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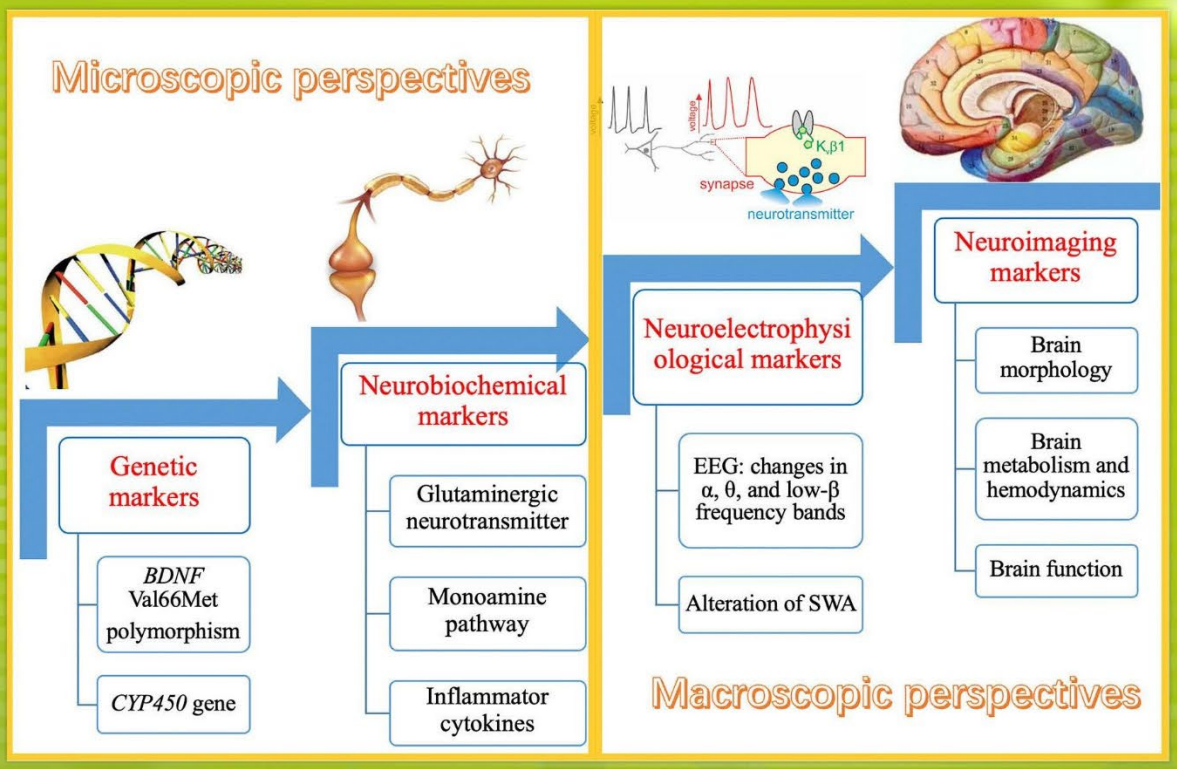

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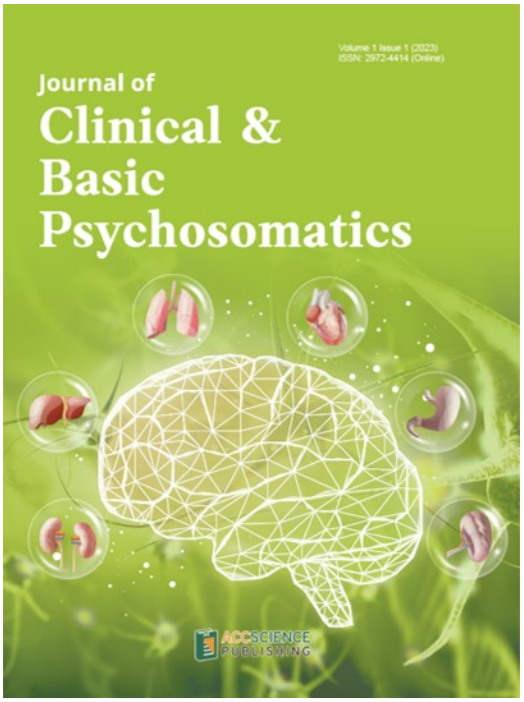

