.

RESULTS

Hypnosis group participants had a significantly lower TAS score at posttest (t = -21.827, P < 0.001) and at follow-up (t = -14.824, P < 0.001), compared to that at pretest. PMR group participants also had a significantly lower TAS score at posttest (t = -10.777, P < 0.001) and at follow-up (t = -7.444, P < 0.001), compared to that at pretest. At the posttest level, the hypnosis group had a significantly lower TAS score than the PMR group (t = -3.664, P < 0.001). At the follow-up level, the hypnosis group also had a significantly lower TAS score than the PMR group (t = -2.943, P = 0.004). Clinically significant improvement was found in both the hypnosis and PMR groups (hypnosis = 64.0%; PMR = 62.22%). Hypnosis was more effective than PMR in reducing test anxiety among medical college students. Hypnosis could modify attentional bias toward threatening stimuli, but PMR could not.

CONCLUSION

These results suggest that attentional bias plays an important role in test anxiety treatment.

Key Words: Test anxiety; Hypnosis; Progressive muscle relaxation; Attentional bias; Randomized controlled trial

Core Tip: We wanted to explore whether hypnosis and progressive muscle relaxation (PMR) could modify medical college students' test anxiety and related attentional bias toward threatening stimuli. We found that hypnosis was more effective than PMR in reducing test anxiety in medical students, and hypnosis could modify attentional bias toward threatening stimuli, but PMR could not. These results suggest that attentional bias plays an important role in the treatment of test anxiety.

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INTRODUCTION

Medical education has always been regarded by students as a high-pressure environment[1], and the incidence rate of test anxiety among medical students is 25%-56%[2]. Research has demonstrated a series of adverse effects associated with test anxiety, such as impaired academic achievement and mental health problems[3,4]. Test anxiety comprises two interdependent factors: Emotionality (or physiology) and worry (or cognition)[5,6]. Emotionality, or physiology, involves awareness of physiological arousal associated with test situations: Increased heart rate, perspiration, muscle tension, and blood pressure[7]. Worry, or cognition, is a psychological phenomenon related to the overwhelming distress associated with testing situations[8].

There are different interventions for test anxiety that target either emotionality or cognition. For instance, progressive muscle relaxation (PMR) is a common behavioral approach to easing physiological reactivity to test situations. PMR targets emotionality/physiology rather than worry/cognition[9]. Several studies have suggested that PMR effectively reduces test anxiety in students[9,10]. Cognitive methods, on the other hand, aim at reducing the psychological detriments of test anxiety[11]. A recent study provided evidence for the utility of integrating integrated imagery work with cognitive-behavioral therapy for treating test anxiety[12]. Recently, a meta-analysis of the efficacy of interventions for test-anxious university students found that although interventions were superior to control conditions in reducing test anxiety, overall confidence should be tempered. The authors concluded that other psychological interventions for test anxiety are needed in future studies[13].

Hypnosis is "a state of consciousness involving focused attention and reduced peripheral awareness characterized by an enhanced capacity for response to suggestion"[14]. There are different types of

hypnosis, *i.e.*, waking or active-alert[15]. The present study employed the traditional definition of hypnosis. Hypnosis is a rapid and cost-effective intervention for anxiety and anxiety-related disorders [16]. During a hypnotic induction phase, a state of relaxation can be induced by maintaining eye fixation, following suggestions of calmness, closing the eyes, and imagery. A core component of hypnosis seems to involve facilitating a state of focused attention in a suggested direction that supports emotional well-being[17]. We therefore proposed that both the relaxation and cognitive components of hypnosis can make it effective in reducing test anxiety.

Attentional bias is believed to be associated with the onset and maintenance of anxiety[18]. Its effect is that anxious individuals tend to direct their attention toward and maintain attentional focus on threat-related stimuli, at the expense of attending to other more critical stimuli in the environment[19]. The same is true for test anxiety; highly test-anxious individuals demonstrate an attentional bias to threat and test-related information[20,21]. Recent research has shown that experimentally manipulating attentional bias away from a threat is effective for the individuals preparing for an exam[22]. Hypnosis also can treat individuals with test anxiety by modifying their attentional bias *via* hypnotic suggestion. For example, the participants received hypnotic suggestions to remain calm and relaxed when they received information related to the exam or got to the situation related to the exam. Further, they could no longer fixate their attention on the information. That is, they could no longer have attentional bias toward the information.

According to attention theory, visual memory is closely related to attentional bias[23], and attentional bias may reflect facilitated orienting of attention to negative information or slowed attentional disengagement from negative information[24]. Although various experimental paradigms have been used to evaluate attentional bias, most of them have not been able to differentiate its two mechanisms [9]. A recently-developed odd-one-out visual search task seems to have uncovered the specific processes underlying attentional bias[25]. In this paradigm, participants were presented with a matrix of stimuli and asked whether the matrix included one stimulus from a different category. The anxious participants demonstrated speeded detection of and slowed disengagement from the threatening stimuli[25].

Attentional bias may be considered an essential target in treating test anxiety. This study was designed as a pilot randomized clinical trial comparing the effects of hypnosis to PMR for test anxiety and the associated attentional bias. The hypnosis developed by this study was intended to target the two components of test anxiety: Emotionality/physiology and worry/cognition, while the PMR targeted only emotionality/physiology. PMR involves the voluntary stretching and relaxing of large muscle groups[26]. We hypothesized that both hypnosis and PMR would reduce anxiety symptoms. Yet, only hypnosis participants demonstrated a significant change in attentional bias to test-related stimuli, compared with those receiving PMR. To the best of our knowledge, this study is the first to use hypnosis to help individuals reduce test anxiety and attentional bias toward threatening stimuli. This is also the first study to use PMR to reduce attentional bias in students, although several studies have found that PMR effectively reduces test anxiety[10,27].

MATERIALS AND METHODS

Participants

The study was conducted at Anhui Medical University in China. The participants were college students. A total of 598 medical students were screened. The participants were divided into higher and lower test anxiety groups according to their scores on the test anxiety scale (TAS)[28]. The inclusion criteria were: Participants with a TAS score higher than 20 formed a high-anxiety group (n = 102), while participants with a score lower than 12 formed a low-anxiety group (n = 62). Twelve participants in the high-anxiety group refused to participate in the study. The remaining 90 participants were randomly assigned to either a hypnosis group or a PMR group, with 45 students in each group. Forty-five of 62 participants with low test anxiety scores were randomly selected for baseline comparisons (control group). The purpose of using the baseline control group was to explore whether the highly test-anxious individuals in both the hypnosis and PMR groups showed an attentional bias to test-related information at the pretest, compared to the participants with low test anxiety. Randomization was performed by the project leader using a computer-generated random list of numbers. Randomization information was sealed in sequentially numbered boxes that were identical in appearance.

The exclusion criteria were: The therapist (the first author) conducted a semi-structured interview to ensure that none of the participants had a history of psychiatric or neurological disease, medication use, or chronic illness, or a current major psychiatric disorder. The study was approved by Anhui Medical University's Human Ethics Committee (Trial Registration: ChiCTR1900025058). All participants provided written informed consent and were paid 180 Chinese Yuan for participating in the study. Participants, therapists, and independent evaluators were blinded to the study arm.

Design

There were two groups with high test anxiety in this study: The hypnosis group and the PMR group. The low-test anxiety group served as a baseline control group. This was a randomized clinical trial in

which two treatment conditions (hypnosis and PMR) were compared with a baseline condition at a ratio of 1:1:1. A series of face-to-face assessments were performed at pretest and posttest, and a follow-up at 2 mo after the intervention (mailed responses). Given that group interventions on test anxiety reduction produced more significant effects than individual interventions[11], group interventions were conducted for the purposes of this study. Data was collected between February 2018 and May 2019.

Intervention and therapists

The intervention sessions took place in a quiet classroom in the university. The intervention was conducted weekly for 6 wk, and each session lasted approximately 30 min. The total intervention time and number of intervention sessions for the hypnosis and PMR groups were equal.

Hypnosis group: An experienced hypnosis therapist conducted the hypnosis. Using a standard hypnotic induction procedure, the students were induced into a hypnotic state[29]. This procedure took approximately 15 min. The participants were then given hypnotic suggestions of mild to high test anxiety exposure, with imagery. In the meantime, the participants were given suggestions of relaxation and pleasant experiences. Suggestions were also made to change the participants' cognition and attention on the test (see more details in Supplementary material).

PMR group: The participants in the PMR group received PMR training with the guidance of a relaxation therapist. The procedure was initially developed by Jacobson[30] and was standardized by Bernstein and Borkovec[31]. Although several studies have attempted to combine PMR with guided imagery to expose patients to specific positive thoughts[32], this study utilized the PMR procedure based on Jacobson[30]'s theory and technique. The PMR technique mainly involved standardized and validated methods[31,33]. During the PMR exercises, the participants deliberately applied tension to specific muscle groups and then released it. The tension-relaxation response started with the hands, moved through the whole body, and ended with the feet.

Control group: Those with low TAS scores, who were included for baseline comparisons, received no intervention. Group hypnosis and group PMR were performed by a hypnosis specialist (Li XM) and a PMR therapist (Zhang Y). These individuals' mean duration of practice in psychiatry was 9 years. Each therapist received 20 h of additional training specific to the requirements of the study. To ensure adherence to the treatments, the therapists followed manuals for hypnosis and PMR and completed a checklist recording the techniques used in treatments.

Outcome measures

Primary outcome measure: The TAS was designed to evaluate test anxiety[34]. The scale contains 37 true-false statements on test-taking, and the total number of "true" checks represents the TAS. The interpretation of TAS scores is as follows: 0 to 12 indicates no or mild test anxiety, 13 to 20 indicates moderate test anxiety, and > 20 signifies severe test anxiety. This study made use of an adapted Chinese version of the TAS that showed sufficient and comparable reliability and validity[28].

Attentional bias was evaluated by the odd-one-out search task adapted from the procedure used by Rinck *et al*[25]. The participant was seated approximately 50 cm from a 17-inch computer screen. Each trial started with a fixation cross (500 ms) in the screen center, followed by a 2 × 2 matrix of four words. The participant was instructed to determine whether there was a target word that belonged to a different category within the matrix by pressing 'A' (yes) or 'L' (no). The matrix contained four words with the same category or three words with the same category and a target word with a different category. The matrix remained on the screen until a response was given. The words represented three categories of emotional relevance: Threatening words related to the test (n = 60), positive words related to positive emotion (n = 60), and neutral words such as 'furniture' and 'natural environment' (n = 120). Attentional bias was assessed: Accelerated detection and slowed disengagement. Eighty trials assessed speeded detection as follows: (1) Twenty trials presented the matrix containing three neutral words and one positive word; (2) Twenty trials showed the matrix containing three neutral words and one threatening word; and (3) Forty trials presented the matrix containing four neutral words. Eighty trials assessed slowed disengagement as follows: (1) Twenty trials showed the matrix containing three positive words and one neutral word; (2) Twenty trials presented the matrix containing three threatening words and one neutral word; (3) Twenty trials showed the matrix containing four positive words; and (4) Twenty trials presented the matrix containing four threatening words.

The location of the target word in each matrix was random for each trial and each participant. All participants engaged in both sessions, and the order of the sessions was counterbalanced across the participants. We conducted a pilot study on a sample of 45 college students to validate all words with a 9-point Likert scale assessing valence and arousal levels.

Secondary outcome measures: The state-trait anxiety inventory (STAI) consists of two sub-scales[35]. One scale assesses the temporary condition of state anxiety, while the other scale evaluates the long-standing quality of trait anxiety. Each scale contains 20 statements rated on a 4-point Likert scale ranging from 0 (almost never) to 3 (almost always). A higher score indicates higher anxiety. We used a validated Chinese version of the STAI with satisfying reliability and validity[36].

Before the intervention, the hypnotic susceptibility of participants, regarded as a control variable, was evaluated using the Stanford Hypnotic Susceptibility Scale (SHSS), Form C[29]. The scale consists of 12 motor items. The participant receives one score if they follow the motor suggestion and produce the movement. The total score is 12, and a higher score suggests greater hypnotic susceptibility.

Sample size estimation

The power of the sample size was calculated using G*power software. We used an independent sample *t*-test between the hypnosis and PMR groups for sample size estimation with a power of 0.90 at $P = 0.05$ using a two-sided test. Moreover, we adjusted for any drop-outs at the rate of 15% during the follow-up test, resulting in the final sample size of 135 participants.

Data analysis

Statistical analyses were conducted using SPSS 20.0. The intention-to-treat analyses were conducted on data from all participants who completed the pretest assessments. The missing data were treated using the last observation carried forward for those who did not complete the follow-up test. First, one-way analysis of variance (ANOVA) was conducted to test baseline differences among the three groups. At the pretest, planned comparisons were conducted between higher and lower test anxiety groups and the hypnosis and PMR groups. Then, the TAS measures were subject to a two-factor mixed design with treatment conditions as the between-group and time as the repeated measure factor. Differences in the TAS measures were compared using analysis of covariance (ANCOVA) with lysergic acid diethylamide *post hoc* comparisons on the adjusted means. Third, to test potential training effects, ANCOVA was performed to compare the hypnosis and PMR groups, using posttest scores as dependent variables and the corresponding pretest scores as covariate. Finally, a reliable change index (RCI) for TAS scores from pretreatment to posttest was computed using the formula reported by Jacobson and Truax[37]. Participants with an RCI score greater than a 1.96 reduction in TAS score at posttest were regarded as having a clinically significant improvement. Effect sizes were reported as partial eta squared (η_p^2), eta squared (η^2), Cohen's *d*, or Cramer's φ. Categorical data were analyzed using χ^2 tests. Significance was defined at $P = 0.05$.

RESULTS

Demographic characteristics of samples and baseline comparison

The enrollment of participants and the study flow are shown in Figure 1. A total of 135 participants were assigned to three groups: Hypnosis, PMR, and control groups. Characteristics of the participants are presented in Table 1. The results of ANOVA conducted on the pretest scores in TAS, STAI, and attentional bias measures are shown in Table 1. For attentional bias measures on speeded detection trials, the speeded detection score is reaction time for neutral words - reaction time for threatening stimuli or positive words. On slowed disengagement trials, the slowed disengagement score is reaction time for threatening stimuli or positive stimuli - reaction time for neutral stimuli. One-way ANOVA was significant for: TAS ($F = 1008.808$, $P < 0.001$), STAI-trait ($F = 401.431$, $P < 0.001$), STAI-state ($F = 385.483$, $P < 0.001$), speeded detection to threatening stimuli ($F = 401.431$, $P < 0.001$), speeded detection to positive stimuli ($F = 401.431$, $P < 0.001$), slowed disengagement from threatening stimuli ($F = 401.431$, $P < 0.001$), and slowed disengagement from positive stimuli ($F = 401.431$, $P < 0.001$). There were significant differences between the higher and lower test anxiety groups in the planned comparisons, while there were no significant differences between the hypnosis and PMR groups at pretest. Given that test anxiety is a situation-specific disorder[13], this study also considered when assessments were made. The three groups did not differ in the number of days until the next exam at pretest ($F = 1.786$, $P > 0.05$), posttest ($F = 2.384$, $P > 0.05$), or follow-up ($F = 2.730$, $P > 0.05$).

Intervention effects on TAS scores

The difference in TAS scores between the two groups was analyzed using 2 (group: Hypnosis and PMR) × 3 (time: Pretest, posttest, and follow-up) repeated measures ANOVA. Significant primary effects of time ($F = 334.444$, $P < 0.001$, $\eta_p^2 = 0.792$) and group ($F = 10.619$, $P = 0.002$, $\eta_p^2 = 0.108$), and the significant interaction effect between time and group ($F = 8.869$, $P = 0.002$, $\eta_p^2 = 0.092$) were revealed.

A simple effect analysis was conducted at each level of the group variable. The results are summarized as follows: (1) For the hypnosis group, a significant effect of time was revealed ($F = 304.878$, $P < 0.001$, $\eta_p^2 = 0.874$), and the paired *t*-test suggested that the participants had a significantly lower TAS score at posttest [$t = -21.827$, $P < 0.001$, Cohen's $d = 4.111$, 95% confidence interval (CI): 10.218-12.297] and at follow-up ($t = -14.824$, $P < 0.001$, Cohen's $d = 3.108$, 95%CI: 6.567-8.632), compared with that at pretest. The participants had a significantly higher TAS score at follow-up compared with posttest [$t = 10.551$, $P < 0.001$, Cohen's $d = 1.110$, 95%CI: (-4.356)-(-2.959)]; and (2) For the PMR group, a significant effect of time was revealed ($F = 93.195$, $P < 0.001$, $\eta_p^2 = 0.679$), and the paired *t*-test suggested that the participants had a significantly lower TAS score at posttest ($t = -10.777$, $P < 0.001$, Cohen's $d = 2.067$,

Table 1 Characteristics of the participants and baseline comparison among three groups at pre-test

	Control (*n* = 45)		Hypnosis (*n* = 45)		PMR (*n* = 45)		Hypnosis & PMR *vs* control			Hypnosis *vs* PMR		
	M	*SD*	*M*	*SD*	*M*	*SD*	*t*/χ^2	*P* value	*Cohen's d*/Cramer's φ	*t*/χ^2	*P* value	*Cohen's d*/Cramer's φ
Female, *n*	17		27		26		5.35	0.02	0.19	0.05	0.83	0.02
Age	20.94	0.94	20.76	1.05	20.84	0.85	0.13	0.90	0.08	-0.44	0.66	0.08
Education	14.71	0.84	14.80	1.14	14.96	0.82	-0.97	0.33	0.18	-0.76	0.45	0.16
SHSS	8.08	1.92	7.88	1.80	7.57	1.45	1.13	0.26	0.19	0.91	0.37	0.18
TAS score	8.66	1.33	23.74	1.63	23.97	2.42	45.03	< 0.001	8.77	0.53	0.60	0.11
STAI score												
Trait	36.78	1.75	49.38	3.14	50.20	2.47	28.14	< 0.001	5.51	1.38	0.17	0.29
State	36.06	1.89	48.34	2.92	49.14	2.59	27.59	< 0.001	5.33	1.37	0.17	0.29
Speeded detection												
Threatening words	-6.99	212.68	-381.10	159.76	-397.49	189.92	-10.37	< 0.001	1.89	-0.94	0.35	0.19
Positive words	-403.62	163.41	-219.88	170.82	-226.21	254.62	4.95	< 0.001	0.94	-0.14	0.89	0.03
Slowed disengagement												
Threatening words	111.19	341.38	379.48	437.92	431.94	386.65	4.14	< 0.001	0.78	0.62	0.55	0.13
Positive words	100.93	291.41	-173.90	353.80	-113.31	403.44	-3.80	< 0.001	0.72	0.76	0.45	0.16

False Discovery Rate correction for multiple comparisons was applied to the *P* values.
PMR: Progressive muscle relaxation; SHSS: Stanford hypnotic susceptibility scale; STAI: State-Trait Anxiety Inventory; TAS: Test anxiety scale.

95%CI: 6.620-9.665) and at follow-up (t = -7.444, P < 0.001, Cohen's d = 1.408, 95%CI: 3.896-6.789), compared with that at pretest. The participants had a significantly higher TAS score at follow-up compared with posttest [t = 22.164, P < 0.001, Cohen's d = 0.572, 95%CI: (-3.055)-(-2.545)].

The simple effect analysis at each level of time variable was conducted by planned t-test. At the posttest level, the hypnosis group had a significantly lower TAS score than the PMR group [t = -3.664, P < 0.001, Cohen's d = 0.772, 95%CI: (-5.156)-(-1.530)]. At the follow-up level, the hypnosis group also had a significantly lower TAS score than the PMR group [t = -2.943, P = 0.004, Cohen's d = 0.621, 95%CI: (-4.164)-(-0.807)] (Figure 2).

Intervention effects in the attentional bias and STAI

The two higher test anxiety groups were compared with regard to their post-test scores of attentional bias and STAI, including pre-test scores as covariate. The results are displayed in Table 2. On speeded

Table 2 Analysis of covariance comparing hypnosis and progressive muscle relaxation groups in post-test scores with pre-test as covariate

	Hypnosis (n = 45)		PMR (n = 45)		ANCOVA		
	M	*SD*	*M*	*SD*	*F*	*P* value	η^2
Speeded detection							
threatening words	-346.00	279.88	-91.86	199.57	30.35	< 0.001	0.26
Positive words	-203.59	299.03	-300.54	242.72	10.03	0.002	0.10
Slowed disengagement							
threatening words	260.04	398.21	387.18	420.11	3.36	0.070	0.04
Positive words	-4.78	369.07	-117.22	372.78	11.46	0.001	0.12
STAI scores							
State	35.11	2.53	36.32	1.92	6.04	0.02	0.07
Trait	38.21	2.51	38.39	2.34	0.12	0.73	0.001

PMR: Progressive muscle relaxation; STAI: State-Trait Anxiety Inventory; ANCOVA: Analysis of covariance.

detection trials, the hypnosis group was slower in detecting threatening stimuli and faster in detecting positive words than the PMR group. On slowed disengagement trials, the hypnosis group had a faster reaction time to threatening stimuli (one-tailed $P = 0.035$) or to positive words than the PMR group.