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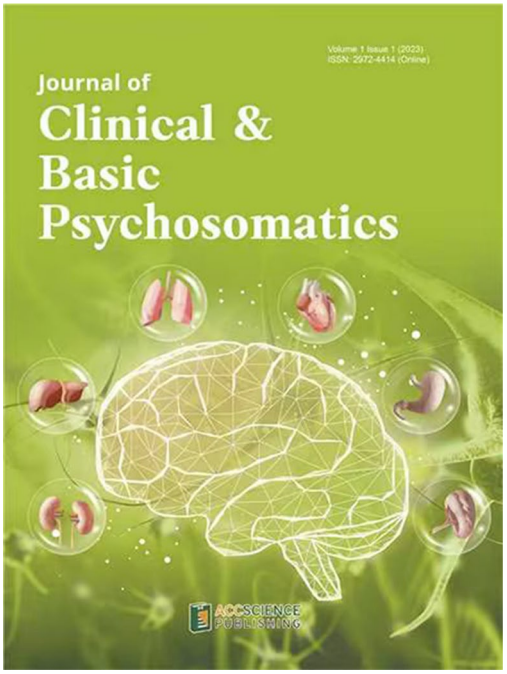

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REVIEW ARTICLE

Eudaimonia as a treatment goal in psychotherapy and psychosomatic medicine

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Abstract

Psychotherapy encompasses a broad range of goals, ranging from the alleviation of symptoms and the prevention of recurrence to the enhancement of well-being. These goals are mostly cross-sectional and hedonic-oriented in the sense of wellness, happiness, and absence of pain. However, an alternative goal is eudaimonia, which involves mastery of life from a long-term perspective. This pursuit entails embracing and even seeking hardship and confrontation with adversities for the sake of higher goods and goals. Eudaimonia, both an attitude and a behavior, is essential for everybody, especially individuals facing challenging circumstances and burdensome life situations, such as familial burdens, job problems, and illness. Eudaimonia can be attained through wisdom, which is regarded in lifespan psychology as a multidimensional capacity for coping with complex challenges and dilemmas in life. Initial studies suggest that wisdom skills are trainable, opening additional avenues in psychotherapy and psychosomatic medicine. It is argued that eudaimonia deserves increased attention in psychotherapy and psychosomatic medicine.

Keywords: Mastery of life; Dilemmas; Goals in life; Hedonia; Euthymia

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1. Introduction

Ancient philosophers such as Demokrit, Plato, and Aristotle have described "eudaimonia" as a state of inner harmony, virtue, striving to divine excellence, self-realization, interpersonal connection, and rational activity in pursuing higher goals in life. This concept stands in contrast to hedonia, which pertains to wellness and the absence of negative feelings.[1-5] Eudaimonia entails mastery of life in a socially responsible manner, irrespective of inevitable hardships and adversities. In modern psychology, eudaimonia has gained increasing interest within the context of well-being, lifespan development, and social interaction, closely linked with the notion of wisdom.[6-9] These research findings must be translated from basic science into clinical concepts.[10-12] This paper presents a scoping review delineating the concepts of eudaimonia and wisdom and offers recommendations of integrating these concepts into psychotherapy and psychosomatic medicine.