The average posttest scores on state anxiety and trait anxiety are presented in Table 2. The table shows that the hypnosis group had a lower state anxiety score than the PMR group, while there was no significant difference in the trait anxiety scores of the two groups. Additionally, we compared the differences in attentional bias and STAI scores between pretest and posttest. For the hypnosis group, there were significant differences between pretest and posttest in speeded detection of threatening words ($t = -9.143$, $P < 0.001$, Cohen's $d = 1.600$), speeded detection of positive words ($t = 3.010$, $P = 0.004$, Cohen's $d = 0.384$), slowed disengagement from threatening words ($t = -4.444$, $P < 0.001$, Cohen's $d = 0.285$), and slowed disengagement from positive words ($t = 3.865$, $P < 0.001$, Cohen's $d = 0.468$). However, for the PMR group, there were no significant differences in any of the above scores ($P > 0.05$). For the hypnosis group, there were significant differences between pretest and posttest in trait anxiety ($t = 608.99$, $P < 0.001$, Cohen's $d = 4.815$) and in state anxiety ($t = 150.83$, $P < 0.001$, Cohen's $d = 5.491$). For the PMR group, there were significant differences between pretest and posttest in trait anxiety ($t = 42.481$, $P < 0.001$, Cohen's $d = 3.969$) and in state anxiety ($t = 27.646$, $P < 0.001$, Cohen's $d = 4.864$).

Clinically significant change

The results show that 39 participants in the hypnosis group (86.67%) and 28 participants in the PMR group (62.22%) met the criteria for clinically significant change (RCI score greater than 1.96 in TAS score at posttest; $\chi^2 = 7.07$, $P = 0.008$).

DISCUSSION

This study investigated the efficacy of hypnosis and PMR for treating individuals with test anxiety. Both treatments appeared sound and demonstrated high within-group effect size in primary outcomes of test anxiety after intervention and at 2-mo follow-up. An important finding is that hypnosis was more effective than PMR in reducing attentional bias to threatening stimuli. For the group comparisons at pretest, the highly test-anxious individuals in both the hypnosis and PMR groups showed an attentional bias to threat and test-related information, consistent with previous studies[20,21]. Moreover, the higher test anxiety groups had significantly higher trait and state anxiety than the lower test anxiety group. Previous studies have also found positive correlations between the test anxiety score and STAI[4].

Compared with the pretest, the test anxiety of participants in both the hypnosis and PMR groups significantly decreased after 6-wk intervention and at 2-mo follow-up. Our data add to evidence from previous randomized controlled trials showing that hypnosis and PMR effectively reduce test anxiety [10,27]. Notably, the hypnosis group demonstrated lower test anxiety than the PMR group at posttest and at follow-up. This finding suggests that, in the present study, hypnosis was more effective than PMR in reducing test anxiety. Furthermore, analyses exploring clinically significant change showed that 86.67% of participants in the hypnosis group and 62.22% of those in the PMR group exhibited clinically significant reductions in test anxiety from baseline to posttest. This difference in response rates was

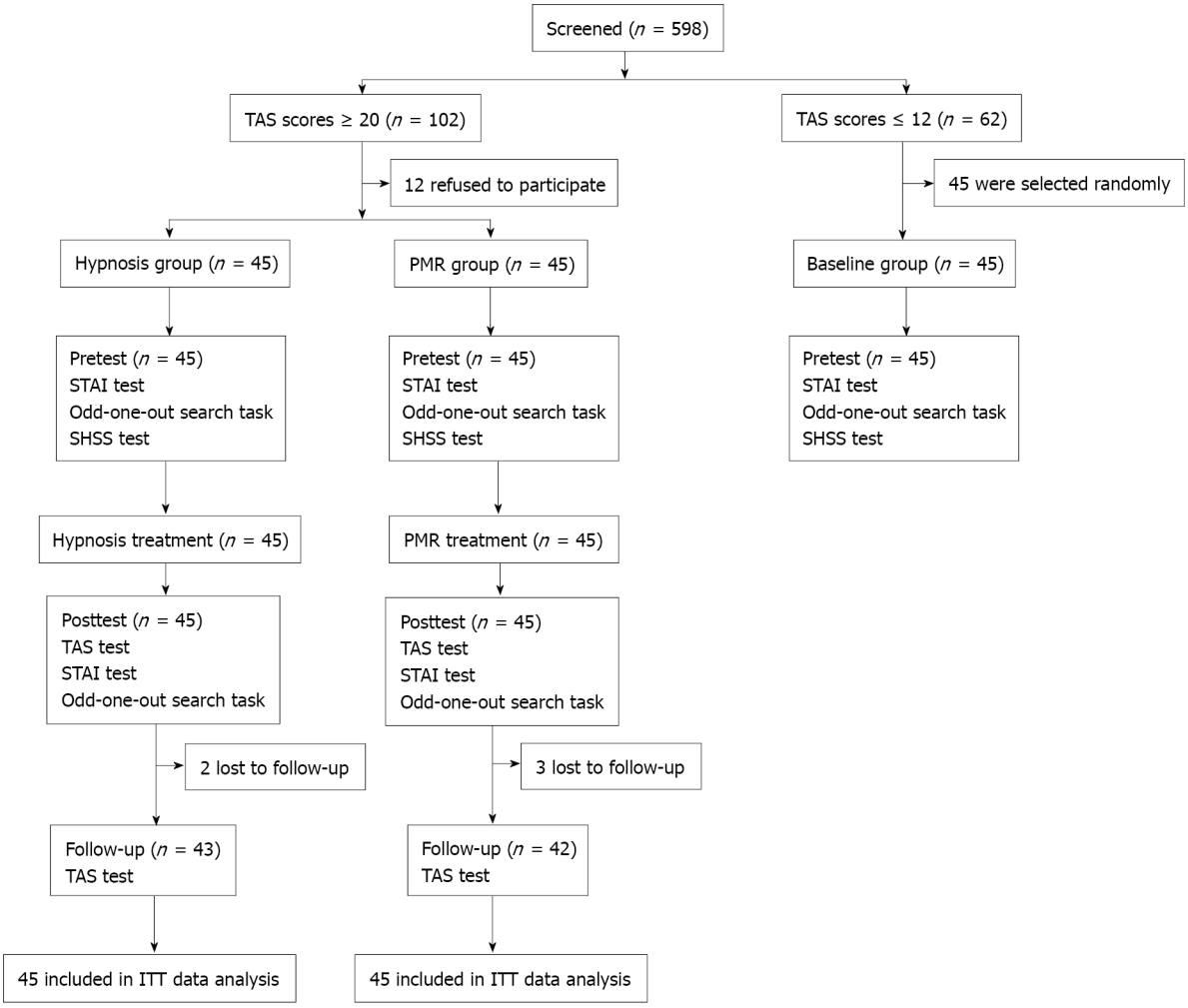

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Figure 1 Enrollment and study flow. PMR: Progressive muscle relaxation; TAS: Test anxiety scale; STAI: State-trait anxiety inventory; SHSS: Stanford hypnotic susceptibility scale; ITT: Intention-to-treat.

statistically significant, demonstrating that hypnosis outperformed PMR in test anxiety symptom reduction. In the hypnotic state, the participants were given suggestions of relaxation that produced positive and pleasant experiences. This method could help individuals reduce anxiety in a relaxed state and facilitate the link between anxious situations and pleasurable experiences. By establishing conditioning, individuals learn to anticipate pleasant experiences following threatening stimuli such as test situations. These findings have the important clinical implication that a combination of hypnosis and other psychotherapies would be more productive in treating anxiety disorders than hypnosis alone. Indeed, a previous study suggested that combined treatment using cognitive behavior therapy and hypnosis produces better effects than hypnosis alone[38].

Both the hypnosis and PMR groups demonstrated reduced trait anxiety and state anxiety at the posttest compared with the pretest, suggesting that test anxiety is relevant to both trait and state anxiety. Interestingly, state anxiety was reduced more in the hypnosis group than in the PMR group, while there was no significant difference in trait anxiety between the two groups at the posttest. State anxiety is unstable and specific to certain situations, which seems to make it more sensitive to training and intervention. This finding is consistent with previous studies reporting more beneficial effects from intervention on state anxiety than on trait anxiety[39].

Notably, this study investigated the attentional bias of test-anxious students by calculating two indices: Speeded detection and slowed disengagement. After the intervention, the individuals in the hypnosis group demonstrated reduced detection speed and slowed disengagement toward threatening stimuli. Significantly, the hypnosis group showed a reversed speeded detection of and delayed disengagement from positive stimuli after the intervention. Taken together, hypnosis appears to help individuals be less sensitive to threatening stimuli but more sensitive to positive stimuli, an effect more significant than PMR intervention.

These findings prove that hypnosis effectively reduced attentional bias to threatening stimuli and increased attentional bias to positive stimuli. In contrast, the PMR had little effect in lowering attentional bias to threatening stimuli. Hypnosis relies on hypnotic and posthypnotic suggestions to

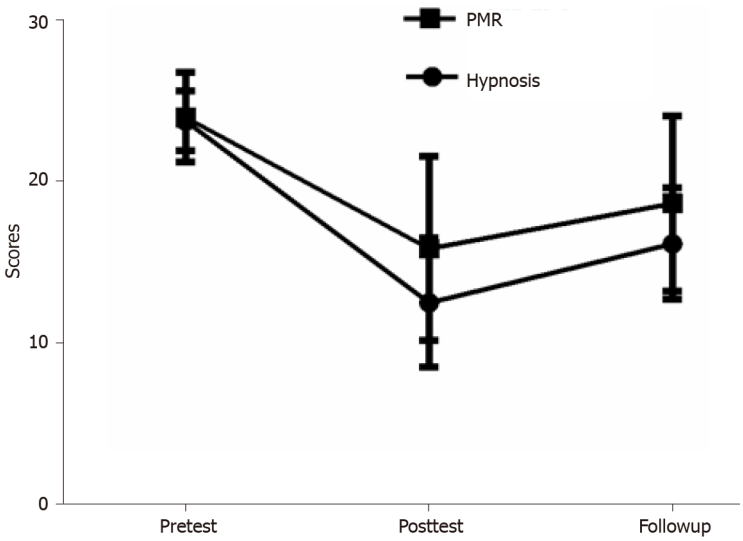

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Figure 2 Test anxiety scores for two groups at pretest, posttest, and 2-mo follow-up test. Error bars represent standard deviation. PMR: Progressive muscle relaxation.

modify participants' cognition and attention, whereas PMR is merely a relaxation technique that can affect the physiological and emotional components of test anxiety[5,6]. However, PMR may have little impact on cognition and attention. Two significant components of hypnosis are cognition and relaxation; combining those two components would be more effective in reducing anxiety[40].

General cognitive models of anxiety suggest that anxious individuals tend to direct their attention toward threatening information in the environment[41,42], thereby facilitating the development and maintenance of the anxious state[43]. Several studies have emphasized the vital influence of attentional bias on anxiety[44,45]. Mathews and MacLeod[46] further indicated that attentional bias has causal effects on vulnerability to anxiety. Therefore, attentional bias should be regarded as an essential target in treatment, and various training paradigms such as attentional bias modification have, in fact, been developed to target it, with promising effects in reducing test anxiety[22] and other disorders[47,48].

Our findings indicate that hypnosis, targeting both muscle relaxation and attentional bias, could decrease anxiety vulnerability to test-related stimuli and reduce attentional bias toward test-related stimuli. With hypnotic suggestions, the participants could remain calm and relaxed when facing information related to the exam, and thus they could cease fixating on the information. However, the PMR, which targeted muscle relaxation, could only change anxiety vulnerability and not attentional bias. All these suggest that it is crucial to look for an underlying mechanism as a target for prevention and treatment.

Hypnosis is not effective for everybody, because some patients respond quickly to hypnotic suggestions, while others are unaffected[49]. It appears that hypnotic susceptibility may affect the outcome, and it is an important control variable. Hypnotic susceptibility indicates proneness to accepting suggestions in and out of hypnosis[50]. Fortunately, there was no significant difference in hypnotic susceptibility among the three groups, and thus the influence of hypnotic susceptibility on the treatment can be ignored.

This study concluded that hypnosis is efficacious in treating test anxiety by reducing anxiety vulnerability and attentional bias to threatening stimuli. However, it had several limitations. First, we did not examine participants' physiological indices, such as skin conductance response, blood pressure, and heart rate. This would provide an objective measure more sensitive to the changes induced by the intervention. Moreover, a lack of physiological measures also makes it difficult to differentiate whether hypnosis did better than PMR due to better physical relaxation or attentional bias, or maybe some other factor. Second, the study did not evaluate the influence of the intervention on exam performance. Finally, we only considered a 2-mo follow-up, leaving the long-term effects of hypnosis in this context inconclusive.

CONCLUSION

Hypnosis is more effective than PMR in reducing test anxiety in medical students; hypnosis could modify attentional bias toward threatening stimuli, but PMR could not. The reason for this may be that the hypnosis developed in this study targeted both anxiety symptoms and attentional bias, suggesting that targeting attentional bias is an important factor in treating test anxiety or other anxiety disorders.

Additionally, hypnosis integrated with some form of therapy may have enhanced effects on mental disorders.

ARTICLE HIGHLIGHTS

Research background

Test anxiety is prevalent among medical students and leads to impaired academic performance. Test-related attentional bias has been identified as an important maintaining factor in test-anxious individuals.

Research motivation

The present study aimed to evaluate whether hypnosis and progressive muscle relaxation (PMR) could modify medical college students' test anxiety and attentional bias.

Research objectives

This study was designed as an initial pilot randomized clinical trial comparing the effects of hypnosis to the effects of PMR on test anxiety and its associated attentional bias. This study is the first to use hypnosis to help individuals reduce test anxiety and attentional bias toward threatening stimuli, and is also the first to use PMR to reduce attentional bias in students.

Research methods

A total of 598 medical students were screened. The participants were divided into higher and lower test anxiety groups according to their scores on the test anxiety scale (TAS). Ninety medical college students with high TAS scores were randomly assigned to a hypnosis or PMR group. Another 45 students with low TAS scores were included for baseline control group. The intervention was conducted weekly for 6 wk, and each session lasted approximately 30 min. The total intervention time and the number of intervention sessions were matched between the hypnosis and PMR groups. Data were collected at pretest, posttest, and 2-mo follow-up.

Research results

Hypnosis group participants had a significantly lower TAS score at posttest (t = -21.827, P < 0.001) and at follow-up (t = -14.824, P < 0.001), compared with that at pretest. PMR group participants also had a significantly lower TAS score at posttest (t = -10.777, P < 0.001) and at follow-up (t = -7.444, P < 0.001), compared with that at pretest. At the posttest level, the hypnosis group had a significantly lower TAS score than the PMR group (t = -3.664, P < 0.001). At the follow-up level, the hypnosis group also had a significantly lower TAS score than the PMR group (t = -2.943, P = 0.004). Clinically significant improvement was found in both the hypnosis and PMR groups (hypnosis = 64.0%; PMR = 62.22%). Hypnosis was more effective than PMR in reducing test anxiety among medical college students. Hypnosis could modify attentional bias toward threatening stimuli, but PMR could not.

Research conclusions

Hypnosis is more effective than PMR in reducing test anxiety in medical students; hypnosis could modify attentional bias toward threatening stimuli, but PMR could not. Additionally, hypnosis integrated with some form of therapy may have enhanced effects on mental disorders. Our findings have important implications for the design and optimization of hypnotic treatments for anxiety disorders.

Research perspectives

This study concluded that hypnosis is efficacious in treating test anxiety by reducing anxiety vulnerability and attentional bias to threatening stimuli. The findings imply that attentional bias can be an important target in future research on treating test anxiety or other anxiety disorders.

FOOTNOTES

Author contributions: Zhang Y, Yang XX, and Luo JY collected the data; Liang M, Li N, and Ma LJ undertook the statistical analysis; Tao Q modified the manuscript; Li XM designed the study and wrote the first draft of the manuscript; and all authors contributed to and approved the final manuscript.

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Observational Study

Composition of treatment alliance in bipolar disorder: A cross-sectional study of patients' perspectives

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Abstract

BACKGROUND

Treatment alliance has an impact on several key patient outcomes in all psychiatric disorders, including bipolar disorder (BD). It has been suggested that the construct of treatment alliance is different among patients from routine psychiatric settings compared to psychotherapeutic settings. However, research on the composition of treatment alliance in psychiatric disorders, such as BD, is relatively limited.

AIM

To determine whether a broader construct of treatment alliance was prevalent among outpatients with BD.

METHODS

This is a cross-sectional study, conducted in the psychiatric unit of a multi-specialty hospital in north India over 12 mo (September 2018 to September 2019). A consecutive sample of 160 remitted adult outpatients with BD on mood stabilizers for at least a year were selected. The principal instrument to assess treatment alliance was the Working Alliance Inventory-client version (WAI-Client). Other potential constituents of the alliance explored were perceived trust in clinicians assessed by the Trust in Physicians (TRIP) scale, perceived support from clinicians assessed by the Psychosocial Care by Physicians (PCP) scale, and perceived treatment satisfaction assessed by the Patient Satisfaction Questionnaire (PSQ). Associations between scores on all scales were determined by correlational and multiple regression analyses. Exploratory factor analysis of combined items of all scales was conducted using a principal components analysis.

RESULTS

Scores on all the three WAI-Client subscales were significantly correlated with each other (r = 0.66-0.81; P < 0.0001). The total TRIP scores were associated with the total WAI-Client scores (r = 0.28; P < 0.01). The total TRIP scores and the total

PCP scores were also significantly associated with the WAI-Client scores on the Task subscale (r = 0.28-0.29; $P < 0.01$). The total TRIP scores were significantly associated with the total PSQ scores (r = 0.45; $P < 0.0001$). Factor analysis yielded two independent and coherent factors, which explained 69% of the variance in data. Factor-1 ("alliance and support"), which explained about 41% of the variance, was comprised of a combined WAI-Client goal-task-bond component as well as the PCP support items. Factor-2 ("trust and satisfaction"), which explained about 28% of the variance, consisted of all the TRIP trust and the PSQ treatment satisfaction items.

CONCLUSION

A broader construct of treatment alliance in BD was found. Apart from collaborative components, this construct included patients' perceptions regarding trust in clinicians, support from clinicians, and treatment satisfaction.

Key Words: Treatment alliance; Bipolar disorder; Composition; Factor-analysis

Core Tip: Research on the composition of treatment alliance in bipolar disorder (BD) is relatively limited. This study examined its composition in 160 remitted adult outpatients with BD using four different scales. Factor analysis yielded two independent factors explaining 69% of the variance. Factor-1 comprised of a combined Working Alliance Inventory goal-task-bond component and perceived clinicians' support. Factor-2 consisted of items relating to the perceptions of trust in clinicians and satisfaction with treatment. This study suggested that in addition to collaborative components, treatment alliance among patients with BD also includes patients' perceptions of clinicians' trust, clinicians' support, and treatment satisfaction.

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INTRODUCTION

Interest in the alliance between patients and clinicians has been gaining ground in mental health care because of its pivotal role in all aspects of psychiatric practice. Though the evidence is relatively scarce, stronger clinician-patient alliances appear to influence a variety of patient outcomes across different psychiatric disorders[1,2]. The principal benefit of an effective alliance is enhanced treatment adherence and engagement[1-5]. Other benefits for patients include reduced symptom severity, improved quality of life and functioning, favorable treatment attitudes, and greater treatment satisfaction[1-3]. The construct of treatment alliance in mainstream psychiatry has its roots in psychotherapy[1-3,6,7]. Of all the frameworks proposed, psychiatric practice in clinical settings has found Bordin's collaborative concept of working alliance the easiest one to adopt[1,2]. This model has a tripartite structure comprised of mutual agreements between clients and therapists on the goals and tasks of treatment, along with emotional bonds between them consisting of shared feelings of trust, acceptance, and confidence[8-11]. However, even this model is not readily transposed from psychotherapeutic to conventional psychiatric settings because of several discrepancies between the two treatment milieus[2-4,6,7]. These include the dissimilarities in nature, goals, and duration of treatment, the differences in types of patients, the diversities in treatment locations and professionals providing care, and the conflicts between the legal responsibilities of clinicians and their roles as therapists. Additionally, the notion of treatment alliance in psychiatry has also been influenced by other subsequent developments, such as the need for patient-centered care and shared decision-making (SDM), recovery-orientated approaches to care, and theories of clinician-patient communication[1,4,5,7,12]. This has led to proposals for enlarging the concept of treatment alliance in psychiatry by incorporating theoretical perspectives other than psychotherapeutic ones[2-4,6,7]. Focused research on the construct of alliance to determine its exact composition among patients from routine psychiatric settings has also been recommended[1,3,4,6,7]. However, despite such recommendations, research on the constituents of treatment alliance in psychiatric disorders has been limited[2,4,6,7].