2. Hedonia and absence of suffering in psychotherapy

Traditional psychotherapy aims at alleviating suffering and pain while improving subjective wellness and positive mood. The initial focus is on reducing symptoms and other signs of illness (symptom relief), measured through self- and observer-

rated assessments of suffering. Once symptom relief is achieved, or even in cases where only partial remission is possible, the next goal is to prevent deterioration, relapse, and recurrence. Given that complete remission and long-term stability may not always be feasible, patients must learn to accept irreversibility and develop coping strategies, as outlined in mindfulness therapy, acceptance and commitment therapy, and dialectical behavior therapy.[13-15] Furthermore, patients require resilience and hardiness to withstand given adversities.[16,17] Next, addressing capacity limitations and impairment typically associated with long-term illness is essential, including enhancing communication skills, endurance during a workday, and adaptability to changing demands, as described in the International Classification of Functioning Disability and Health.[18] In cases where persistent capacity limitations result in participation restrictions, environmental demands can be adapted to accommodate the patients' capacities, such as changing work structures, providing sheltered employment, and offering support at home, in the sense of context modification and support of participation.[19,20] Even when symptoms of illness and suffering persist, a further treatment goal is to induce positive mood (hedonic and euthymic well-being).[11,21,22]

3. Eudaimonia and mastery of life

Apart from conventional hedonic treatment targets, the concept of "eudaimonia" is an additional topic for psychotherapy. Hedonism and personal wellness are not most important in life. Philosophers such as Democritus, Plato, and Aristotle described that solely pursuing hedonic wellbeing could be considered selfish, emphasizing instead the importance of societal responsibilities and moral virtues.[1,2] Beyond individual happiness, there is mastery of life, coping with and enduring irrevocable hardships, considering the needs and rights of other persons, and striving for higher goods. This concept can even entail embracing hardship and suffering.

Various definitions, connotations, and misunderstandings surround the concept of eudaimonia.[1-10,23-27] Some authors translate it into "happiness," which can be misconstrued as mere momentary pleasure. A related term, "euthymia," also denotes emotional well-being, although it, at least in part, also includes certain aspects of eudaimonia. The "euthymia scale"[28] includes items such as "I generally feel calm and relaxed," "I generally feel active and vigorous," along with statements such as "I am able to adapt to changing situations" and "I try to be consistent in my attitudes and behaviors." This illustrates that the scale covers a mixture of hedonic well-being, resilience, self-efficacy, and overarching goal-oriented behavior.

The difference between hedonic and eudaimonic well-being can be explained through everyday dilemmas. For example, hedonic well-being may suggest indulging in eating and drinking alcohol for momentary pleasure. Conversely, eudaimonic well-being suggests eating and drinking alcohol considering the implications for one's health and legal responsibilities, such as maintaining a valid driver's license. Another example is when hedonic well-being suggests staying in bed at night and ignoring your crying baby, whereas eudaimonic well-being entails getting up to attend to the crying baby, despite feeling tired, stressed, and even fed up. In this scenario, parents may experience hedonic discomfort on one side but, at the same time, derive eudaimonic satisfaction from meeting the needs of their baby, prioritizing their responsibilities over immediate personal desires. Eudaimonia is often the opposite of pleasure and wellness if not even undermining hedonia. Nevertheless, it remains important for the mastery of life. Eudaimonia is not only a goal and orientation in life but also a behavior and a way of managing life.

There is also neuroscientific data that may aid in understanding eudaimonia. Lewis *et al*.,[29] reported an association of eudaimonia subscales of the Ryff scale,[30] which measure personal growth, positive relations, and purpose in life, with the grey matter volume of the right insular cortex. In a review of further neurobiological findings, Berridge and Kringelbach[31] discussed subcortical hedonic hotspots in the nucleus accumbens, ventral pallidum, and brainstem, as well as regions for cognitive hedonic coding in the mid-anterior and mid-lateral zone of the orbitofrontal region. They observed interactions between hedonic brain circuits and circuits that assess meaningful relationships of self to social others. Of particular interest in this regard is the "default network," including the anterior cingulate and orbitofrontal cortices, dorsolateral prefrontal, and other parietal and temporal cortex networks, which encode evaluations of self and life meaning, potentially mediating might mediate eudaimonic appraisals. The difference between hedonia and eudaimonia as two distinguishable forms of well-being has also been explored in genetic research. Baselmans and Bartels[32] discussed two genome-wide significant independent loci for eudaimonic well-being and six independent loci for hedonic well-being. Joint analyses revealed a high genetic correlation (rg = 0.78) between eudaimonic and hedonic well-being, indicating substantial shared genetic etiology, with divergent (environmental) factors contributing to their phenotypic differences. Loci regulating expression demonstrated significant enrichment in the brain cortex, brain cerebellum, frontal cortex, and cerebellar hemisphere for eudaimonic well-being. In summary, these neurobiological findings suggest that eudaimonia is

a complex psychological construct that involves various brain regions.

4. Eudaimonia and wisdom

When defining eudaimonia as mastery of life, guided by higher values within a lifespan perspective, the question naturally arises: "How can this be achieved?" Again, Greek philosophers recognized centuries ago that wisdom is a pathway to eudaimonia. A substantial body of basic research on wisdom exists within lifespan and developmental psychology.[33-35] There is a general consensus that wisdom entails expertise in mastering difficult to solve and adversary situations in life. This definition closely aligns with that of eudaimonia. Wisdom is a capacity inherent in all humans, though to varying degrees, similar to social competency. It is indispensable for managing everyday life and navigating the course of life, aiding in coping with dilemmas and difficult problems. Wisdom has been described as a protective and resilience factor.[12,36-38] This process includes finding meaning, one's vocation, and goals in life, as well as reacting wisely to dilemmas, demands, and unsolvable problems. There are irrevocable dilemmas, such as the death of a beloved one, the infidelity of a partner, or public humiliation. Then, there are dilemmas in the form of difficult decisions, such as whether to marry, relocate for professional reasons, or whether to spend money for more expensive bio-products or instead buy cheaper no-name products to safe the money for activities with the kids. Further dilemmas arise from vocations, challenges in life, and decisions about important goals and objectives. These challenges include managing marital relationships, careers, and children's education. They are important aspects of life, complex topics that are often difficult to handle and lack clear-cut solutions, requiring long-term goals and perspectives. Wisdom capacities and skills are essential "to solve such unsolvable problems",[39(p.27)] handle ambiguity, and master exceptional as well as day-to-day dilemmas and problems.

When summarizing the various scientific concepts of wisdom, about a dozen subdimensions can be distinguished.[12,34,35,40,41] Wise individuals can recognize and accept factual information, even if it contradicts their own wishes (knowledge of facts). They possess procedural knowledge about effective actions of strategies (procedural knowledge). They acknowledge the role of contexts, understanding that the same event may be judged differently depending on the situational framework (contextualism). They know the importance of their own values while respecting the validity of differing values held by other people (value relativism). They are able to understand the perspective of others (change of perspective) and exhibit empathy, even toward potential enemies (empathy). They can apprehend and accept how they are perceived by other people and what others think about them (self-distance). They know about the relativity of their problems and aspirations (relativization of aspirations) and recognize that they are not the center of the world (modesty). They are adept in recognizing and accepting their own emotions, especially those they may wish to avoid (perception and acceptance of emotions). They exhibit emotional control, preventing emotions from clouding their views and actions (serenity and humor). They can come to terms with the past and forgive infringements (forgiveness). They approach the future with optimism (optimism) and make their decisions with a long-term perspective in mind (sustainability). They can live with uncertainty, acknowledging that they cannot predict the future with certainty yet continue to act and move forward (uncertainty tolerance).