Research on treatment alliance is particularly scarce for conditions such as bipolar disorder (BD) in spite of ample evidence suggesting that treatment alliance in BD has a similar impact on medication adherence and other patient outcomes[5,13-16]. This consideration prompted the current attempt at examining the composition of treatment alliance among outpatients with BD attending a hospital-based

psychiatric service. Factor analytic studies have been carried out in different groups of patients with psychiatric disorders using a variety of scales. These have shown that, particularly from the patient's perspective, collaborative aspects (task, goal, bond), trust in clinicians, cooperation, therapist support, and treatment satisfaction are the core components of the treatment alliance[17-20]. Additionally, existing studies of BD also indicate that apart from patients' views on collaboration with clinicians, their perceptions of trusting and supportive clinician-patient relationships, and their satisfaction with treatment is also associated with the strength and quality of alliances[21-25]. Thus, based on the existing evidence regarding treatment alliance, it was hypothesized that a broader construct of the alliance was more likely to exist among such patients. Therefore, in addition to collaborative aspects, other contributions to the construct of treatment alliance explored among patients of this study were perceived trust in clinicians, perceived clinicians' support, and treatment satisfaction.

MATERIALS AND METHODS

Participants

This was a part of a larger cross-sectional study which had examined the association of treatment alliance with medication adherence among outpatients with BD undergoing treatment at the psychiatry department of a multi-specialty hospital in north India. Sample size estimation, based on non-adherence rates of 30%, indicated that a minimum of 160 patients was required (alpha = 80%; $P < 0.05$).

Patients aged more than 18 years, with a Diagnostic and Statistical Manual of Mental Disorders-IV diagnosis of BD and on mood stabilizer treatment for at least a year before intake were selected. Patients with organic mental disorders, intellectual disabilities, acute illnesses, and potential for self-harm or violence were excluded. Patients had to be in remission during intake. Remission was defined as current scores of less than seven on the Hamilton Depression Rating Scale and less than six on the Young Mania Rating Scale. Finally, patients had to be accompanied by caregivers who were healthy adults involved in the patient's care.

Of the initial consecutive sample of 250 patients obtained over 12 mo (September 2018 to September 2019), 90 had to be excluded because they did not meet selection criteria. Thus, 160 patients formed the eventual sample of this study. The study was approved by the institutional review committees. Written informed consent was sought from the participants before inclusion and other ethical safeguards were also followed throughout the study.

Assessments

The diagnoses were re-confirmed using the Mini International Neuropsychiatric Interview[26]. Clinical details were compiled using the Self-Rated Retrospective Life Chart Form of the National Institute of Mental Health[27]. Assessment of the collaborative components of treatment alliance was carried out using the Working Alliance Inventory-client version (WAI-Client)[8]. The WAI-Client has 36 items grouped into three subscales of goal, task, and bond, with a seven-point rating for each item. Higher scores (range 36-252) reflect more positive ratings of the alliance. Patients' perceptions of support from clinicians were assessed with the Psychosocial Care by Physicians (PCP) scale and their perceived trust in clinicians was measured with the Trust in Physicians-Short Form scale (TRIP)[28,29]. Both these scales are derived from the validated Cologne Patient Questionnaire and have a four-point item rating system. The 15-item PCP has four subscales of "Emotional Support", "Supportive Behavior" (subjective perceptions of support from physicians) "Informational Support", and "SDM". Higher scores (range 15-60) indicate greater levels of perceived support. Higher scores on the three-item TRIP (range 4-12) suggest greater levels of trust in physicians and their competence. Treatment satisfaction was examined using the Patient Satisfaction Questionnaire (PSQ)[30]. Higher scores on this four-item scale (range 0-12) denote greater satisfaction. To ensure uniformity of assessments, scale items were read out to all the patients and caregivers while eliciting their responses.

Statistical analysis

The data were analyzed using the Statistical Package for the Social Sciences, version 23 for Windows. The nature of the distribution was ascertained by the Kolmogorov-Smirnov test. All continuous variables were normally distributed. Thus, Pearson's coefficients were used to determine the correlation between the scores on all scales and between the subscales of the WAI-Client. The Bonferroni correction was used to minimize chance associations. The significance level after the Bonferroni correction was set at 0.0003. Results from the stepwise multiple regression analyses, which were a part of the larger study were also used to determine associations between different scales. The composition of treatment alliance in BD was examined using exploratory factor analysis of items from all four scales. After the optimum number of factors was determined, a principal components analysis using orthogonal rotation with the varimax technique was conducted to determine the final factor solution. The analysis was approved by a biomedical statistician.

RESULTS

Patient profiles

The majority of the participants were middle-aged males who were married, literate, and employed, and came from rural, middle-class, nuclear families. Ratings of the course of their illness by patients and caregivers revealed indicators of favorable as well as adverse course and outcome. Though the patients had been ill for 18 years on average, they had also been on treatment for an average of 17 years. Moreover, their age of onset was relatively late, with episodes that were not frequent and were only of mild to moderate severity. At intake, the patients were in prolonged remission, with adequate insight and functioning, and low levels of residual symptoms. However, about half of them had predominantly manic episodes, episodes with psychotic symptoms, inadequate adherence, and multiple breakthrough episodes, relapses, or hospitalizations. Other indicators of poor outcome present in about 20%-30% of the patients included rapid-cycling course, comorbid physical or psychiatric disorders, and lifetime suicidal attempts. These details are included in Table 1.

Treatment alliance: Component scores and correlations

The results of the treatment alliance component scores and their correlations are depicted in Table 2. The average total WAI-Client scores were high, suggesting that patients had predominantly positive views about their alliances with clinicians. Mean scores were significantly higher on the Bond subscale, followed by the Task and Goal subscales. The mean PCP scores were similarly high, indicating that patients' subjective perceptions were that their clinicians had been supportive of them. Weighted mean PCP scores were highest on the "Supportive behavior" subscale, followed by the subscales measuring emotional support, SDM, and informational support. The TRIP scores also revealed high levels of trust in the clinicians and their competence. The PSQ scores correspondingly indicated that patients were quite satisfied with the care they were receiving, including their access to clinicians and the competence displayed by them.

Scores on all the three WAI-Client subscales were significantly correlated with each other. The highest values of correlation coefficients were obtained for association between the Goal and Task subscale scores ($r = 0.81$; $P < 0.0001$), followed by the association between the Bond and Task subscale scores ($r = 0.69$; $P < 0.0001$), and the association between the Bond and Goal subscale scores ($r = 0.66$; $P < 0.0001$). The total TRIP scores were significantly associated with the total WAI-Client scores ($r = 0.28$; $P < 0.01$) and scores on the Task subscale ($r = 0.29$; $P < 0.01$). The total PCP scores were significantly associated with the WAI-Client Task subscale scores ($r = 0.28$; $P < 0.01$). The PCP-SDM subscale scores were significantly associated with the total WAI-Client scores ($r = 0.28$; $P < 0.01$) and scores on the goal subscale ($r = 0.28$; $P < 0.01$). However, the results of the stepwise multiple regression analyses (not included here) found that the PCP-SDM scores explained only about 3%-4% of the variance in the total WAI-Client and Goal subscale scores, while the TRIP scores contributed very little to the variance in the WAI-Client scores. Finally, the total TRIP scores were significantly associated with the total PSQ scores ($r = 0.45$; $P < 0.0001$).

Composition of treatment alliance: Results of the exploratory factor analysis

The Bartlett's test of Sphericity and the Kaiser-Meyer-Olkin measure both indicated that factor analysis was appropriate for the combined data from all the scales. Only factors with eigenvalues > 1 were retained and loadings that were ≥ 0.4 were identified as significant loadings for each factor. The Scree plot also tailed off at two factors. Thus, the final factor solution that provided the best fit for the data consisted of two factors, which explained 69% of the variance in the data. Factor-1 or the "alliance and support" factor explained about 41% of the variance. It was made up of a combined WAI-Client component comprising of goals, tasks, and bonds as well as all the PCP support items. Factor-2 or the "trust and satisfaction" factor explained about 28% of the variance and consisted of all the TRIP trust items and the PSQ treatment satisfaction items. The results of the factor analysis are shown in Table 3.

DISCUSSION

The existing literature suggests that a broader construct of treatment-alliance may be prevalent among patients from conventional psychiatric settings[2,4,6,7]. Nevertheless, studies of the composition of alliance among these patients are relatively few compared to studies among psychotherapy clients. The majority of studies among patients receiving psychotherapy have found a two-factor structure of treatment alliance, employing either the WAI or other measures[31-34]. These two factors have usually included a "relationship" or bond factor and another "collaborative" or combined task and goal factor[1,2,10,11], although the second factor has also included treatment satisfaction and help from therapists[17,18]. Others have found a single factor structure of alliance that incorporates the three dimensions of task, goal, and bond[31,35-38]. An equal number of studies have found separate factors for the three dimensions, but have noted a great deal of overlap between the task and goal components[39-41]. Among patients with psychiatric disorders, factor-analytic studies of the WAI or the Helping Alliance

Table 1 Participants' profiles

Demographic & clinical variables	Patients with BD, *n* = 160
Age (yr)	
mean ± SD (range)	43.96 ± 13.51 (18-65)
Sex	
Male, *n* (%)	107 (67)
Female. *n* (%)	53 (33)
Marital status	
Currently single, *n* (%)	27 (17)
Currently married, *n* (%)	133 (83)
Year of education	
mean ± SD (range)	11.85 ± 3.27 (5-18)
Occupation	
Not earning, *n* (%)	43 (26)
Earning, *n* (%)	117 (74)
Family income, in rupees per month	
mean ± SD (range)	36977 ± 29385 (1500-131500)
Family type	
Nuclear, *n* (%)	106 (66)
Non-nuclear, *n* (%)	54 (34)
Residence	
Rural, *n* (%)	128 (80)
Urban, *n* (%)	32 (20)
Middle socioeconomic class, *n* (%)	110 (69)
Diagnosis	
BD type I, *n* (%)	157 (98)
BD type II, *n* (%)	3 (02)
Most recent episode	
Manic or hypomanic[1], *n* (%)	88 (55)
Depressive, *n* (%)	72 (45)
Age of onset (yr)	
mean ± SD (range)	26.11 ± 09.50 (12-60)
Duration of illness (mo)	
mean ± SD (range)	210.88 ± 132.73 (12-600)
Duration of treatment (mo)	
mean ± SD (range)	202.05 ± 129.01 (12-570)
Duration of current remission (mo)	
mean ± SD (range)	19.82 ± 38.99 (4-456)
HDRS score	
mean ± SD (range)	2.24 ± 1.18 (1-7)
YMRS score	
mean ± SD (range)	1.56 ± 0.830 (1-6)
Insight-YMRS item 11 score	

mean ± SD (range)	0.50 ± 0.56 (0-2)
Insight-HDRS item 17 score	
mean ± SD (range)	0.55 ± 0.4 (0-2)
GAF score	
mean ± SD (range)	69.04 ± 11.245 (48-92)
Total number of episodes	
mean ± SD (range)	6.94 ± 5.77 (1-40)
Number of manic episodes[1]	
mean ± SD (range)	3.68 ± 3.62 (0-30)
Number of depressive episodes	
mean ± SD (range)	2.73 ± 2.71 (0-12)
Most recent episode polarity	
Manic or hypomanic[1], *n* (%)	88 (55)
Depressive, *n* (%)	72 (45)
Average severity of manic episodes[1,2], *n* (%)	1.77 ± 0.62 (1-3) median 2
Average severity of depressive episodes[2], *n* (%)	1.49 ± 0.56 (0-3) median 1
Patients with at least one episode of psychotic mania, *n* (%)	107 (67)
Patients with at least one episode of psychotic depression, *n* (%)	84 (53)
Rapid cycling affective disorder, *n* (%)	30 (19)
Seasonal pattern, *n* (%)	62 (39)
Lifetime suicidal attempts, *n* (%)	34 (21)
Patients with any lifetime psychiatric comorbidity, *n* (%)	43 (27)
Patients with comorbid substance use disorders, *n* (%)	34 (21)
Patients with comorbid anxiety disorders, *n* (%)	18 (12)
Patients with lifetime comorbid physical illness, *n* (%)	54 (34)
Lifetime history of inadequate medication-adherence, *n* (%)	77 (48)
Lifetime history of relapses or breakthrough episodes, *n* (%)	85 (53)
Any history of hospitalization, *n* (%)	82 (51)
On mood stabilizer prophylaxis, *n* (%)	160 (100)
On lithium carbonate, *n* (%)	116 (73)
Average dose	720 ± 193 mg/d
On sodium valproate, *n* (%)	42 (27)
Average dose	1021 ± 284 mg/d
On antipsychotics, *n* (%)	105 (66)
On antidepressants, *n* (%)	40 (25)

[1]Manic and hypomanic episodes have been clubbed together and referred to as mania/manic episodes.
[2]Severity was graded as 0-3 with 0 representing remission, 1 representing a mild episode, 2 representing a moderate episode, and 3 representing a severe episode.
BD: Bipolar disorder; GAF: Global Assessment of Functioning Scale; HDRS: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale.

Questionnaire (HAQ) have also found alliance to consist of either two[17,18,32] or three factors[19,20]. Other studies have found a single factor structure of treatment alliance[18,42], including studies of those with BD[21,43].

The approach used in this study to determine the constituents of treatment alliance in BD was partly driven by the collaborative theory of alliance and partly by incorporating components of possible relevance to the alliance in BD, such as patients' perceptions of clinicians' trust, clinicians' support, and

Table 2 Components of treatment alliance: Scores on the four scales

Scores	Patients with BD, *n* = 160, mean ± SD (range)
WAI-Client scores	
Total WAI-Client scores	222.82 ± 20.14 (142-252)
Goal subscale	72.24 ± 7.97 (45-84)
Bond subscale	76.94 ± 7.97 (44-84)
Task subscale	73.64 ± 7.55 (49-84)
PCP scores[1]	
Total PCP scores	40.34 ± 5.86 (22-60)
Emotional support subscale	14.45 ± 3.23 (8-33)
Informational support subscale	6.5 ± 1.03 (4-8)
SDM subscale	9.68 ± 1.57 (5-12)
Supportive behaviour (support) subscale	9.69 ± 1.35 (4-12)
TRIP scores	
Total TRIP scores	10.12 ± 1.45 (8-12)
I completely trusted my doctors	3.40 ± 0.50 (2-4)
I had the impression that the doctors are very competent	3.38 ± 0.51 (2-4)
With the doctors in this hospital one is in good hands	3.40 ± 0.50 (2-4)
PSQ scores	
Total PSQ scores	9.39 ± 1.99 (6-12)
Satisfied with places and times of appointment	2.30 ± 0.59 (1-3)
Satisfied with time available for talking about problems	2.31 ± 0.55 (1-3)
Feel confident that members of service are competent to deal with problems	2.39 ± 0.49 (2-3)
Pleased with the care received from the service so far	2.38 ± 0.50 (1-3)
Correlations between scores on different scales and subscales	Pearson's coefficients[2]
Goal and Task subscale scores of the WAI-Client	0.81[a]
Bond and Task subscale scores of the WAI-Client	0.69[a]
Bond and Goal subscale scores of the WAI-Client	0.66[a]
Total TRIP scores and WAI-Client total scores	0.28[b]
Total TRIP scores and WAI-Client Task subscale scores	0.29[b]
Total PCP scores and WAI-Client Task subscale scores	0.28[b]
PCP-SDM subscale scores and WAI-Client total scores	0.28[b]
PCP-SDM subscale scores and WAI-Client Goal subscale scores	0.28[b]
Total scores on the TRIP and the PSQ	0.45[a]

[a]$P < 0.0001$.
[b]$P < 0.01$.
[1]Weighted mean scores were highest on the "Supportive behavior" subscale (subjective perceptions of support by physicians), followed by the subscales measuring emotional support, shared decision-making and informational support.
[2]Only significant associations that persisted after the Bonferroni corrections are shown. Significant associations were also noted between the Working Alliance Inventory-client version (WAI-Client) total and subscale scores and the Trust in Physicians scores, between the WAI-Client total and subscale scores and the Psychosocial Care by Physicians total and subscale scores, but these did not cross the Bonferroni threshold.
BD: Bipolar disorder; PCP: Psychosocial Care by Physicians; PSQ: Patient Satisfaction Questionnaire; SDM: Shared decision-making; TRIP: Trust in Physicians; WAI-Client: Working Alliance Inventory-client version.

treatment satisfaction. In common with other studies from psychotherapeutic and clinical settings, two relatively independent factors were found to constitute the treatment alliance in BD based on patients' perceptions. The two-factor structure represented a statistically valid factor solution that accounted for a

Table 3 Components of treatment alliance: Results of factor analysis

Components	Initial eigen values[1]			Rotation sums of squared loadings[1]		
	Total	Percentage of variance	Cumulative percentage	Total	Percentage of variance	Cumulative percentage
1	2.789	46.482	46.482	2.459	40.980	40.980
2	1.336	22.272	68.754	1.666	27.774	68.754
Components[2]	Factor 1			Factor 2		
WAI-Client Task scores	0.913			-		
WAI-Client Goal scores	0.903			-		
WAI-Client Bond scores	0.850			-		
PCP total scores	0.552			-		
TRIP total scores	-			0.820		
PSQ total scores	-			0.795		

[1]Bartlett's Test of Sphericity - χ^2 = 356.39; df = 15; P < 0.001; Kaiser-Meyer-Olkin measure = 0.72 - this indicated that factor analysis was appropriate for the data.

[2]Only factors with Eigen values of > 1 were retained and loadings that were ≥ 0.4 were identified as significant loadings for each factor. The Scree plot tailed off at 2 factors.

PCP: Psychosocial Care by Physicians scale; PSQ: Patient Satisfaction Questionnaire; TRIP: Trust in Physicians; WAI-Client: Working Alliance Inventory-client version.

large proportion of variance in the data. The variance explained (69%) was comparable to earlier studies using a variety of instruments among clients from psychotherapeutic settings[31,32,38,39] or among patients from clinical settings[17], including those with BD[21]. Then again, the composition of factors obtained in this study was a little different from the existing studies. Factor-1 of this study consisted of a combined goal-task-bond component ("alliance") and perceived clinicians' support ("support"), while factor-2 consisted of patients' perceptions of trust in clinicians ("trust") and their satisfaction with the treatment received ("satisfaction").

The aggregation of goals, tasks, and bonds into a single component as a part of factor-1 was not unexpected given that there is a great deal of overlap between these dimensions. Significant correlations between the three WAI subscales found in this study have also been reported in several earlier ones and are commonly cited as evidence for this overlap[8,31,35,36,40]. Additionally, a similar integrated alliance factor combining goal, task, and bond items of the WAI has also been replicated across several factor-analytic studies[31,35,36,38,42]. It has been proposed that the integration of the three dimensions could be unique to patients' perceptions of the alliance[10,38,40]. Unlike therapists, patients do not differentiate between the three components of tasks, goals, and bonds and view them as a unified entity. The three dimensions may seem also indistinguishable to patients because they develop simultaneously during treatment. Moreover, it appears that for patients, the quality of their attachment with their clinicians is of primary importance[10,11,42]. Therefore, stronger bonds with clinicians are likely to enhance their agreement on goals and tasks of treatment. Nevertheless, the importance of collaboration as a part of the treatment alliance in BD is supported by several studies that have shown that patients assign a key role to the quality of interactions with their clinicians while rating alliance[23,25,44-46]. The presence of a "support" component as a part of factor-1 was also in keeping with the existing literature on the composition of alliances. One of the earliest concepts of treatment alliance formulated by Horvath and Luborsky[10] was based on patients' perceptions of their therapists as being supportive and helpful in addition to a sense of working together with them[11,17,18]. Since then many factor-analytic studies of the WAI, the HAQ, and other scales have consistently shown that perceived therapist supportiveness and helpfulness is an integral part of the alliance[17,31,36,39]. Additionally, these studies have found that the dimensions of perceived helpfulness and collaboration are highly correlated. This was similar to the association of the PCP support scores and the scores on the goal and tasks components of the WAI-Client in this study. It is also likely that perceived clinician support plays a greater role in patients' rather than clinicians' views of the alliance[36,46]. Moreover, quite a few studies of BD have shown that patients believe clinician support and helpfulness to be a central part of the treatment alliance[24,45-48].

The second factor consisted of a combination of trust in clinicians and treatment satisfaction among patients of this study. Although Bordin's concept of bonds includes feelings of mutual trust between patients and therapists[8-10], perceived trust in clinicians, favorable views about their competence, and treatment satisfaction could have emerged as independent constituents of treatment alliance in this

study simply because separate scales were used to measure these aspects. Moreover, cultural influences on alliance may have had some bearing in this study. The scores on various scales suggested the pre-eminence of trust, bonds, and emotional support as opposed to the goal and task dimensions of the alliance. This is in keeping with the suggestions that not only are Asian patients more likely to have a global view of treatment alliance, but they may also place a much higher value on their relationship with clinicians than on the collaborative aspects of treatment[38]. Consistent with this notion, studies of BD among Chinese patients have shown that patients' trust in clinicians and respect for their authority was far more influential in forging effective alliances than mutual agreements on tasks and goals[49,50]. However, the finding that trust in clinicians and positive beliefs regarding clinicians' competence is a necessary part of treatment alliance seems to be a universal finding[3,51]. Accordingly, the contribution of perceived trust to alliance formation found in this study has been noted by other factor-analytic studies with the WAI and other scales[17,31,32,52]. Studies of patients with BD have also shown that the trusted physician is regarded by them as a positive asset[22,23,44,53]. The treatment satisfaction component of factor-2 consisted of patients' satisfaction with the outcome of treatment, their confidence in the clinicians' abilities, and their access to the clinicians. Factor-analytic studies of the HAQ have shown that perceived satisfaction with treatment outcome is an essential component of alliances[18]. Similarly, patients' confidence in the clinician's competence has formed a part of the construct of alliance in other studies[31,32,52]. Moreover, these studies have also shown that there is considerable overlap between trust or bond, treatment satisfaction, and confidence in clinicians[18,31,52], which was similar to the significant association between the scores on the trust (TRIP) and the patient satisfaction (PSQ) components of this study. Finally, studies of BD have also found treatment satisfaction is associated with patients' perceptions of treatment alliances[21,25,49,50,53]. This suggests that the "trust and satisfaction" factor of this study was a conceptually valid component of treatment alliance in BD.

Limitations

This exploratory study of treatment-alliance in BD had some limitations. Patients of this study had relatively higher total and subscale scores on the WAI-Client compared to other studies of BD using the same scale[54]. Moreover, unlike the other studies, scores on the bond subscale were significantly higher than the task and goal subscales in this study[35,36]. The precedence given to emotional support on the PCP was also different from other studies[28,29], but was in keeping with priority given to emotional bonds with clinicians. Apart from the cultural influences mentioned above, these differences could have been due to the favorable demographic attributes and the relatively stable course of illness among these patients, especially at the time they were assessed. Therefore, these findings will need to be replicated across different patient samples before they can be considered conclusive. This study focused exclusively on patients' perceptions of alliance in BD. Although the existing literature is somewhat inconclusive regarding differences between patients' and clinicians' perceptions of treatment alliance [55], it has to be acknowledged that patients' perceptions represent only one-half of the total picture. The cross-sectional design of this study could have been a limiting factor, though many studies have shown that factor structures remain stable over time[33,37,42]. Some scales used in this study, including the WAI, have not been validated in Indian patients. Finally, though factors like clinicians' support and treatment satisfaction have been considered as indicators of patient outcome, they are also included as a part of several alliance measures[3].

CONCLUSION

Despite these limitations the findings of this study have provided preliminary evidence in favor of a broader concept of treatment alliance among outpatients with BD. The composition of alliance in these patients went beyond the usual collaborative elements to include perceptions of trust in clinicians, perceived support from them, and satisfaction with their treatment. Such an expanded concept of treatment alliance would also be congruent with the results of studies of BD, which have found that patients' views on collaboration with clinicians, clinicians' support, trust in clinicians and their expertise, and treatment satisfaction are associated with effective treatment alliances in BD[5,13-16]. The results emphasize the need for further research into the construct of treatment alliance in BD given its likely impact on adherence and other treatment outcomes. The findings of this study might also provide clinicians with insights into the kind of treatment relationships their patients seek from them. It appears that patients appreciate a collaborative and supportive relationship that promotes mutual trust and enhances perceived satisfaction. Therefore, treatment alliances that incorporate these components are more likely to help patients with BD.

ARTICLE HIGHLIGHTS

Research background

Treatment alliance has an impact on several key patient outcomes in all psychiatric disorders, including bipolar disorder (BD). It has been suggested that the construct of treatment alliance is different among patients from routine psychiatric settings compared to psychotherapeutic settings; however, research on the composition of treatment alliance in psychiatric disorders, such as BD, is relatively limited. The findings of this study might provide clinicians with insights into the kind of treatment relationships their patients seek from them. It appears that patients appreciate a collaborative and supportive relationship that promotes mutual trust and enhances perceived satisfaction. Therefore, treatment alliances that incorporate these components are more likely to help patients with BD.

Research motivation

There is evidence to suggest that the concept of treatment alliance may differ among patients with psychiatric disorders seeking treatment in routine clinical settings. This study attempted to determine whether a broader construct of treatment alliance was prevalent among outpatients with BD. However, this was a preliminary exploratory study of treatment-alliance in BD that had some methodological limitations. The results emphasize the need for further, methodologically advanced research into the construct of treatment alliance in BD given its likely impact on adherence and other treatment outcomes.

Research objectives

Based on the existing evidence regarding treatment alliance, it was hypothesized that a broader construct of the alliance was more likely to exist among such patients. Therefore, in addition to collaborative aspects, other contributions to the construct of treatment alliance explored among patients of this study were perceived trust in clinicians, perceived clinicians' support, and treatment satisfaction.

Research methods

This was a cross-sectional study, conducted in the psychiatric unit of a multi-specialty hospital in north India over 12 mo (September 2018 to September 2019). A consecutive sample of 160 remitted adult outpatients with BD on mood stabilizers for at least a year were selected. The principal instrument to assess treatment alliance was the Working Alliance Inventory-client version (WAI-Client). Other potential constituents of the alliance explored were perceived trust in clinicians assessed by the Trust in Physicians (TRIP) scale, perceived support from clinicians assessed by the Psychosocial Care by Physicians (PCP) scale, and perceived treatment satisfaction assessed by the Patient Satisfaction Questionnaire (PSQ). Associations between scores on all scales were determined by correlational and multiple regression analyses. Exploratory factor analysis of combined items of all scales was conducted using a principal components analysis.

Research results

Scores on all the three WAI-Client subscales were significantly correlated with each other (r = 0.66-0.81; P < 0.0001). The total TRIP scores were associated with the total WAI-Client scores (r = 0.28; P < 0.01). The total TRIP scores and the total PCP scores were also significantly associated with the WAI-Client scores on the task subscale (r = 0.28-0.29; P < 0.01). The total TRIP scores were significantly associated with the total PSQ scores (r = 0.45; P < 0.0001). Factor analysis yielded two independent and coherent factors, which explained 69% of the variance in data. Factor-1 ("alliance and support"), which explained about 41% of the variance, was comprised of a combined WAI-Client goal-task-bond component as well as the PCP support items. Factor-2 ("trust and satisfaction"), which explained about 28% of the variance, consisted of all the TRIP trust and the PSQ treatment satisfaction items.

Research conclusions

A broader construct of treatment alliance in BD was found. Apart from collaborative components, this construct included patients' perceptions regarding trust in clinicians, support from clinicians, and treatment satisfaction.

Research perspectives

More focused research is needed to determine the components of treatment alliance in BD. Future research should also determine the relative importance of the different components of alliance and their impact on key patient outcomes.

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ORIGINAL ARTICLE

Observational Study

Disrupted leptin-fatty acid biosynthesis is an early manifestation of metabolic abnormalities in schizophrenia

Mohammad M Khan

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Abstract

BACKGROUND

Insulin resistance (IR) and impaired energy expenditure (IEE) are irreparable metabolic comorbidities in schizophrenia. Although mechanism(s) underlying IR and IEE remains unclear, leptin and fatty acid signaling, which has profound influence on insulin secretion/sensitivity, glucose metabolism and energy expenditure, could be disrupted. However, no association of plasma leptin with erythrocyte membrane fatty acids, body mass index (BMI), and psychotic symptoms in the same cohort of untreated patients with first-episode psychosis (FEP) or medicated patients with chronic schizophrenia (CSZ) is presented before. These studies are crucial for deciphering the role of leptin and fatty acids in the development of IR and IEE in schizophrenia.

AIM

To determine the association between plasma leptin, erythrocyte membrane fatty acids, particularly, saturated fatty acids (SFAs), BMI and psychotic symptoms in patients with FEP and CSZ.

METHODS

In this study, twenty-two drug naive patients with FEP, twenty-one CSZ patients treated with atypical antipsychotic drugs, and fourteen healthy control (CNT) subjects were analyzed. Plasma leptin was measured using sandwich mode enzyme-linked immunosorbent assay. Erythrocyte membrane SFAs were measured using ultrathin capillary gas chromatography. BMI was calculated by using the formula: weight (kg)/height (m^2). Psychiatric symptoms were evaluated at baseline using brief psychiatric rating scale (BPRS), and positive and negative

syndrome scale (PANSS). The total BPRS scores, positive and negative symptom scores (PANSS-PSS and PANSS-NSS, respectively) were recorded. Pearson correlation coefficient (r) analyses were performed to find the nature and strength of association between plasma leptin, PANSS scores, BMI and SFAs, particularly, palmitic acid (PA).

RESULTS

In patients with FEP, plasma leptin not BMI was significantly lower (P = 0.034), whereas, erythrocyte membrane SFAs were significantly higher (P < 0.005) compared to the CNT subjects. Further, plasma leptin showed negative correlation with erythrocyte membrane SFAs-PA (r = −0.4972, P = 0.001), PANSS-PSS (r = −0.4034, P = 0.028), and PANSS-NSS (r = −0.3487, P = 0.048). However, erythrocyte membrane SFAs-PA showed positive correlation with PANSS-PSS (r = 0.5844, P = 0.0034) and PANSS-NSS (r = 0.5380, P = 0.008). In CSZ patients, plasma leptin, BMI, and erythrocyte membrane SFAs, all were significantly higher (P < 0.05) compared to the CNT subjects. Plasma leptin showed positive correlation with BMI (r = 0.312, P = 0.032) but not with PANSS scores or erythrocyte membrane SFAs-PA. However, erythrocyte membrane SFAs-PA showed positive correlation with PANSS-NSS only (r = 0.4729, P = 0.031). Similar changes in the plasma leptin and erythrocyte membrane SFAs have also been reported in individuals at ultra-high risk of developing psychosis; therefore, the above findings suggest that leptin-fatty acid biosynthesis could be disrupted before the onset of psychosis in schizophrenia.

CONCLUSION

Disrupted leptin-fatty acid biosynthesis/signaling could be an early manifestation of metabolic comorbidities in schizophrenia. Large-scale studies are warranted to validate the above findings.

Key Words: Schizophrenia; Leptin; Fatty acids; Insulin resistance; Impaired energy expenditure

Core Tip: Insulin resistance (IR) and impaired energy expenditure (IEE) are untreatable metabolic comorbidities in schizophrenia. Leptin and fatty acids have profound influence on insulin synthesis, secretion and energy metabolism. Although previous studies have measured plasma leptin and membrane fatty acids in schizophrenia, findings are very heterogeneous, and moreover, no single study has ever measured both plasma leptin and membrane fatty acids together in the same cohort of schizophrenia patients. These studies are crucial not only for analyzing the relationship between leptin and fatty acids in the same cohort of schizophrenia patients, but also for deciphering their role in the development of IR and IEE.

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INTRODUCTION

Schizophrenia is a complex multisystem disorder, which apart from displaying psychotic symptoms and cognitive deficit also manifests a range of metabolic abnormalities including insulin resistance (IR) and impaired energy expenditure (IEE)[1-4]. Evidence suggests that IR and IEE may develop before the onset of psychosis and deteriorate further following antipsychotic intervention, prompting premature antipsychotic withdrawal, a leading cause of relapse in schizophrenia[5-9]. Deciphering the underlying mechanism(s) may help in developing appropriate therapies for minimizing IR and IEE and increasing treatment adherence and outcome in schizophrenia.

While several mechanisms may contribute in the development of IR and IEE, disrupted adipokine and fatty acid (FA) signaling could play a central role. Leptin is an important adipokine, which at physiologically elevated condition strongly inhibits insulin synthesis and secretion and causes weight gain by stimulating lipogenesis and adipogenesis while concurrently inhibiting fatty acid oxidation[10-12]. Removing leptin from blood circulation has been shown to normalize body weight and hyperglycemia in obese animals[13].

FAs, specially, saturated FAs (SFAs) stimulate insulin secretion from pancreatic β-cells[14], but inhibit both leptin synthesis and secretion from adipose tissue[15,16]. Since adipose tissue (adipocytes), like

erythrocytes, contain high percentage of SFAs; consequently, SFAs could be the main regulators of leptin synthesis and secretion from adipose tissue. Evidence suggests that elevated SFAs can impair glucose and FA metabolism by inducing endoplasmic reticulum stress and mitochondrial dysfunction [17]. Moreover, while intracellular accumulation of all FAs can provoke IR, effect of SFAs could be more detrimental and persistent due to the development of various inflammatory cues[18].

Although previous studies have measured plasma leptin and membrane SFAs in schizophrenia, findings are very conflicting and association between leptin, SFAs and body mass index (BMI) has not been studied. Moreover, no study has ever measured plasma leptin, membrane SFAs and BMI together in the same cohort of patients with schizophrenia. These studies are crucial not only for analyzing the relationship between leptin, SFAs, and BMI in schizophrenia, but also for deciphering their role in the development of IR, IEE, and other metabolic comorbidities.

In this study, association between plasma leptin, erythrocyte membrane SFAs, and BMI was determined in the drug-naive patients with first-episode psychosis (FEP), medicated patients with chronic schizophrenia (CSZ), and healthy control (CNT) subjects. While our group has published earlier preliminary data on the membrane FAs including SFAs, monounsaturated FAs and polyunsaturated FAs[19], data on the plasma leptin and BMI and its association with erythrocyte membrane SFAs, BMI and clinical symptoms in patients with FEP and CSZ is naive and is presented here. In addition, possible mechanisms delineating the role of leptin and SFAs in the development of IR and IEE are discussed.

MATERIALS AND METHODS

Patients and control subjects

A total of twenty-two (n = 22) drug-naïve FEP patients, twenty-one (n = 21) medicated patients with CSZ, and fourteen (n = 14) male control (CNT) subjects were analyzed in this study. Patients with FEP were enrolled from consecutive admissions at the Department of Psychiatry, Dwight David Eisenhower Army Medical Center (DDEAMC), Fort Gordon, GA. The patients were mostly active duty army personal diagnosed with schizophrenia or schizophreniform disorder using DSM IV criteria, and after six months follow-up period during subsequent hospitalization. The BMI was calculated according to the formula BMI = kg/m^2, where kg is body weight in kilogram and m is the height in meters[20]. Clinical symptoms of the patients were evaluated at baseline using brief psychiatric rating scale (BPRS) and the positive and negative syndrome scale (PANSS)[21,22]. The total BPRS scores, positive symptoms scores (PANSS-PSS: sum of scores on conceptual disorganization, hallucination, delusions, unusual thoughts, contents, and suspiciousness), and negative symptom scores (PANSS-NSS: sum of scores on emotional withdrawal, blunted effect and motor retardation) were examined in this study. The mean age at the onset of psychosis was 22.40 ± 4.08 years. Patients with CSZ were enrolled at the outpatient clinic of Mental Health Service, VA Medical Center (VAMC), Augusta, GA. The clinical symptoms of these patients were analyzed using the same methodologies as used for patients with FEP. The CSZ patients were on treatment with various atypical antipsychotic drugs (AAD) including clozapine (n = 14), olanzapine (n = 4), or risperidone (n = 3) for the past 1-5 years. It is important to point out that FEP patients after discharge from Army Medical Centers such as DDEAMC are admitted to the Psychiatry Services at the VA Medical Centers. Therefore, both patient groups in this study represent unique populations with demographic similarities except, the years of illness and treatment. The CNT subjects (n = 14) consisted of healthy volunteers recruited *via* advertisements at the Medical College of Georgia (MCG), VAMC, and DDEAMC. The CNT subjects were matched for age and gender with the patients with FEP. The demographic and clinical characteristics of the patients are presented in the Table 1. Institutional Review Boards of DDEAMC and MCG, Augusta, GA approved the research protocol, and a signed consent was taken from all the patients and CNT subjects.

Regarding inclusion and exclusion criteria, all patients with FEP and CSZ were included in this study on the basis of the following criteria; they were medically healthy except psychosis, and none had a history of seizures or severe head injury with loss of consciousness or a history of substance abuse within the last one year. Patients with any of these complications were excluded from the study. Moreover, during the six months follow up period of patients with FEP, those patients who did not meet DSM IV criteria for diagnosis or who turned out to have primary bipolar or major depression were also excluded from the study. A total of 38 patients with FEP were followed up for six months, 29 patients (23 male and 6 female) were found to be eligible. Out of 29 patients, 6 female patients were excluded and 1 male patient plasma sample was not used due to turbidity, so only only 22 male patients with FEP were analyzed.

Analysis of erythrocyte membrane FAs and plasma leptin

The procedures for measuring erythrocyte membrane FAs has been published earlier by our group, it is not discussed here for brevity[19,23]. For measuring plasma leptin, fasting blood was drawn in Lavender vaccutainer containing EDTA. The blood was centrifuged at 2500 rpm for 10 min at 5C. Plasma was carefully separated and stored at -20C before use. Sandwich mode enzyme-linked immunosorbent assay (ELISA) was used to measure plasma leptin using a commercially available Kit

Table 1 Demographic and clinical characteristics of the study subjects

Characteristics	CNT	FEP	CSZ
Age (yr)	25 ± 7.6	23.54 ± 4.65	42.23 ± 5.12
Gender (M:F)	14:0	22:0	21:0
Age at onset of psychosis		22.80 ± 4.78	23.15 ± 6.35
Years of Illness		≤ 5.0 d	22.77 ± 7.21
Total BPRS Total		45.18 ± 12.53	38.17 ± 6.96
Total PANSS-PSS		21.03 ± 4.81	12.88 ± 4.10
Total PANSS-NSS		20.91 ± 5.10	07.82 ± 2.31
Plasma leptin (ng/mL)	5.79 ± 0.80	4.77 ± 1.35	08.33 ± 1.25
BMI (kg/m^2)	25.1 ± 2.61	23.2 ± 2.14	29.86 ± 3.60
Smoking		2/23	3/21
Antipsychotic use			+++
Tobacco			
Cannabis			

CNT: Control subjects; FEP: First-episode psychosis; CSZ: Chronic schizophrenia; BPRS: Brief psychiatric rating scale; PANSS-PSS: Positive symptom scores; PANSS-NSS: Negative symptom scores; BMI: Body mass index.

from Signet Laboratories (Dedham, MA). The ELISA procedure was performed in accordance with the directions of the manufacturer in a sandwich mode using two monoclonal antibodies to leptin: a coating antibody and an HRP-conjugated antibody. The ELISA plates were supplied pre-coated with the coating antibody. All samples were diluted to 1:3000 (in PAT buffer provided with kits) before use. The plates were incubated in duplicates with 100 L of diluted samples overnight at 4C in dark. The wells were washed three times with 250 L of PT buffer (PBS-Tween 20 buffer provided with kit). Plates were then incubated with 100 L of diluted conjugate (HRP-conjugated leptin antibody) for 2 h at room temperature in the dark. The plates were then extensively (3-4 times) washed with 250 L of PT buffer followed by incubation with 150 L O-Phenylenediamine substrate for 20 min at room temperature in the dark to allow color formation. Reaction was stopped by the addition of 50 L of 5.0 M sulfuric acid and the color intensity was read at dual wavelengths using 492 nm as the test wavelength and 620 nm for the reference wavelength. All samples were analyzed twice simultaneously.

Statistical analysis

All statistical analyses were performed using Prism software and the values are expressed as mean ± SE. The values of slope and intercept for the standard samples were calculated by the linear regression method. The data was further analyzed for significance between groups using Student's *t*-test (two-tailed variance) or One-Way ANOVA, and a P value < 0.05 was considered significant. Pearson correlation coefficient (r) analysis was performed to find the nature and strength of association between different variables including SFAs, plasma leptin, BMI, and clinical symptoms including PANSS-PSS and PANSS-NSS.