Given the complexity of eudaimonia, mastery of life, and wisdom, the question arises of how to operationalize and measure these features. Classical assessments of psychological traits and clinical symptoms are insufficient, and there is no instrument to measure success in life as a whole. The closest approach is to measure eudaimonic well-being and wisdom competencies. A scale commonly used to assess eudaimonia orientation is the Questionnaire for Eudaimonic Well-Being (QEWB).[42] Items on this scale include "I believe I know what my best potentials are, and I try to develop them whenever possible," "I can say that I have found my purpose in life," "I feel best when I'm doing something worth investing a great deal of effort in," and "I believe I know what I was meant to do in life." There are further numerous scales available to measure wisdom dimensions.[43,44] One example is the Multidimensional Wisdom Competency Scale (MWC-15).[45,46] This instrument assesses problem-solving behavior and skills in managing difficult situations and dilemmas in life, with one item for each of the aforementioned wisdom subdimensions. The introductory statement reads: "When I am confronted with a problem or dilemma in life…," which is followed by the items such as "I take my time to check what exactly happened" (knowlegde of facts), "I look what alternative solutions are at my disposition" (procedural knowledge), "I accept that the context is as it is and can often not be changed" (contextualism), "I am aware that there are always many views on the same situation" (value relativism), "I first of all try to understand why everybody has acted as they did" (change opf perspective), "I try to feel what emotions all others have in this situation" (emotional empathy), "I am aware that everything could be much worse" (relativization of aspirations), "I try to be content with what I still have " (modesty), "I accept that I have negative or even undesirable feelings" (emotional acceptance), "I first of all try to calm down and control

my emotions" (serenity), "I am aware that humor means to laugh nevertheless" (humor), "I avoid to reheat old stories and events" (forgiveness), "I accept that many things cannot be changed (self-distance), "I always see the chances which come out of problems" (optimism), and "I know that time is a great healer" (sustainability).

5. Wisdom training and therapy

Given the significant role of eudaimonia and wisdom in life, this topic holds relevance for patients as well. Teaching eudaimonia and wisdom should be a target not only in education and counseling but especially in psychotherapy and psychosomatic medicine. However, this perspective has been widely neglected and underrecognized, as underlined by Oldhameditor of the *Journal of Psychiatric Practice*, who admitted in a 2022 editorial that he had only recently learned the "new word" eudaimonia.[47]

Empirical evidence suggests that wisdom training and wisdom psychotherapy can help individuals in various facets of life, offering avenues for individuals to find their goals, purpose, and meaning in life, as well as to cope with burdens and difficult situations in life. Moreover, they aid in striking a balance between personal aspirations with the rights and wishes of other people, fostering self-acceptance and acceptance of the given reality. These practices facilitate reconciliation with the past, fostering forgiveness for negative events, while simultaneously encouraging a forward-looking perspective. They empower individuals to enhance their self-control and autonomy, enabling them to withstand hardship and embrace suffering when necessary, all while steadfastly fulfilling their responsibilities, even in the face of discomfort.[12,39,48-52] It is important to note that the goal is not to pursue happiness but rather to help individuals live a decent life.

In addressing these aspects, wisdom therapy sis a psychotherapeutic approach, which is part of cognitive behavior therapy.[39,49,53] When examining the aforementioned subdimensions of wisdom, the potential for effective psychotherapeutic intervention becomes evident. Psychotherapists have long understood how to facilitate changes in perspective, foster empathy, enhance uncertainty tolerance, or cultivate forgiveness. Such strategies can also be used in wisdom psychotherapy. Furthermore, there exists the "method of unsolvable problems" to teach individuals how to navigate complex situations and dilemmas.[39] Patients are confronted with fictitious case vignettes, which describe negative and irrevocable problems. For instance, they involve a scenario featuring a perpetrator, a victim, and a winning bystander: "Mrs. Miller, who has lived with a man for some time and in recent years even cared for him lovingly when he fell ill. After his death, she learned that he had bequeathed all his money to his earlier wife." Patients are then asked to comment on the problem from the perspective of the victim, then the bystander, and finally, the wrongdoer. Through this process, individuals can experience and develop skills such as change of perspective, value relativism, contextualism, emotional empathy and serenity, control of aspirations, forgiveness, and sustainability. The use of fictitious problems follows the "Solomon paradox"[54] and the general knowledge that it is easier to give advice to others but difficult to accept advice oneself. Manuals for individual and group psychotherapy describing the details of the therapeutic process are available.[39,53]