RESULTS

Table 1 shows the demographic and clinical characteristics of the patients and CNT subjects. Figure 1 shows statistical analyses of plasma leptin, BMI, erythrocyte membrane SFAs including palmitic acid (PA) and stearic acid (SA) in CNT subjects, FEP and CSZ patients. Average plasma leptin (Figure 1A) in FEP patients (4.77 ± 1.35 ng/mL) was significantly (P = 0.028) lower than CNT subjects (5.79 ± 0.80 ng/mL), whereas, in CSZ patients, plasma leptin (8.33 ± 1.25 ng/mL) was significantly higher than FEP patients (P = 0.006). The average BMI value (Figure 1B) of FEP patients (23.21 ± 2.14) was statistically similar to the BMI value of CNT subjects (25.10 ± 2.61, P = 0.144). However, the average BMI value (Figure 1B) of AAD treated CSZ patients (29.86 ± 3.60) was significantly (P = 0.012) higher than FEP patients, and the increase was in parallel with the increase in plasma leptin (Figure 1A). Regarding erythrocyte membrane SFAs, both PA (Figure 1C) and SA (Figure 1D) were significantly (P < 0.005) higher in both FEP and CSZ patients compared to the CNT subjects suggesting that membrane SFA abnormalities in schizophrenia are untreatable.

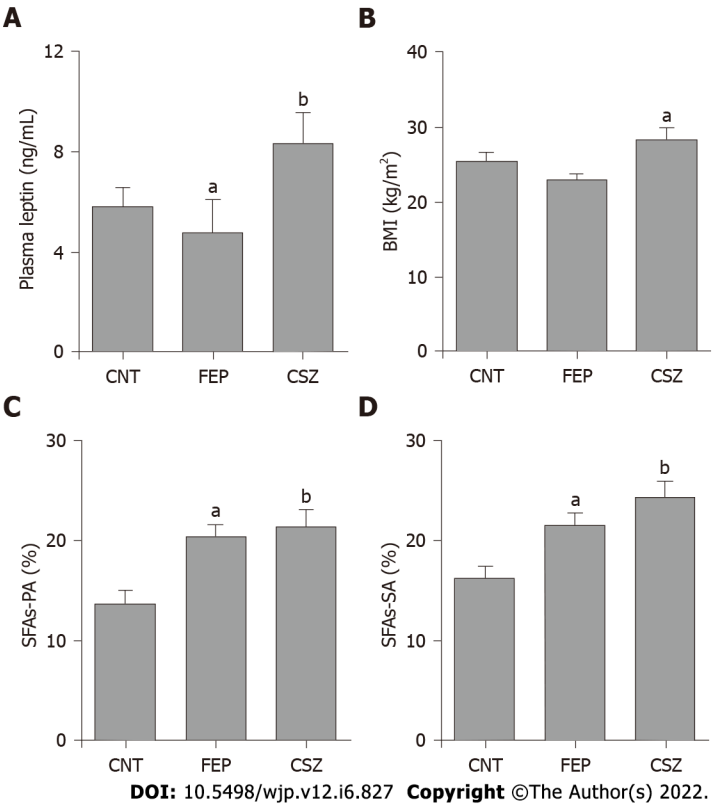

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Figure 1 Statistical analyses of plasma leptin, body mass index, erythrocyte membrane saturated fatty acids in healthy control subjects, first-episode psychosis and chronic schizophrenia patients. A: Average plasma leptin (Figure 1A) in first-episode psychosis (FEP) patients (4.77 ± 1.35 ng/mL) was significantly (P = 0.028) lower than healthy control (CNT) subjects (5.79 ± 0.80 ng/mL). In chronic schizophrenia (CSZ) patients, plasma leptin (8.33 ± 1.25 ng/mL) was significantly higher than FEP patients (P = 0.006); B: The average body mass index (BMI) value of FEP patients (23.21 ± 2.14) was statistically similar to the BMI value of CNT subjects (25.10 ± 2.61, P = 0.144). The average BMI value of clozapine treated CSZ patients (29.86 ± 3.60) was significantly (P = 0.012) higher than FEP patients; C and D: Erythrocyte membrane palmitic acid and stearic acid, respectively were significantly (P < 0.005) higher in both FEP and CSZ patients compared to the CNT subjects. CNT: Healthy control; FEP: First-episode psychosis; CSZ: Chronic schizophrenia; BMI: Body mass index; SFAs: Saturated fatty acids; PA: Palmitic acid; SA: Stearic acid. ^{a}P < 0.05 and ^{b}P < 0.01.

Figure 2 shows the association of plasma leptin with clinical symptom scores. In patients with FEP, plasma leptin showed negative association with both PANSS-PSS (Figure 2A, r = −0.4034, P = 0.028) and PANSS-NSS (Figure 2B, r = −0.3487, P = 0.05). In CSZ patients, although negative association was observed between plasma leptin and either PANSS-PSS (Figure 2C, r = −0.3055, P = 0.18) or PANSS-NSS (Figure 2D, r = −0.3001; P = 0.13), it did not return significance. This could be due to treatment-induced alterations in both plasma leptin and PANSS scores compared to the drug-naive patients with FEP.

Figure 3 shows the association of erythrocyte membrane SFAs-PA with the clinical symptom scores. In patients with FEP, erythrocyte SFAs-PA showed positive correlation with both PANSS-PSS (Figure 3A, r = 0.5844, P = 0.0034) and PANSS-NSS (Figure 3B, r = 0.5381, P = 0.008). In AAD treated CSZ patients, erythrocyte SFAs-PA showed significant positive correlation with PANSS-NSS (Figure 3D, r = 0.4729; P = 0.031), but it was not significant in case of PANSS-PSS (Figure 3C, r = 0.2485, P = 0.28). These findings suggest that elevated erythrocyte SFAs could be associated more strongly with the negative symptoms in patients with both FEP and CSZ.

Since SFAs strongly inhibit leptin synthesis and secretion, therefore, association of leptin with erythrocyte SFAs-PA and BMI was also determined. In FEP patients, plasma leptin was negatively associated with SFAs-PA (Figure 4A, r = −0.4335, P = 0.0194) but not with BMI (Figure 4B, r = 0.2169, P = 0.3206), whereas, in patients with CSZ, plasma leptin showed positive association with BMI (Figure 4C, r = 0.4135, P = 0.0152) but not with erythrocyte SFAs-PA (Figure 4D, r = 0.3331, P = 0.1401). Moreover, SFAs-PA was elevated in both FEP and CSZ patients (Figure 1C and D), whereas, plasma leptin (Figure 1A) and BMI (Figure 1B) were elevated only in patients with CSZ suggesting that elevated plasma leptin could be involved in increasing BMI in CSZ patients.

DISCUSSION

In this study, significant changes in plasma leptin, BMI, and erythrocyte membrane SFAs were observed in patients with FEP and CSZ compared to the CNT subjects. These changes were also significantly

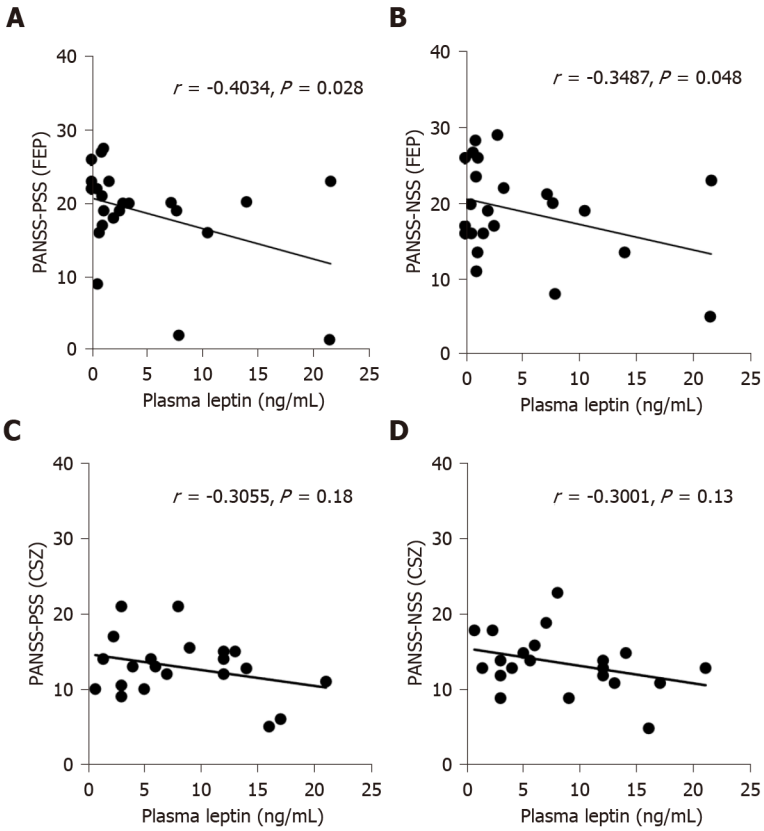

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Figure 2 Association of plasma leptin with clinical symptom (positive and negative syndrome scale) scores. A and B: In first-episode psychosis patients, plasma leptin showed negative correlation with both positive symptom score (PANSS-PSS) (r = −0.4034, P = 0.028) and negative symptom score (PANSS-NSS) (r = −0.3487, P = 0.05); C and D: In chronic schizophrenia patients, no significant negative correlation was observed between plasma leptin and either PANSS-PSS (r = −0.3055, P = 0.18) or PANSS-NSS (r = −0.3001; P = 0.13). PANSS-PSS: Positive and negative syndrome scale-positive symptom score; PANSS-NSS: Positive and negative syndrome scale-negative symptom score; FEP: First-episode psychosis; CSZ: Chronic schizophrenia.

associated with clinical symptoms in both groups of patients. The central message is that in patients with FEP, plasma leptin was significantly low and showed negative association with PANSS scores, whereas, SFAs were significantly higher and showed positive association with PANSS scores. Additionally, plasma leptin showed negative association with SFAs, which is in line with the negative effects of SFAs on leptin synthesis and secretion[15]. In AAD treated CSZ patients, plasma leptin, SFAs and BMI all were significantly higher, which is also in agreement with previous studies showing increased leptin synthesis, and weight gain after AAD treatment[24-26].

This is the first report that shows disrupted leptin and erythrocyte membrane SFA biosynthesis in the same cohort of drug-naive patients with FEP and ADD treated patients with CSZ. In addition, negative association between plasma leptin and erythrocyte SFAs has not been reported before. These findings together with the literature discussed below, suggest that leptin-fatty acid signaling, which plays a central role in insulin secretion, sensitivity, food-intake and energy metabolism, could be disrupted in schizophrenia.

Before discussing the role of leptin and SFAs in the development of IR and IEE, it can be argued that how elevated erythrocyte SFAs could relate to the changes in adipose tissue where leptin and other adipokines are synthesized[27]. Since both erythrocytes and adipose tissue share developmental relationship, and contain high percentage of SFAs[28,29], reduced leptin production in patients with FEP could be a result of increased SFA contents in the adipose tissue. And this effect should to be mediated, specifically, by the cytosolic pool of SFAs, accumulated either due to reduced FA oxidation or increased *de novo* FA biosynthesis or both because, studies have shown that SFAs circulating in the plasma or present in the extracellular space have no significant effect on leptin synthesis and secretion [15,30]. Further, like erythrocytes, SFAs could also be elevated in other tissues of FEP patients as a result of increased oxidative stress and inflammation, as both these conditions strongly stimulate *de novo* SFA biosynthesis[31-35]. Moreover, excess SFAs can be transported from intracellular space to the membrane and outside the cells by specific fatty acid transporter proteins[36].

Elevated SFAs in schizophrenia, and their role in the development of IR and IEE

Over the past thirty years, extensive efforts have been made to understand the role of membrane FAs in the pathophysiology and psychopathology of schizophrenia and other psychiatric disorders. Regarding

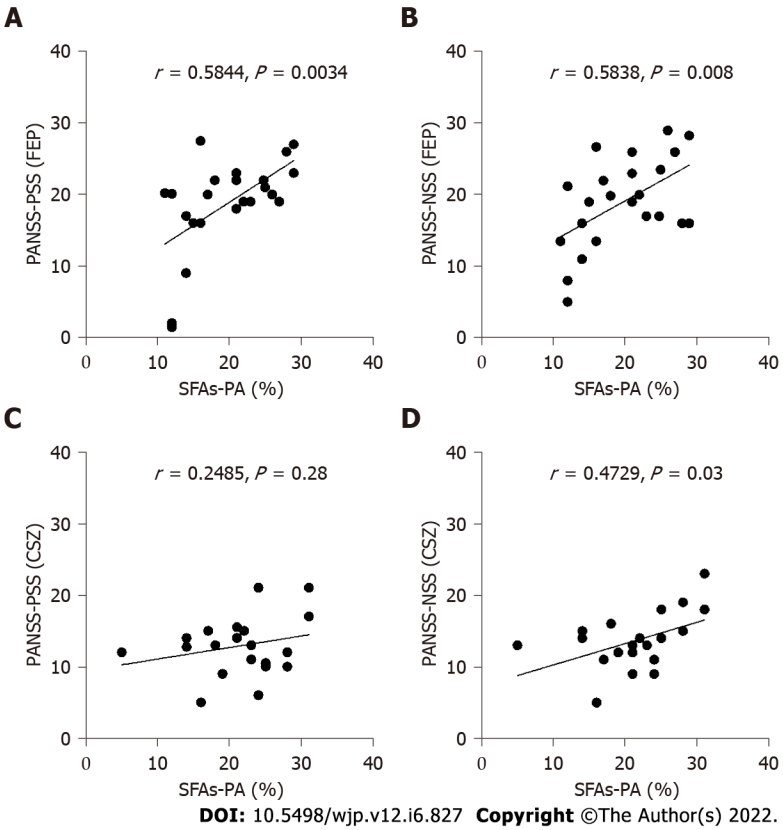

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Figure 3 Association of erythrocyte membrane saturated fatty acids-palmitic acid with clinical symptoms (positive and negative syndrome scale) scores. A and B: In first-episode psychosis patients, erythrocyte saturated fatty acids (SFAs)-palmitic acid (PA) showed positive correlation with both positive symptom score (PANSS-PSS) (A, r = 0.5844, P = 0.0034) and negative symptom score (PANSS-NSS) (B, r = 0.5381, P = 0.008); C and D: In chronic schizophrenia patients, erythrocyte SFAs-PA showed positive correlation with PANSS-NSS (D, r = 0.4729; P = 0.031), but it was not significant in case of PANSS-PSS (C, r = 0.2485, P = 0.28). Similar results were obtained with erythrocyte membrane stearic acid (data not shown). PANSS-PSS: Positive and negative syndrome scale-positive symptom score; PANSS-NSS: Positive and negative syndrome scale-negative symptom score; FEP: First-episode psychosis; CSZ: Chronic schizophrenia; SFAs: Saturated fatty acids; PA: Palmitic acid.

membrane FAs compositions, although there may be some contradictory findings, most studies including our own have shown that erythrocyte membrane PUFAs are reduced, whereas, SFAs are increased in drug-naive patients with FEP[19,37-39]. Similar alterations in PUFAs and SFAs have also been observed in the brain tissue from the patients with FEP[40]. Specially, prefrontal cortex regions have been shown to have deficit in various PUFAs, whereas, proportion of SFAs (particularly, PA) was increased in the specific phospholipid moieties[40]. Likewise, skin fibroblasts from patients with FEP have been shown to have abnormal membrane FA compositions[41].

Intriguingly, erythrocyte FA abnormalities have also been reported in individuals at ultra-high risk of developing psychosis. In a recent study, significant reduction in various PUFAs and increase in SFAs including PA in the erythrocyte membrane has been reported in individuals at ultra-high risk of developing psychosis[42]. These findings strongly support the observations that we reported nearly 20 years ago in FEP patients, and also corroborate findings published by other groups in recent years[15,40]. In conclusion, disrupted FA biosynthesis comprising of reduced PUFAs and increased SFAs could be an early manifestation of schizophrenia pathophysiology.

Regarding the cause of SFA elevation, hypoxia-induced oxidative stress, and inflammation appear to be the potential causative factors in schizophrenia. Hypoxia has been shown to induce *de novo* FA biosynthesis in embryonic neurons and potentiate pro-inflammatory effects of SFAs in macrophages[32,43]. In addition, recent studies have shown that elevated SFAs under hypoxic conditions may serve as hydrogen acceptors, an effect that favors a shift towards anaerobic glycolysis leading to increased lactate production, an indication of IEE[32,33]. Since glutamate/glutamine are required for the *de novo* SFA biosynthesis in neurons under hypoxia[32], increased SFA biosynthesis therefore also support the findings that have shown impaired glutamate/glutamine ratio in patients with FEP and CSZ[44].

Concerning the role of FAs in schizophrenia pathophysiology, although reduced membrane PUFAs have been linked with cognitive deficit and psychotic symptoms[19,38,45,46], consensuses have not reached on the role of elevated SFAs. Since SFAs are the major fuel for energy production and utilization during resting state, increased SFA levels in patients with FEP could be an indication of impaired resting state energy expenditure. Indeed, several recent studies have shown that FEP patients and their first-degree relatives display IEE[47-52]. Also, several lines of evidence suggest that elevated

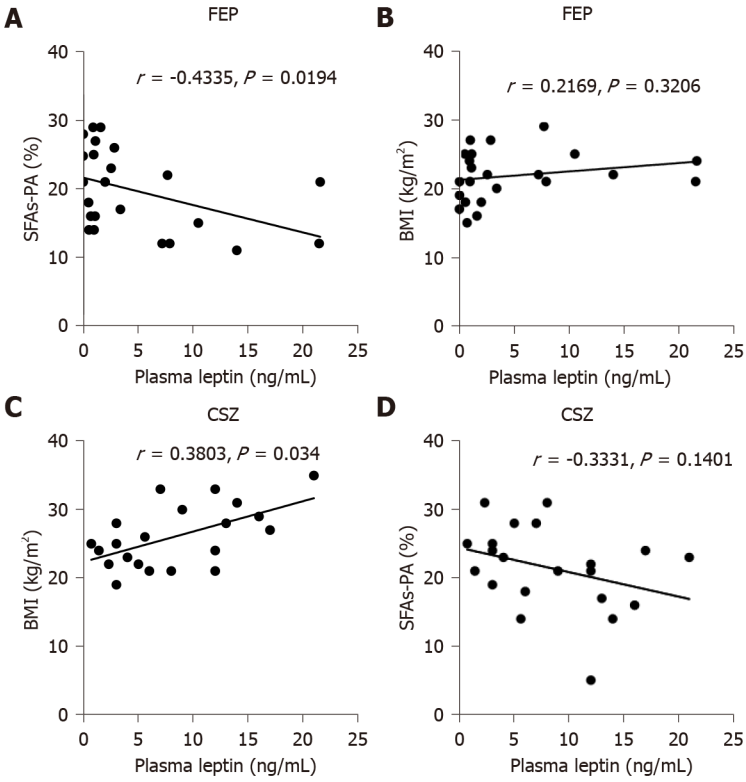

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Figure 4 Association of plasma leptin with erythrocyte saturated fatty acids and body mass index. A-D: In first-episode psychosis patients, plasma leptin showed negative correlation with saturated fatty acids (SFAs)-palmitic acid (PA) (A, r = −0.4335, P = 0.0194) but not with body mass index (BMI) (B, r = 0.2169, P = 0.3206), whereas, in chronic schizophrenia patients, plasma leptin showed positive correlation with BMI (C, r = 0.4135, P = 0.0152) but not with erythrocyte SFAs-PA (D, r = 0.3331, P = 0.1401). FEP: First-episode psychosis; CSZ: Chronic schizophrenia; BMI: Body mass index; SFAs: Saturated fatty acids; PA: Palmitic acid.

SFAs, particularly, PA could be a major risk factor for IR and IEE[53,54].

An overwhelming body of evidence suggests that most of the adverse effects including IR, IEE and increased lactate formation induced by SFAs occur as a result of increased oxidative stress and inflammation (see Figure 5 for detail mechanisms). It has been shown that SFAs, particularly, PA can cause abrupt release of Ca^{2+} from endoplasmic reticulum (ER) thereby depleting ER Ca^{2+} store, which in turn leads to a drastic increase in cytosolic and mitochondrial Ca^{2+} concentration *via* entry through store-operated Ca^{2+} channels[55-57]. This process stimulates reactive oxygen species (ROS) formation causing ER stress and mitochondrial dysfunctions (Figure 5). Evidence suggests that PA can induce ER stress in almost all the cellular systems including pancreas, cardiomyocytes, vascular smooth muscle cells, endothelial cells, skeletal muscle cells, glomerular podocytes, hepatocytes, adipose tissue, and brain by disrupting intracellular Ca^{2+} homeostasis[58].