6. Conclusion

Therapists treat human beings, not just illnesses. Patients experience hardship due to illness and related symptoms, insecurity about the future, participation restrictions, and dilemmas across various life domains. While alleviating suffering is important, achieving mastery of life, finding contentment with life, and experiencing eudaimonia are equally important. Although clinicians universally recognize this, there is a lack of corresponding theoretical concepts in psychotherapy, compounded by a lack of elaborated therapeutic strategies and empirical evidence. Scientific evidence and clinical experiences suggest that integrating wisdom psychology into psychotherapy holds promise for fostering eudaimonia. Nonetheless, further research is necessary for the refinement of concepts and the development of treatments.

Although there exists a large body of literature on eudaimonia and wisdom, as briefly summarized above, numerous questions remain unanswered. There are variations in definitions, leading to challenges in differentiation or overlap between hedonia and eudaimonia. This discrepancy includes the role of individual subdimensions, as demonstrated by Mise and Busseri,[8] who have found that correlations were strongest for well-being and weakest for motives. In addition, the role of time is a factor. Huta[55] has discovered evidence suggesting that eudaimonia and hedonia are clearly distinct in the momentary time span, yet less so over a longer duration. Furthermore, differences across individuals exist, as data from the MIDUS study[56] suggest that hedonia and eudaimonia largely converge in about 70% of observed persons, while the remaining 30% experience divergent levels. These conceptual problems can be explained in part by problems in the assessment of these highly complex constructs. Nevertheless, there are theoretical and clinical justifications for maintaining the distinction between both concepts. They target different topics, and, in some cases, even stand in opposition to each

other. Consequently, they require different measurements and specific interventions.

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REVIEW ARTICLE

The neurobiological mechanism underlying ketamine's rapid-acting antidepressant effect

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Abstract

Depression is one of the most common disabling mental disorders. However, first-line treatments for depression are typically slow-acting. Ketamine, a glutamatergic modulator with rapid antidepressant effects, has proven effective in treating both refractory depression and suicidal tendencies. The neurobiological mechanisms underlying the effects of antidepressants have become a research hotspot; yet, the exact processes remain unclear. Brain imaging studies have provided important evidence from macroscopic perspectives, such as brain structure and function, while biochemical studies have made significant discoveries from microscopic perspectives, including proteomics and genomics. Previous reviews have summarized a broad range of biomarkers related to the ketamine response, encompassing studies in imaging, electrophysiology, metabolism, immunology, genetics, and neurotrophy. In this review, we systematically summarize a number of potential biomarkers for predicting and modulating the efficacy of ketamine, from both macroperspectives (such as neuroimaging and neuroelectrophysiological markers) and microperspectives (such as neurobiochemical and genetic markers). Although research in this area is still in its infancy, these biomarkers can help clinicians identify whether ketamine intervention is needed for treatment-resistant depression, thereby reducing the burden on patients and society. However, the majority of biomarkers are still in the preclinical exploratory stage, and existing findings are limited. To realize the clinical application of these biomarkers, future studies should combine biomarkers of different types to investigate the relationships and interactions between them. This approach aims to optimize clinical outcomes by enhancing the involvement of biological targets in new models.

Keywords: Depression; Ketamine; Rapid-acting; Biomarker

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1. Introduction

Depression is the most common disabling mental disorder. At present, the first-line treatment for depression is selective serotonin reuptake inhibitors, which have shortcomings such as slow onset, low cure rate, and significant side effects. Therefore, the development of new antidepressants has become a major challenge in the field of psychiatry. In this context, ketamine has been used.