Additional toxicity of SFAs can be produced by their ceramide derivatives because; elevated SFAs have also been shown to stimulate ceramide synthesis[59,60]. Indeed, while studies analyzing skin fibroblasts from patient with schizophrenia have found reduced total ceramide concentration, SFAs (PA) based ceramide concentration was increased compared to the CNT subjects[61-63]. Similarly, altered production of ceramides, containing PA and other SFA, has also been reported in other tissues from patients with FEP and CSZ[61-63]. Although ceramides have many important functions, their increased production can be detrimental as they can induce inflammation, obesity-associated insulin resistance, abnormal FA oxidation and other toxic effects in various tissues by inducing ER stress, mitochondrial dysfunction, and ROS formation (Figure 5)[59,60,64].

Regarding pro-inflammatory effects, SFA accumulation has been shown to induce pro-inflammatory response in adipose tissue, skeletal muscle, and liver[34,57,65]. In these events, PA activated adipocytes as well as intercalated macrophages, particularly inflammatory type (M1 type) have been shown to play a major role by secreting several pro-inflammatory cytokines including IL-1b, IL-6, IL-8, and TNF-α[57-59,65]. These and other inflammatory cytokines have been found elevated in the brain and plasma of patients with FEP and CSZ[66]. Although treatment with AAD has been shown to reduce various cytokines, IL-1b, IL-6, IL-8 and TNF-α remained elevated despite years of treatment[66,67]. Since we observed that like drug-naive patients with FEP, erythrocyte PA and other SFAs were also elevated in AAD treated CSZ patients, therefore, accumulation of SFAs could be the major contributing factor to the elevated pro-inflammatory response throughout the course of schizophrenia illness.

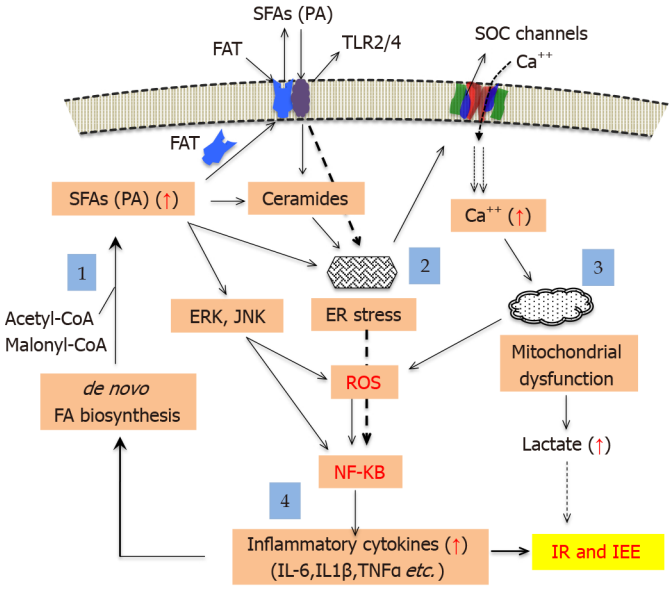

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Figure 5 Mechanisms underlying saturated fatty acids-(palmitic acid)-induced insulin resistance and impaired energy expenditure. Saturated fatty acids (SFAs) are synthesized *de novo* in the cytoplasm from acetyl-CoA and malonyl-CoA (light blue box 1), and are transported by fatty acid transporter proteins from intracellular space to the membrane and to the extra cellular space. Excess SFAs-palmitic acid (PA) can also be converted into ceramides, which together with PA can induce endoplasmic reticulum (ER) stress *via* depletion of stored calcium (light blue box 2). ER stress leads to increased calcium influx *via* plasma membrane-bound store operated calcium channels, resulting into the elevation of cytoplasmic and mitochondrial calcium and production of reactive oxygen species (ROS) as a result of mitochondrial dysfunction (light blue box 3). Both PA and ceramides can also activate plasma membrane TLR2/4 receptor resulting in the activation of MAPK/ERK and JNK pathways. Activation of these pathways leads to the production of ROS and NF-κB activation (light blue box 4), which enhances expression of inflammatory cytokine genes resulting into generation of inflammatory response and development of insulin resistance (IR) and impaired energy expenditure (IEE). SFA-induced mitochondrial dysfunction also stimulates anaerobic glycolysis leading to enhanced production of lactate, which also contributes in the development of IR and IEE. SFAs: Saturated fatty acids; PA: Palmitic acid; SOC: Store operated calcium; ROS: Reactive oxygen species; ER: Endoplasmic reticulum; IR: Insulin resistance; IEE: Impaired energy expenditure.

Altered leptin synthesis in schizophrenia and its role in the development of IR and IEE

Although adipose tissue secretes several adipokines[68], leptin and adiponectin have generated huge interest in schizophrenia. However, here the discussion is limited only to leptin for two reasons. First, several studies have shown that leptin but not adiponectin production is reduced in patients with FEP [69]. Second, if elevated above the normal physiological concentration for longer duration, leptin inhibits insulin secretion, increases fat mass accumulation, and obesity *via* its pro-inflammatory and pro-adipogenic actions[11,13].

In schizophrenia, while previous studies have measured plasma leptin in patients with FEP, findings are very conflicting. For instance, a recent meta-analysis and clinical studies found that plasma leptin production was significantly reduced in antipsychotic-naïve FEP patients compared to the CNT subjects [69-71], whereas other studies found opposite results[72-74]. The reasons for these discrepancies are not clear; however, a number of factors including gender, sex hormones, age, eating behavior, duration of illness, smoking, and other medications may affect leptin production. For instance, plasma leptin levels have been found higher in women than men of the same age, and are also affected by smoking[72-75].

Regarding the role of leptin in the development of IR and IEE, animal studies have shown that leptin deficiency can lead to IR and hyperglycemia, whereas, leptin administration can reverse these abnormalities[76]. Thus, normal leptin concentration is required for maintaining glucose homeostasis. Although leptin is a potent regulator/inhibitor of insulin secretion from pancreatic β-cells under physiological condition[11], it can normalize blood glucose level both by insulin dependent and insulin independent mechanisms and with or without involving central nervous system (CNS). For instance, in a rat model of insulin deficiency diabetes, leptin infusion directly into the brain reversed hyperglycemia, suggesting involvement of CNS dependent mechanism[77,78]. Leptin administration in these model animals also normalized plasma levels of glucagon and corticosterone, which are potent hyperglycemic factors. Likewise in mouse model of type-2 diabetes with normal leptin but defect in insulin like growth factor-1 and leptin receptor signaling, leptin administration significantly prevented insulin resistance and hyperglycemia[79].

Leptin also has profound influence on FA metabolism and energy homeostasis both in adipose and non-adipose tissues. It stimulates FA oxidation and glucose uptake in skeletal and cardiac muscles, inhibits glucose output and lipogenesis in liver[80,81]. In white adipose tissue also, leptin has been shown to directly inhibit *de novo* FA biosynthesis, and increase the release and oxidation of FA[82]. Thus, low plasma leptin in patients with FEP that is observed in this study, could be one of the

contributing factors in the increased membrane SFA levels in patients with FEP.

In the present study, although leptin was significantly low in drug-naive patients with FEP, it was significantly elevated in AAD treated CSZ patients, which is in agreement with previous reports showing increased leptin production by AAD treatment[24,25,69]. Leptin elevation by AAD could be a result of their direct antagonistic action at various calcium channels leading to reduce calcium influx, as optimum intracellular calcium is crucial for optimal leptin synthesis and secretion[16,83]. Several lines of evidence suggest that elevated leptin can cause obesity by inducing pro-inflammatory, pro-lipogenic, and pro-adipogenic response[12,13,24]. Leptin has been shown to increase the production of pro-inflammatory cytokines including TNF-α, IL-10, and IL-6 from adipocytes[12]. Along with TNF-α, leptin can also activate macrophages, intercalated within the adipose tissue, to secrete pro-inflammatory cytokines leading to further amplification of inflammatory response[84-86]. It has been suggested that pro-inflammatory effects of leptin, directly or through TNF-α or both, may lead to the inflammation of the pancreas causing βb-cell dysfunction and reduced insulin secretion[10,11,84], which are typically seen in patients with schizophrenia after long-term treatment with AAD.

Pro-adipogenic effect of leptin is further potentiated by its pro-lipogenic and pro-inflammatory responses[12]. Leptin has been shown to increase the production of PLIN1, CAV-1, PPARγ, SREBP1C, and/or adiponectin during differentiation[12]. Together, these proteins orchestrate signaling mechanisms that increase transcription of various genes required for adipocyte differentiation. Further, leptin has been shown to induce lipid accumulation in adipocytes *via* an mTOR-dependent signaling[12], even in the absence of insulin, which plays a crucial role in pre-adipocyte differentiation. This suggests that leptin may induce adipocyte differentiation and lipogenesis even in the absence of insulin signaling. In support of this, a recent study has shown that removing circulating plasma leptin reduced body weight and normalized hyperglycemia in obese animals[13]. This is an important finding, which may help in designing leptin-based therapies for treating obesity and diabetes in schizophrenia and other psychiatric disorders.

This study has some strengths and limitations. Regarding the strengths: (1) The patients and CNT subjects had comparable socioeconomic and demographic characteristics; (2) FEP patients had shortest reported duration of illness (≤ 5 d); (3) no drug abuse; (4) no prior antipsychotic exposure; (5) minimum smoking (2/21); (6) no sedentary life style of FEP patients as all were active duty army personals; (7) no female hormone (estrogens) influence on plasma leptin and membrane FAs as all patients were male; and (8) restricted food diet. Regarding the limitations: (1) The sample size/number of patients were modest and therefore larger studies are needed to validate the above findings; (2) plasma insulin and IR were not measured in these patients; although, several studies have reported IR in drug-naive patients with FEP, and CSZ; and (3) first visit BMI data of CSZ patients was not available; however, these patients were included mainly for comparison purpose, and similar demographic characteristics of patients and CNT subjects.

CONCLUSION

Over the years it has become increasingly clear that IR and IEE are irreparable metabolic comorbidities in schizophrenia. Although evidence suggests that IR and IEE may appear long before the onset of psychosis, antipsychotic intervention further deteriorates IR and IEE, prompting premature antipsychotic withdrawal, a leading cause of relapse in schizophrenia.

Although various signaling mechanisms could be involved in the development of IR and IEE, in schizophrenia these mechanisms seem to stimulate *de novo* FA biosynthesis leading to increased intracellular concentration of SFAs and their subsequent incorporation into the membrane. Elevated levels of erythrocyte SFAs have also been reported in individuals at ultra-high risk of developing psychosis, therefore, disrupted *de novo* FA biosynthesis could be an early manifestation and underlying cause of IR, IEE and other metabolic comorbidities in schizophrenia.

Antipsychotic drugs have been shown to further aggravate the severity of IR and IEE, which could be related to their ineffectiveness in reducing *de novo* SFA biosynthesis. In addition, all AAD have been shown to increase synthesis of leptin, which if elevated above physiological concentration, stimulates *de novo* FA biosynthesis and lipogenesis while concurrently suppressing lipolysis and FA oxidation. Consequently, leptin elevation by AAD may coincide with the onset of weight gain in schizophrenia. Further, as leptin has been shown to directly inhibit insulin secretion from pancreatic β-cells, its elevation could be a major risk factor associated with the reduced insulin secretion and hyperglycemia, which is typically observed in patients with CSZ during extended treatment with AAD.

One of the strongest evidence for the role of elevated SFAs in the development of IR and IEE is provided by a recent study, which showed that adipocytes overloaded with both SFAs and PUFAs provoked IR irrespective of the inflammatory response suggesting that intracellular accumulation of FAs is sufficient to induce IR whether it increases inflammatory cytokine secretion or not. However, unlike PUFAs, the effect of SFAs could be more detrimental and persistent due to the development of various inflammatory cues. Since oxidative stress and inflammation are potential stimulators of *de novo* FA biosynthesis, therapies aimed at reducing oxidative stress and inflammation or *de novo* FA biosyn-

thesis could be highly effective in reducing IR, IEE and other metabolic comorbidities in patients with schizophrenia and other psychiatric conditions. Additionally, therapies aimed at normalizing leptin level could also be highly effective in increasing insulin level and controlling weight gain during long-term treatment. Since calcium is a potential regulator of leptin synthesis and secretion in adipose tissue, use of calcium supplementation could normalize the plasma levels of both inulin and leptin during schizophrenia treatment.

ARTICLE HIGHLIGHTS

Research background

Apart from classical symptoms of psychosis, patients with first-episode psychosis and their first-degree relatives display a range of metabolic comorbidities including insulin resistance and impaired energy expenditure. One of the major hurdles in treating schizophrenia psychosis is that intervention with antipsychotic drugs further exacerbates the severity of metabolic comorbidities, which leads to premature antipsychotic withdrawal, a leading cause of relapse in schizophrenia. Finding the underlying mechanism(s) is crucial for designing effective therapies for minimizing the development or exacerbation of metabolic comorbidities during antipsychotic treatment in schizophrenia.

Research motivation

Finding the mechanism(s) underlying metabolic comorbidities is crucial for enhancing treatment adherence and outcome in schizophrenia. Finding such mechanism(s) will also help in designing effective therapies for minimizing the development or exacerbation of metabolic comorbidities during antipsychotic treatment in schizophrenia.

Research objectives

Since leptin and fatty acids together have profound influence on insulin secretion/sensitivity, and energy homeostasis, this study is directed to determine the association between plasma leptin, body mass index, and erythrocyte membrane fatty acids, particularly, saturated fatty acids (SFAs) in patients with first-episode psychosis (FEP).

Research methods

Plasma leptin was measured using sandwich mode enzyme-linked immunosorbent assay; whereas, erythrocyte membrane SFAs were measured using ultrathin capillary gas chromatography. Body mass index was calculated by using the formula: weight (kg)/height (m^2). Psychiatric symptoms were evaluated at baseline using brief psychiatric rating scale, and positive and negative syndrome scale (PANSS). Pearson correlation coefficient (r) analyses were performed to find the nature and strength of association between plasma leptin, PANSS scores, body mass index (BMI) and SFAs, particularly, palmitic acid (PA).

Research results

Plasma leptin not BMI was significantly lower, whereas, erythrocyte membrane SFAs were significantly higher in patients with FEP compared to the healthy control subjects. Further, plasma leptin showed negative correlation with erythrocyte membrane SFAs-PA, and PANSS scores. However, erythrocyte membrane SFAs-PA showed positive correlation with PANSS scores. Since, similar changes in the plasma leptin and erythrocyte membrane SFAs have also been reported in individuals at ultra-high risk of developing psychosis, the above findings suggest that leptin-fatty acid biosynthesis could be disrupted from the early stage of the illness in schizophrenia.

Research conclusions

Disrupted leptin-fatty acid biosynthesis/signaling could be an early manifestation and underlying cause of metabolic comorbidities in patients with FEP.

Research perspectives

Although large-scale studies are needed for validation of the above results, the data presented above will help in developing appropriate therapies for minimizing the development of insulin resistance and other metabolic comorbidities and increasing treatment adherence and outcome in schizophrenia. Since oxidative stress and inflammation are the major risk factors for the disrupted leptin-fatty acid biosynthesis/signaling, supplementation with calcium, anti-oxidant and/or anti-inflammatory agents will be highly effective in reducing the development or exacerbation of preexisting metabolic comorbidities in schizophrenia.

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FOOTNOTES

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ORIGINAL ARTICLE

Observational Study

Dimensions of emotional distress among Brazilian workers in a COVID-19 reference hospital: A factor analytical study

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Abstract

BACKGROUND

The coronavirus disease 2019 (COVID-19) pandemic is an unprecedented challenge for public health and has caused the loss of millions of lives worldwide. Hospital workers play a key role in averting the collapse of the health system, but the mental health of many has deteriorated during the pandemic. Few studies have been devoted to identifying the needs of workers on frontline duty.

AIM

To investigate dimensions of common emotional symptoms and associated predictors among Brazilian workers in a COVID-19 reference hospital.

METHODS

This is an observational study of the mental health of professionals in a COVID-19 hospital in the city of São Paulo. We invited all hospital employees to respond to an online survey between July and August 2020, during the first peak of the pandemic. Data of 1000 participants who completed the survey were analyzed (83.9% were women and 34.3% were aged 30 to 40). Hospital workers self-reported the presence of symptoms of depression, anxiety, trauma-related stress, and burnout through the Patient Health Questionnaire-9, the Generalized Anxiety

Disorder-7, the Impact of Event Scale-Revised and the Mini-Z Burnout Assessment respectively. Responses were assembled and subjected to exploratory factor analysis to reveal workers' core emotional distress. Multiple linear regression models were subsequently carried out to estimate the likelihood of dimensions of distress using questions on personal motivation, threatening events, and institutional support.

RESULTS

Around one in three participants in our sample scored above the threshold of depression, anxiety, post-traumatic stress disorder, and burnout. The factor analysis revealed a three-factor structure that explained 58% of the total data variance. Core distressing emotional domains were avoidance and re-experience, depression-anxiety, and sleep changes. Regression analysis revealed that institutional support was a significant protective factor for each of these dimensions (β range = -0.41 to -0.20, $P < 0.001$). However, participants' personal motivation to work in healthcare service was not associated with these emotional domains. Moreover, the likelihood of presenting the avoidance and re-experience dimension was associated with having a family member or close friend be hospitalized or die due to COVID-19 and having faced an ethical conflict.

CONCLUSION

Distressing emotional domains among hospital workers were avoidance and re-experience, depression and anxiety, and sleep changes. Improving working conditions through institutional support could protect hospital workers' mental health during devastating public health crises.

Key Words: COVID-19; Pandemics; Health personnel; Mental health; Psychological distress; Occupational medicine

Core Tip: Although the literature contains many reports on the deteriorating mental health of hospital workers during pandemics, few investigations have focused on the core mental health needs of this specific population. Hence, we subjected the common emotional symptoms of hospital workers to exploratory factor analysis. The main emotional dimensions were avoidance and re-experience, depression-anxiety, and sleep changes. Institutional support was found to be the most relevant protective factor for these emotional dimensions. This investigation could contribute to a better understanding of work-related distress from a dimensional perspective and has indicated comprehensive coping strategies in healthcare settings during a public health emergency.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) is an infectious disease that emerged in Wuhan, China in late 2019, and rapidly spread worldwide. A dramatic loss of human life, economic disruption, unemployment, and food insecurity, all caused by the pandemic, have imposed a monumental challenge on communities. Millions of people are at risk of being infected by a life-threatening virus and falling into extreme poverty due to economic and social hardships. During the lockdown, to mitigate the spread of the epidemic, hospital workers (HWs) have played a key role in the fight against disease outbreaks, but without the privilege of confinement. Besides saving lives in exhaustive duties, HWs face an insurmountable burden of increased risk of infection, fear of infecting family members, increased workload, inadequate support, and discrimination[1]. The healthcare workforce is a particularly vulnerable population because the majority lack work protection and access to quality personal protection equipment (PPE). Thus, HWs are exposed to an overwhelmingly stressful environment, which contributes to the deterioration of their mental health, with subsequent development of multiple emotional symptoms.

Frontline HWs directly involved with patient care present greater vulnerability to developing disabling emotional symptoms, as shown in previous epidemics of Ebola virus disease and severe acute

respiratory syndrome[2,3]. Among different psychological reactions, symptoms of anxiety were the first to emerge in the early stages of epidemics. Although anxiety sometimes wanes over the course of the observation, symptoms of depression and distress may persist or intensify[4]. A recent cross-sectional study involving 1257 Chinese COVID-19 healthcare workers (HCWs) has indicated that 71.5% of the sample experienced symptoms of distress, 44.6% anxiety, 50.4% depression, and 34% insomnia[5]. Globally, a comprehensive review confirmed the high frequency of depression (24.3%), anxiety (25.8%), and stress (45%) among frontline HCWs caring for COVID-19 patients[6]. Likewise, a high frequency of symptoms of burnout was also reported in over one-third of Italian healthcare professionals[7]. Regarding the Brazilian context, a study composed of Brazilian HCWs from different regions also found high rates of anxiety (43.3%), depression (40.2%), trauma (36%), and insomnia (61.5%)[8]. Nevertheless, these rates present large fluctuations because data collection relies on individual and contextual aspects of vulnerability, such as socio-demographic characteristics, social support, time of data collection, institutional infrastructure, and public responses, among other factors. Thus, these quantitative rates are limited indicators for clarifying the psychological impact of the COVID-19 and the possibilities of coping with it.

Bearing in mind the plethora of observational studies describing the poor mental health of HWs during the pandemic, few studies have determined the symptomatic clustering of occupational distress during the pandemic. Because most of the emotional symptoms of HWs appear at the same time, we took advantage of a data reduction method of factor analysis to examine the structure of self-reported symptoms in this population. We estimated both individual and contextual factors that were potentially associated with dimensions of distress. The next logical step is to understand how to prevent or reduce emotional distress in healthcare settings. Hypothetically, we posited that core dimensions of emotional distress among HWs would manifest as a sound structure, and that protective or risk factors for this distress would indicate meaningful coping strategies.

The primary objective of the present study was to determine the structure of the mental health of HWs during the COVID-19 pandemic, as related to anxiety, depression, event-related stress, and burnout. Secondarily, we aimed to determine correlated factors of HWs' mental health. These findings could contribute to a greater understanding of the human capacity to face extreme working conditions during global sanitary crises. The implications of potential factors that could improve preventive and supportive strategies in pandemic contexts are discussed.

MATERIALS AND METHODS

Study design

Data of the current observational study were cross-sectionally collected between July 1 and August 28, 2020, using an online survey on the REDCap platform (https://www.project-redcap.org/). This is the baseline data of an ongoing longitudinal study on HWs' mental health.

At the time of data collection for this study, Brazil was one of the pandemic epicenters of the world, with high rates of new cases and deaths per day. The country had 2662485 confirmed cases, and 92475 deaths as of July 31, 2020[9]. Most of these cases were reported in the state of São Paulo, the most populous in Brazil. São Paulo had 542304 confirmed cases and 22997 deaths in the same period[9]. The Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP) became the main reference healthcare facility for COVID-19 care in the state. Wards of the HCFMUSP main building were entirely reconfigured into a full capacity of 900 beds for the exclusive care of COVID-19 patients. Between July and August of 2020 - around the decline of the first wave of the pandemic - the well-being of hospital professionals in this large care center was on the verge of collapse.

Participants

The inclusion criterion was that participants had to be working at the hospital, in person or from home, at the time of data collection. Medical doctors, nurses, nursing assistants, dentists, speech therapists, psychologists, occupational therapists, dieticians, physical therapists, social workers, pharmacists, clinical laboratory technicians, radiological technologists, and administrative professionals were included as HWs. Professionals from all hospital sites were invited, including the emergency room, inpatient wards, intensive care units, outpatient care, operating room, pharmacy, and laboratory. There were few exclusions as current workers were all adults and able to respond to an online questionnaire. Potential participants did not present linguistic problems, but limited access to the internet from a computer or mobile phone could have been an obstacle to participation.

At the time of the baseline survey, 22056 employees were working in the hospital complex. The online invitation was sent to all HWs through the institutional e-mail, in addition to social media advertising and wall posters in the hospital. Moreover, participants were also encouraged to forward the online survey to eligible colleagues. Respondents could complete the survey, which took approximately 15 min to answer in its entirety, at any time. Using non-probabilistic sampling, data were gathered from 1377 respondents, but only 1000 provided complete data for inclusion in the analysis.

Measurement tools

The following instruments were used: Socio-demographic questionnaire: This instrument consisted of questions about age, gender, marital status, educational level, occupational status, living with children or elderly adults, and time of direct contact with COVID-19 patients (hours per week, as an ordinal scale). Questions related to changes in daily routine and individual's ability to cope with distress were also included.

The Impact of Event Scale-Revised (IES-R) was used to screen and rate the severity of distress symptoms in the previous seven days, based on the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria of post-traumatic stress disorder (PTSD)[10]. The IES-R is a 22-item self-report scale, with a five-point ordinal scale from "not at all" (score 0) to "extremely" (score 4) for each item[10]. Total scores ranged from 0 to 88. Scores of 9, 26, and 44 are used as the cut-off points for mild, moderate, and severe post-traumatic symptoms, respectively[10]. The cut-off point ≥ 26 was adopted in this study, based on previous literature for a probable case of PTSD[5]. Cronbach's alpha coefficient of the IES-R was α = 0.96, indicating an adequate internal consistency.

The Patient Health Questionnaire-9 (PHQ-9) was used to screen and rate the severity of depressive symptoms in the previous two weeks, based on the DSM-IV[11]. The PHQ-9 is a nine-item self-report scale, with a four-point ordinal scale from "not at all" (score 0) to "nearly every day" (score 3) for each item[11]. The total score ranged from 0 to 27. Scores of 5, 10, 15, and 20 are used as the cut-off points for mild, moderate, moderately severe, and severe depression, respectively[11]. The cut-off point ≥ 10 has a sensitivity of 88% and a specificity of 88%, in comparison to the diagnosis of major depressive disorder [12]. Cronbach's alpha coefficient of the PHQ-9 was α = 0.90, indicating good internal consistency.

The Generalized Anxiety Disorder-7 (GAD-7) was used to screen and rate the severity of anxiety symptoms in the previous two weeks, based on DSM-IV criteria[13]. The GAD-7 is a seven-item self-report scale, with a four-point ordinal scale from "not at all" (score 0) to "nearly every day" (score 3) for each item[13]. The total score ranged from 0 to 21. Scores of 5, 10, and 15 are used as the cut-off points for mild, moderate, and severe anxiety, respectively[13]. The cut-off point ≥ 10 has a sensitivity of 89% and a specificity of 82%, in comparison to the diagnosis of generalized anxiety disorder[14]. Cronbach's alpha coefficient of the GAD-7 was α = 0.92, indicating appropriate internal consistency.

The validated single-item Mini-Z Burnout Assessment was used to evaluate the experience of burnout[15,16]. This question instructs respondents to define burnout for themselves: "Overall, based on your definition of burnout, how would you rate your level of burnout?". Responses are scored on a five-category ordinal scale and the threshold of burnout was indicated by a rating ≥ 3. Score 3 was applied to respondents who chose "I am definitely burning out and have one or more symptoms of burnout, such as physical and emotional exhaustion"; score 4 for those who chose "The symptoms of burnout that I'm experiencing won't go away. I think about frustration at work a lot"; and score 5 for those who chose "I feel completely burned out and often wonder if I can go on. I am at the point where I may need some changes or may need to seek some sort of help.". This single-item scale was validated against the exhaustion subscale of the Maslach Burnout Inventory, with a correlation of 0.64 ($P < 0.001$) [15], and previous studies have used it to evaluate burnout during the current pandemic[17].

Psychoactive substance use: Straightforward questions about increased consumption of alcohol and tobacco were included to assess changes in substance use patterns. Answers were recorded as dichotomous yes/no answers.

Threatening events: HWs were asked about the following three self-reported items, with dichotomous yes/no answers, to assess COVID-19 related threatening events: having had a confirmed COVID-19 diagnosis, having had a close family member or friend hospitalized or dying due to COVID-19, and having experienced an ethical conflict during COVID-19 patient care. Ethical issues covered a broad array of extreme contexts such as lack of PPE, disagreement with clinical decisions, overwork, mandatory work despite belonging to a risk group for COVID-19, use of public transportation, *etc.*

Personal motivation: To evaluate contextual variables in the occupational setting, questions about personal motivation and stressors were formulated based on previous literature[2,4,18]. All answers were scored on a five-point Likert scale: "I feel my family, friends or colleagues recognize me for the work I am doing during the COVID-19 pandemic"; "I feel like I'm gaining new knowledge while I am working on the COVID-19 pandemic"; "I feel that my work on the COVID-19 pandemic helps people"; "I am willing to accept the risks because I want to help infected people"; "I feel like I'm developing myself by working on the COVID-19 pandemic"; "I feel motivated to work on the COVID-19 pandemic"; and "I feel part of a movement in my community to take care of infected people".

For statistical analysis, the cumulative score of each of the seven items was calculated, generating a total score labeled "personal motivation". Cronbach's alpha coefficient of personal motivation questions was α = 0.85, indicating appropriate internal consistency.

Institutional support: Based on previous studies[2,4,18], support related to the organizational environment was evaluated using questions on a five-point Likert scale: "I have access to adequate PPE in situations where this is required"; "I have access to equipment and resources needed to provide adequate care to patients"; "I feel that I received adequate training to carry out my work in the COVID-19 pandemic"; "I feel supported by my bosses and by the institution"; "I feel supported by my work team"; "I feel that the patient care protocols are clear in the institution, and I know what must be done"; "If I get infected, I will receive care at my institution"; "If I get infected, my family will receive support";

and "I feel that I have enough rest to continue my job as long as it is necessary".

For statistical analysis, the cumulative score for each of these items was calculated, leading to a total score labeled as "institutional support". These items yielded a Cronbach's alpha coefficient of 0.85, indicating adequate internal consistency.

Statistical analysis

All analyses were performed using R software, version 4.0.4 (https://www.r-project.org/), and corresponding packages detailed below. The significance level was set at $\alpha = 0.05$ for 2-tailed tests. Because data were not normally distributed according to the Shapiro-Wilk test ($P < 0.05$), a descriptive analysis of participant socio-demographic characteristics was presented as percentage (%) for categorical variables and medians with interquartile ranges for continuous variables.

To investigate the factorial structure of mental health in our sample, an exploratory factor analysis (EFA) was performed. All 39 items of the PHQ-9, the GAD-7, the IES-R, and the single-item Mini-Z Burnout Assessment were assembled in a single dataset to determine the underlying latent constructs of separate items. Before factor extraction, the factorability of the data was checked using the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy and Bartlett's test of sphericity. The data were considered adequate for performing EFA because Bartlett's test of sphericity χ^2 value was 31085.35 ($P < 0.001$) and the KMO value was 0.98. The between-item correlation was examined in a matrix containing all 39 individual items of the scales. Factors were extracted using the principal axis factoring method. We used criteria such as Kaiser's eigenvalues > 1[19,20], Cattell's scree plot inspection[19,20], and clinical interpretability of the resulting factor structure to determine the number of factors to be extracted[19,20]. To aid in factor interpretation, the initial solution was subjected to oblique (Oblimin) rotation, assuming that extracted factors would be correlated to reflect the structure of HWs' emotional distress[19,20]. Items presenting factor loadings above 0.40 were retained in each factor, due to their substantial contribution to data variance. The EFA was run with *psych* and *GTArotation* packages in R.

A collinearity analysis was subsequently conducted using the *polycor* package to rule out the correlation between independent variables. All analyzed variables had a Variance Inflation Factor below 3 (for more details, see Supplementary Table 1), suggesting that multicollinearity was not a problem in our data. Two multiple linear regression models were carried out to identify potential predictors for each of the retained factors, using the *beta.lm* function. Factor scores of each of the retained factors were used as dependent variables. After checking for independence, homoscedasticity, normality, and linearity, two regression models were run for each retained factor. First, a crude model included predictor questions on threatening events, personal motivation, and institutional support. Second, the final adjusted model was controlled for sociodemographic variables such as gender, age, marital status, educational level, and occupation. Results were reported as β, 95% confidence interval, and *P* value. Model fit was estimated in terms of R^2.

The statistical methods were reviewed by Wang YP from the Department of Psychiatry, School of Medicine, University of Sao Paulo.

Ethics

The online survey was anonymous and participant confidentiality was assured. Due to social isolation, data were collected by means of an online survey which included an informed consent form explaining the study design, its purpose, and the responsible researcher of the study. This study was approved by the Institutional Board of Research Ethics, protocol # 30710620.2.0000.0068.

RESULTS

Demographic and mental health characteristics

Considering Table 1, out of 1000 participants who completed the survey, 83.9% were women, 34.3% were aged 30 years old to 40 years old, 57.4% were married or living with a partner, and 72.9% had an educational level of university graduate or higher. In terms of occupational characteristics, 74.1% were HCWs directly involved in patient care and the remaining 25.9% had no direct contact with patients infected with COVID-19 (office workers and clinical clerks). Regarding participant occupations, 14% were medical doctors, 34.8% were nurses or nursing assistants, and 25.3% were other healthcare professionals. Although participants were recruited using a non-probabilistic strategy, the distribution of socio-demographic characteristics was similar to the total sample of employees in the institution, in terms of gender, age, and occupation. Regarding threatening events directly related to COVID-19 care, 79.6% had direct contact with COVID-19 patients and 32.8% reported having had COVID-19 themselves. An additional 38.6% reported having had a close family member or friend hospitalized or dying due to COVID-19. Approximately one in five participants reported having had to deal with an ethical conflict related to COVID-19 patient care. Regarding the previous history of mental disorders, 28% reported previous psychiatric or psychological treatment and 13.8% reported psychological or psychiatric treatment after the onset of the pandemic.

Table 1 Sociodemographic and clinical characteristics of participants (*n* = 1000)

Characteristics	*n* (%)
Age bracket	
18-30	211 (21.1)
30-40	343 (34.3)
40-50	252 (25.2)
> 50	194 (19.4)
Gender	
Female	839 (83.9)
Male	159 (15.9)
Other	2 (0.2)
Marital status	
Unmarried	426 (42.6)
Married	574 (57.4)
Educational level	
< University graduate	271 (27.1)
≥ University graduate	729 (72.9)
Living with elderly (> 60 yr)	
Yes	233 (23.3)
No	767 (76.7)
Living with children	
Yes	450 (45.0)
No	550 (55.0)
Occupation	
Medical doctor	140 (14.0)
Nurse and nursing assistants	348 (34.8)
Other healthcare professionals[1]	253 (25.3)
Administrative workers[2]	259 (25.9)
Work sector	
Emergency room	60 (6.0)
Inpatient ward	176 (17.6)
Intensive care unit	157 (15.7)
Outpatient care	128 (12.8)
Operating room	44 (4.4)
Pharmacy	36 (3.6)
Laboratory	84 (8.4)
Other sectors	163 (16.3)
Direct contact with COVID-19 patient (h/wk)	
0	204 (20.4)
1-20	311 (31.1)
21-40	285 (28.5)
> 40	200 (20.0)
Had COVID-19 (self-reported)	

Yes	328 (32.8)
No	672 (67.2)
Close family or friend hospitalized or who died due to COVID-19	
Yes	386 (38.6)
No	614 (61.4)
Changes in daily routine due to pandemic	
Financial failure	387 (38.7)
Lack of public safety	199 (19.9)
Lack of public transport	297 (29.7)
Lack of medical care	292 (29.2)
Distancing from family and friends	620 (62.0)
Previous psychiatric or psychological treatment	
Yes	280 (28.0)
No	720 (72.0)
Previous self-reported diagnoses	
Anxiety	91 (9.1)
Depression	78 (7.8)
PTSD	6 (0.6)
Previous psychotherapy treatment	199 (19.9)
Previous pharmacological treatment	177 (17.7)
Psychological or psychiatric treatment after pandemic beginning	138 (13.8)
Protective health actions	
Physical activities	274 (27.4)
Meditative practices	182 (18.2)
Leisure activities/hobbies	320 (32.0)
Religious practices	310 (31.0)
I'm not doing anything in this sense	354 (35.4)
Ethical conflict	119 (11.9)

[1]Other healthcare professionals: dentists, speech therapists, psychologists, occupational therapists, dieticians, physical therapists, social workers, pharmacists, clinical laboratory technicians, and radiological technologists.
[2]Administrative workers: receptionist, information technicians, secretary, security guard.
COVID-19: Coronavirus disease 2019; PTSD: Post-traumatic stress disorder.

Table 2 shows the range and frequency of the scores of the rating scales IES-R, PHQ-9, GAD-7, and Mini-Z Burnout Assessment. The score was categorized into severity levels, according to the established cut-offs. With reference to clinically significant levels of assessed psychiatric categories, 46.8% of participants scored above the level for a probable case of PTSD, 37.9% for depression, 32.5% for anxiety, and 34.9% for burnout. An additional 7.6% of participants reported increased tobacco consumption and 17.1% reported increased alcohol consumption.

Factor analysis

Table 3 shows the rotated pattern matrix of the EFA solution. The initial solution for the 39 items yielded two factors meeting Kaiser's eigenvalue > 1 criterion. Nevertheless, the scree test suggested a three- or four-factor solution, according to Cattell's criterion. Taking into account these two criteria and the clinical interpretability of the resulting factorial structure, a three-factor solution was chosen as the optimal model, in view of the balance between parsimony and comprehensiveness.

After oblique rotation, salient factor loadings (≥ 0.40) for 38 items were observed in a single factor. Cross-loading occurred with the item "trouble falling or staying asleep, or sleeping too much?" (PHQ-9 #3), which contributed to both factors 2 and 3. All three factors accounted cumulatively for 58% of the total data variance. The correlation between factor 1 and factor 2 was 0.64, 0.56 between factor 1 and

Table 2 Frequency of categories of distress symptoms (*n* = 1000)

Scale and severity categories	*n* (%)
The Patient Health Questionnaire-9	7 (4-13)[1]
Minimal (< 5)	312 (31.2)
Mild (5-9)	309 (30.9)
Moderate (10-14)	177 (17.7)
Moderately severe (15-19)	116 (11.6)
Severe (≥ 20)	86 (8.6)
The Generalized Anxiety Disorder-7	6 (3-12)[1]
Minimal (< 5)	347 (34.7)
Mild (5-9)	328 (32.8)
Moderate (10-14)	154 (15.4)
Severe (≥ 15)	171 (17.1)
The Impact of Event Scale-Revised	24 (11-42)[1]
Minimal (< 9)	197 (19.7)
Mild (9-25)	335 (33.5)
Moderate (26-43)	225 (22.5)
Severe (≥ 44)	243 (24.3)
Mini-Z Burnout Assessment (≥ 3)[2]	349 (34.9)
Increased tobacco consumption	76 (7.6)
Increased alcohol consumption	171 (17.1)

[1]Interquatile range.
[2]Participants with a score above the cut-off point for burnout.

factor 3, and 0.55 between factor 2 and factor 3. Cronbach's alpha coefficient for factors 1, 2, and 3 was α = 0.96, 0.94, and 0.87, respectively, indicating adequate internal consistency of each extracted factor.

The first dominant factor explained 28% of the total variance and included 20 items from the IES-R but excluded #15 - "I had trouble falling asleep" - and #2 - "I had trouble staying asleep". The second factor explained 24% of the total variance and included all the items from the GAD-7, 8 items from the PHQ-9 (except #3 - "Trouble falling or staying asleep, or sleeping too much?"), and the Mini-Z Burnout Assessment. The third factor explained an additional 6% of the total variance and included two items from the IES-R (#15 and #2) and one item from the PHQ-9 (#3).

We consistently examined how each item loaded in each factor to label each one of the latent factors. The first factor was composed of all the IES-R items, except two items related to sleep ("I had trouble falling asleep" and "I had trouble staying asleep"). The following three items presented the highest loadings: "I tried to remove it from my memory", "I found myself acting or feeling as though I was back at that time" and "I was aware that I still had a lot of feelings about it, but I didn't deal with them". These items are related to major PTSD-associated symptom clusters, namely avoidance, and re-experiencing.

The second factor was composed of all the items from the GAD-7, almost all the items from the PHQ-9 (except one item related to sleep, "trouble falling or staying asleep, or sleeping too much?"), and the Mini-Z Burnout Assessment. The following three items presented the highest loadings: "Feeling down, depressed, or hopeless?", "Feeling tired or having little energy?" and "Little interest or pleasure in doing things?". These items mostly relate to major symptoms associated with depression. Hence, the second factor was labeled Depression-anxiety. Lastly, the third factor was composed of three items associated with sleep, two of which loaded 0.7 or higher: "I had trouble falling asleep" and "I had trouble staying asleep". The third factor was labeled Sleep changes.

Predictors of the mental health dimensions

Table 4 shows crude and adjusted multiple linear regression models which were built to evaluate potential predictors for each of the emotional dimensions retained from the EFA. First, models were carried out using the following independent variables: direct contact with a COVID-19 patient, previous psychiatric and psychological treatment, had COVID-19, close family or friend hospitalized or died due to COVID-19, ethical conflict, personal motivation, and institutional support. The fitness of all three

Table 3 Pattern matrix of rotated Oblimin solution as extracted through principal axis factoring

Description	Item	Avoidance and re-experience	Depression-anxiety	Sleep changes	Communality
I tried to remove it from my memory	IES-R-17	**0.81**	-0.10	0.05	0.60
I found myself acting or feeling as though I was back at that time	IES-R-14	**0.79**	0.03	-0.01	0.66
I was aware that I still had a lot of feelings about it, but I didn't deal with them	IES-R-12	**0.79**	-0.13	0.02	0.53
I tried not to think about it	IES-R-11	**0.78**	-0.12	0.04	0.53
Pictures about it popped into my mind	IES-R-9	**0.76**	0.10	0.01	0.70
I was jumpy and easily startled	IES-R-10	**0.75**	0.12	0.02	0.71
I tried not to talk about it	IES-R-22	**0.75**	-0.06	-0.03	0.48
My feelings about it were kind of numb	IES-R-13	**0.72**	-0.02	-0.02	0.48
I thought about it when I didn't mean to	IES-R-6	**0.70**	0.14	0.09	0.73
I had waves of strong feelings about it	IES-R-16	**0.68**	0.12	0.12	0.71
I stayed away from reminders about it	IES-R-8	**0.68**	-0.10	0.03	0.40
I felt watchful or on-guard	IES-R-21	**0.65**	0.19	0.01	0.62
I felt as if it hadn't happened or wasn't real	IES-R-7	**0.62**	0.05	-0.02	0.42
I avoided letting myself get upset when I thought about it or was reminded of it	IES-R-5	**0.62**	0.05	0.07	0.48
Other things kept making me think about it	IES-R-3	**0.61**	0.12	0.22	0.70
Reminders of it caused me to have physical reactions, such as sweating, trouble breathing, nausea, or a pounding heart	IES-R-19	**0.60**	0.20	0.03	0.59
Any reminder brought back feelings about it	IES-R-1	**0.59**	0.19	0.07	0.59
I had dreams about it	IES-R-20	**0.49**	0.12	0.10	0.41
I had trouble concentrating	IES-R-18	**0.45**	0.32	0.12	0.61
I felt irritable and angry	IES-R-4	**0.45**	0.34	0.09	0.60
Feeling down, depressed, or hopeless	PHQ-9-2	0.01	**0.84**	-0.05	0.68
Feeling tired or having little energy	PHQ-9-4	-0.15	**0.78**	0.15	0.60
Little interest or pleasure in doing things	PHQ-9-1	-0.07	**0.75**	0.09	0.58
Feeling nervous, anxious, or on edge	GAD-7-1	0.06	**0.74**	0.02	0.63
Feeling bad about yourself - or that you are a failure or have let yourself or your family down	PHQ-9-6	0.05	**0.74**	-0.09	0.52
Not being able to stop or control worrying	GAD-7-2	0.16	**0.72**	-0.01	0.69
Becoming easily annoyed or irritable	GAD-7-6	0.11	**0.72**	-0.03	0.61
Trouble concentrating on things, such as reading the newspaper or watching television	PHQ-9-7	0.04	**0.68**	0.07	0.55
Worrying too much about different things	GAD-	0.13	**0.68**	0.03	0.62

	7-3				
Trouble relaxing	GAD-7-4	0.01	**0.68**	0.22	0.69
Overall, based on your definition of burnout, how would you rate your level of burnout	Mini-Z	-0.05	**0.67**	0.05	0.45
Moving or speaking so slowly that other people could have noticed	PHQ-9-8	0.18	**0.62**	-0.08	0.49
Poor appetite or overeating	PHQ-9-5	0.04	**0.56**	0.13	0.45
Feeling afraid as if something awful might happen	GAD-7-7	0.31	**0.56**	-0.12	0.53
Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual	PHQ-9-9	0.02	**0.49**	-0.08	0.21
Being so restless that it's hard to sit still	GAD-7-5	0.27	**0.46**	-0.06	0.41
I had trouble falling asleep	IES-R-15	0.21	-0.03	**0.81**	0.85
I had trouble staying asleep	IES-R-2	0.17	0.05	**0.74**	0.77
Trouble falling or staying asleep, or sleeping too much	PHQ-9-3	-0.16	**0.46**	**0.53**	0.60
Eigenvalue; Explained variance (%)		10.76; 28.00	9.22; 24.00	2.50; 6.00	
Total explained variance (%)		28.00	52.00	58.00	

Loadings above 0.40 are typed in bold. PHQ-9: The Patient Health Questionnaire-9; GAD-7: The Generalized Anxiety Disorder-7; IES-R: The Impact of Event Scale-Revised; Mini-Z: Single-item Mini-Z Burnout Assessment.

Table 4 Multiple linear regressions between predictable variables and each of the emotional dimensions of hospital workers (*n* = 1000)

	Avoidance and re-experience		Depression-anxiety		Sleep changes	
	β (95%CI)	β (95%CI)[1]	β (95%CI)	β (95%CI)[1]	β (95%CI)	β (95%CI)[1]
Direct contact with COVID-19 patient (h/wk)	0.05 (-0.01 to 0.11)	0.02 (-0.04 to 0.09)	0.08 (0.02 to 0.13)[b]	0.02 (-0.04 to 0.09)	0.03 (-0.03 to 0.08)	-0.02 (-0.08 to 0.05)
Previous psychiatric or psychological treatment (self-reported)	0.33 (0.2 to 0.46)[c]	0.33 (0.21 to 0.46)[c]	0.38 (0.27 to 0.5)[c]	0.38 (0.26 to 0.49)[c]	0.26 (0.13 to 0.38)[c]	0.25 (0.12 to 0.38)[c]
Had COVID-19 (self-reported)	0.14 (0.02 to 0.26)[a]	0.09 (-0.03 to 0.21)	-0.03 (-0.14 to 0.08)	-0.07 (-0.18 to 0.04)	0.09 (-0.03 to 0.21)	0.05 (-0.07 to 0.17)
Close family or friend hospitalized or who died due to COVID-19	0.14 (0.03 to 0.26)[a]	0.13 (0.02 to 0.25)[a]	0.06 (-0.06 to 0.16)	0.06 (-0.04 to 0.17)	0.14 (0.02 to 0.26)[a]	0.13 (0.01 to 0.24)[a]
Ethical conflict	0.21 (0.03 to 0.39)[a]	0.26 (0.08 to 0.44)[b]	0.08 (-0.09 to 0.25)	0.12 (-0.04 to 0.29)	0.02 (-0.16 to 0.2)	0.03 (-0.15 to 0.21)
Personal motivation	-0.03 (-0.11 to 0.04)	-0.02 (-0.09 to 0.06)	-0.03 (-0.1 to 0.04)	-0.02 (-0.09 to 0.05)	-0.01 (-0.09 to 0.06)	0.01 (-0.07 to 0.08)
Institutional support	-0.26 (-0.34 to -0.18)[c]	-0.26 (-0.33 to -0.18)[c]	-0.41 (-0.49 to -0.33)[c]	-0.41 (-0.48 to -0.34)[c]	-0.2 (-0.28 to -0.12)[c]	-0.2 (-0.28 to -0.13)[c]

[1]Adjusted for age, gender, marital status, educational level, and occupation.
[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.
All models were statistically significant ($P < 0.001$). CI: Confidence interval.

crude models was statistically significant ($P < 0.001$). Likewise, the adjusted R^2 for each of the models was 0.14, 0.25, and 0.08 respectively. Second, three final models were adjusted for age, gender, marital status, educational level, and occupation, yielding an adjusted R^2 of 0.18, 0.29, and 0.09, respectively. All adjusted models were statistically significant ($P < 0.001$) by F test, considering the Bonferroni test for multiple models.

The analysis revealed that institutional support presented a negative association with all dimensions of emotional distress (β = -0.26, $P < 0.001$; β = -0.41, $P < 0.001$; β = -0.22, $P < 0.001$). Personal motivation was not a significantly correlated variable with dimensions of emotional distress. Moreover, the final sociodemographic adjusted models indicated that participants with previous psychiatric or psychological treatments presented a significant likelihood of manifesting the three mental health dimensions (β = 0.33, 0.38, and 0.25, $P < 0.001$, respectively). Chi-squared tests were carried out to evaluate the association between this variable and scores of each used scale, showing a P value < 0.001 for all tests, which points out that pre-pandemic psychopathology was associated with higher rates of mental health outcomes (data not shown, available upon request).

In terms of events related to COVID-19 care, the dimension of avoidance and re-experience also presented a significant association with those HWs who had a close family member or friend who was hospitalized or died due to COVID-19 (β = 0.13, $P < 0.05$) and had experienced an ethical conflict during COVID-19 patient care (β = 0.26, $P < 0.01$). Furthermore, direct contact with COVID-19 patients was positively associated with the depression-anxiety dimension (β = 0.08; $P < 0.01$) and having had COVID-19 (β = 0.14; $P < 0.05$) was associated with avoidance and re-experience in the non-adjusted crude model.

Regarding sociodemographic predictors as data not shown, high educational level was negatively associated with all factors ($P < 0.01$; $P < 0.01$; $P < 0.05$). Age presented a negative association with factors 1 and 2 ($P < 0.01$; $P < 0.001$). Being a nurse was a significant factor associated with the first dimension ($P < 0.01$) when compared with being a medical doctor.

DISCUSSION

The mental health status of 1000 workers in a large COVID-19 reference hospital was assessed through self-reporting scales as applied online during the 2020 pandemic peak, a hectic period for HWs when exhausted professionals needed to continue to fight to stop the frightening level of deaths caused by COVID-19. Unsurprisingly, the results indicated a high frequency of depression, anxiety, stress, and burnout, as well as increased consumption of tobacco and alcohol, which were in line with reported rates found in previous studies[21-23]. Over one in four participants reported previous psychological or psychiatric treatment and an additional 14% of participants reported that they started treatment after the beginning of the pandemic. This incremental figure of HWs in need of care confirmed the vulnerability of this population to emotional distress during a demanding global health crisis. We showed a three-factor structure as a well-fit model for data variance of multiple co-occurring symptoms among HWs. Avoidance and re-experience, depression-anxiety, and sleep changes represent core dimensions of their prevalent emotional symptoms. Moreover, our findings suggested that the support of the organizational environment was the preventive intervention most associated with workers' emotional reactions. Also, professionals who had a close relative or friend present severe COVID-19 or had experienced an ethical challenge also presented a significant likelihood of association with the PTSD-like dimension of avoidance and re-experience. These results only include the suffering experience of a sample of HWs; however, their relevance should be examined in light of their fundamental role in the battle against the COVID-19 pandemic. Protecting their mental health by providing sufficient institutional support could make a difference to HWs' well-being.

Although the method of factor analysis used for examining underlying dimensions of psychopathologies is a well-known technique for data reduction in psychiatry, we are aware of only one factorial study on the mental health of HWs during the pandemic. Chatterjee *et al*[24] conducted a factor analysis of distress among 140 Hindu HCWs and observed a four-factor structure: sleeplessness, anxiety, irritability, and hopelessness. In line with our findings, they also found that symptoms of sleep, anxiety, and depression play an important role in HWs' distress. Unlike them, however, we found that stress-related responses were the most relevant dimension for data variance and sleep changes had the lowest impact. While our second factor included symptoms of depression and anxiety, symptoms such as hopelessness prevailed over irritability or anxiety. The difference could be explained by the fact that they selected a smaller sample size of participants, collected data in different stages of the pandemic course, and used specific instruments to assess only insomnia and perceived stress. Direct comparison between factorial models and their generalizability is not feasible.

Our dominant factor was the stress-related Avoidance and re-experience dimension, which was correlated with the depression-anxiety and sleep changes dimensions. This finding might support the argument that the current pandemic is considered a stressor event capable of triggering PTSD-like responses as well as worsening other related mental health problems such as depression and anxiety [25]. Furthermore, depressive, anxiety and burnout symptoms could be more associated with chronic stressors not directly related to COVID-19 care. Regarding externalizing behaviors, our questionnaire indicated that HWs increased their consumption of psychoactive substances, namely 7.6% tobacco and 17.1% alcohol. However, we did not include these variables in the analysis because of their weak contribution to the factorial model (communality < 0.10, data not shown). Hypothetically, HWs might be using more psychoactive substances to alleviate their distress[26]. This increased consumption is one of the aspects that might be bi-directionally related to their sleep problems[27], disturbing their sleep, or

being a way of dealing with distress caused by inefficient rest. However, a more consistent investigation is warranted.

This study was conducted during the peak of the first wave of COVID-19 in Brazil, which was associated with the highest level of hospitalization of infected patients and produced an overwhelmingly stressful environment for HWs[28]. Our frequency of symptoms of traumatic events (46.8%) was similar to the rate of 49.4% found during the contagion peak in Italy[29]. The current data revealed that while working as a nurse was associated with the likelihood of presenting the avoidance and re-experience dimension, being a HW of older age and higher education level were both protective factors. These findings are in accordance with a recent systematic review that revealed that nurses facing pandemic crises experienced more stress when compared to doctors and that having more experience in healthcare work was a protective factor[30]. We also found that having had a close family member or friend hospitalized or die due to COVID-19 and having experienced an ethical conflict related to COVID-19 patient care had a significant positive association with this dimension. In this regard, recent studies have indicated that the loss of colleagues and dealing with ethical challenges in a time of acute resource shortages were associated with an increased risk of mental disorders[31-33]. Our results suggested that stress-related symptoms like avoidance and intrusive traumatic thoughts are a part of hospital professionals' emotional response to demanding conditions and adverse settings. Hence, it is recommended that hospital providers and administrators pay special attention to the occurrence of these symptoms among workers.

The second factor was labeled Depression-anxiety and the included items were taken from the PHQ-9, the GAD-7, and the burnout assessment. Previous studies have reported high levels of depression, anxiety, and burnout among HWs dealing with the pandemic[31,34,35]. Our findings were in accordance with these studies, showing that the retained dimension accounted for a substantial 24% of the data variance, with symptoms of hopelessness, anhedonia, and anergia being more represented than complaints of anxiety and burnout. A possible explanation for this dimension may be the important role of chronic stress in the workplace and decreased protective health actions for the development of psychological conditions among those professionals, such as high workload, changes in daily routine, reduced physical activity, scarcity of resources, and lack of rest[36-38]. Corroborating this proposition, our analysis did not find a significant correlation between acute threatening events and this dimension, which is also consistent with the suggestion that the association between direct contact with COVID-19 patients and anxiety and depression is based on weak evidence[23].

The third factor, Sleep changes, included three sleep-related items from the IES-R and the PHQ-9. Although no specific scale for screening sleep disorders was employed in this study, our factor analysis suggested an independent and unobservable sleep pattern, with the difficulty of falling or staying asleep having a high impact. This is consistent with previous studies[30,39,40] that have demonstrated an increased level of sleep problems among such professionals, with a frequency reaching 45%. A study describing the experience of supporting HWs in the current pandemic also reported a high frequency of sleep complaints and suggested specific support be provided for this condition[41]. Several aspects may be associated with these sleep changes, including physical exhaustion, quarantine, sleeping in unfamiliar places, separation from family, concerns about getting infected or infecting close contacts, and long work shifts[42,43]. Therefore, this sleep factor represents a neurovegetative dimension and may be triggered by other aspects apart from trauma-related stress, depression, anxiety, and burnout, which might justify its inclusion in a different emotional distress dimension.

Regarding coping strategies, the strongest finding was that aspects related to the organizational environment had a protective effect on overall emotional dimensions, which is in line with previous literature[44,45]. Amid a paucity of information on specific psychological interventions that could be useful to cope with the current pandemic[46], our findings provide some support to interventions that have already been applied in practice[47-51], such as providing adequate PPE and receiving adequate training, implementing an adequate and clear protocol for dealing with possible ethical conflicts, supporting HWs' families, and providing enough rest time for workers to continue their job. For the purposes of the present paper, we only evaluated the institutional support during the peak of the first wave in Brazil. However, several studies have demonstrated concerns about chronic COVID-19 sequelae, which could be associated with mental health outcomes among other clinical conditions, requiring specific treatments and continuous aid[52,53]. Moreover, although altruistic acceptance of risk and support from family and friends have been considered protective coping factors in previous studies [30], our results did not confirm this relationship, showing any association between motivational coping strategies and emotional distress. However, this finding corroborates a recent study that did not find an association between adaptive coping strategies and symptoms of anxiety, depression, and stress[54]. A possible explanation for this is that we analyzed these aspects together as a personal motivation predictor, including items feeling recognized, motivated, and altruistic, which may enable a more consistent assessment of the role of all these variables in preventing the worsening of HWs' well-being.

This study has some limitations. First, although our sample size was large enough, it was not representative of our institutional HWs, with a low response rate of 4.5%, and might be vulnerable to self-selection and response bias. Nevertheless, a good fit factorial model does not require a representative sample, but a large enough size with correlated items[19]. Second, self-reported online questionnaires were used, hence response bias may have occurred, where over or underreporting could not be ruled

out. Third, considering the study design, we could not distinguish preexisting mental health symptoms from new-onset symptoms. Many participants self-reported previous history of mental disorders and treatment, but our rates clearly surpass the pre-pandemic level. Finally, because data were cross-sectionally collected in the baseline wave of an ongoing longitudinal study, causal relationships with predictors should not be stated definitively.

CONCLUSION

This factor analytical study of common psychological symptoms among HWs during the first wave of the current pandemic revealed that avoidance and re-experience, depression-anxiety, and sleep changes were the core reported manifestations. Institutional support was the most relevant protective aspect of the workers' well-being. Mental health professionals, health service administrators, and policy-makers should be mindful of the core dimensions of emotional distress of frontline workers and implement sound safeguarding measures. In the future, interventions should be tailored to improve occupational well-being in health services during subsequent waves of COVID-19 as well as possible forthcoming pandemic crises. Moreover, tracking the longitudinal course of HWs' reactions may help clarify their coping mechanisms for adversity.

ARTICLE HIGHLIGHTS

Research background

The current pandemic has generated a dramatic challenge to public health, in a set of contextual changes throughout the world, including millions of deaths, the collapse of health systems, economic disruption, and food insecurity. During frontline service, hospital workers (HWs) were exposed to an increased risk of becoming infected, fear of infecting family members, ethical conflicts, overwhelming workload, among other stressors. Facing these stressors may contribute to a decline in their psychological well-being. Supporting this suggestion, high rates of depression, anxiety, stress, burnout, and insomnia have been reported among hospital professionals.

Research motivation

Several observational studies have described rates of common psychological responses of HWs facing the current pandemic. Nevertheless, few studies have examined the structure of multiple co-occurring symptoms through exploratory factor analysis. The data reduction approach is a potential asset to expand our understanding of how to prevent or reduce emotional distress in healthcare settings using a smaller number of variables.

Research objectives

We aimed to show core dimensions of common psychological symptoms as well as their associated predictors among HWs in a coronavirus disease 2019 (COVID-19) reference hospital.

Research methods

This is an observational study, and the data were cross-sectionally collected using an online survey during the first peak of the pandemic in Brazil. Data of 1000 HWs who completed the survey were analyzed (83.9% women and 34.3% aged 30 to 40). Self-reported symptoms of depression, anxiety, trauma-related stress, and burnout were subjected to exploratory factor analysis. Multiple linear regression models were then carried out to estimate predictors for each of the factors retained using questions on personal motivation, threatening events, and institutional support as independent variables.

Research results

HWs presented high rates of depression, anxiety, stress, and burnout during their frontline duty, as well as increased tobacco and alcohol consumption. The following three factors were the main dimensions of HWs' distress: avoidance and re-experience, depression-anxiety, and sleep changes. Institutional support was the most significant protective factor for each of these dimensions. Furthermore, scores of the avoidance and re-experience dimension were associated with having a family member or a close friend with severe COVID-19 and having dealt with an ethical challenge. Contrary to expectation, participants' personal motivation to work with COVID-19 patients was not associated with these factors.

Research conclusions

This factor analytic study revealed distressing dimensions of avoidance and re-experience, depression-

anxiety, and sleep changes as the core psychological reactions of a sample of Brazilian HWs during the pandemic. It also highlighted the importance of institutional support in preventing a worsening of hospital professionals' mental health during their pandemic service. These findings have implications for tailoring interventions to maintain HWs' mental health.

Research perspectives

Data reduction methods, such as exploratory factor analysis, contribute to enlarging our understanding of the core psychological reactions of hospital professionals during a sanitary crisis. Multiple co-occurring symptoms can be clustered in a sound dimensional structure. In the future, institutional strategies based on these unobservable patterns could be planned to improve occupational well-being in health settings, either during subsequent waves of COVID-19 or during other future pandemic crises. Lastly, analyzing the longitudinal trajectory of the HWs' reactions could help to elucidate coping mechanisms in similar stressful periods.

FOOTNOTES

Author contributions: Carvalho-Alves MO, Brunoni AR, Malbergier A, Fukuti P, Polanczyk GV, Miguel EC and Corchs F contributed to the study design, data acquisition and interpretation, and revised the manuscript; Wang YP conceived the statistical analysis; Carvalho-Alves MO, Petrilli-Mazon VA, Corchs F and Wang YP conducted the statistical analysis and wrote the preliminary draft; all authors reviewed and approved the manuscript in its final version.

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