Ketamine, a glutamatergic modulator with rapid antidepressant effects, has proven effective in treating both refractory depression and suicidal tendencies.[1-4] The neurobiological mechanisms underlying the effects of antidepressants have become a research hotspot, but the exact processes remain uncertain. Noteworthy, despite its rapid antidepressant effects, the application of ketamine to treat depression is still in its infancy, with many unresolved problems. For instance, the addiction risk associated with the use of ketamine as an antidepressant has not been determined, the total duration of treatment remains unconfirmed, and how to address dissociative symptoms has not been established. These questions might benefit from the discovery of corresponding biomarkers.

Brain imaging studies have provided important evidence from macroscopic perspectives, such as brain structure and function, while biochemical studies have made significant discoveries from microscopic perspectives, including proteomics and genomics. To scientifically clarify the neurobiological mechanisms of ketamine's rapid-acting antidepressant effects, we searched for relevant literature from five electronic databases (2000 – 2023), PubMed, the Cochrane Library, EMBASE, the Web of Science, and clinical trials, using the following terms: "depression," "ketamine," "rapid-acting," and "biomarker." A total of 87 articles were included in this review. We reviewed studies related to the neurobiological mechanisms underlying the rapid-acting antidepressant effects of ketamine from both macro- and microperspectives (Figure 1), identifying hot topics and potential strategies for future investigations. Ultimately, this review provides evidence for the development of accurate and individualized treatments for depression.

2. Neuroimaging markers

Multiple neuroimaging modalities have been used to explore the mechanisms of the rapid antidepressant effects of ketamine. Neuroimaging can identify functional connections and networks associated with the effects of ketamine therapy by revealing how ketamine alters brain structure, function, connectivity, and metabolism. For example, high-resolution three-dimensional structural T1 magnetic resonance imaging (MRI) can measure differences in volume, thickness, and density in cortical and subcortical structures; diffusion tensor imaging (DTI) can assess the integrity of white matter fiber tracts; positron emission tomography (PET) can detect brain glucose metabolism levels through radiotracer labeling; arterial spin labeling (ASL) can detect cerebral blood flow; and functional MRI (fMRI) can measure brain activation level. In this section, three aspects of the rapid antidepressant effects of ketamine are reviewed: morphology, metabolism, hemodynamics, and brain function.

2.1. Brain morphology

Brain morphological changes include alterations in gray matter volume, white matter volume, cortical thickness, density, and white matter fiber integrity. Gray matter volume, white matter volume, cortical thickness, and density can be measured using high-resolution three-dimensional structural T1 MRI, while white matter fiber integrity can be measured using DTI.

The most common morphological change observed is in the volume of the hippocampus. Zhou *et al.*[5] reported that the right hippocampal volume significantly increased after six serial ketamine infusions for 12 days, proposing increased hippocampal volume as a prominent neurobiological biomarker. Abdallah *et al.*[6] found that ketamine treatment increased the left hippocampal volume but reduced the volume of the left nucleus accumbens in patients who achieved remission. They also noted that pretreatment volumes of the left hippocampal were associated with clinical response following ketamine infusions. In addition to the hippocampus, a decrease in the volume of the right dorsolateral prefrontal cortex (dlPFC) was found to be associated with the antidepressant effect of ketamine.[7] Furthermore, a study investigating gray matter density changes after ketamine treatment in bipolar depression patients revealed decreased gray matter density in the bilateral insula, right caudate, and bilateral dlPFC, and increased gray matter density in the bilateral post-central gyrus, subgenual anterior cingulate cortex (sgACC), thalamus, and cerebellum. These changes appeared 24 h post-ketamine treatment, peaked at 1 week, and diminished by the 3rd week.[8]

DTI studies have also revealed important structural alterations in white matter fiber tracts associated with the efficacy of ketamine. Sydnor *et al.*[9] showed that fractional anisotropy (FA) in the forceps minor and bilateral uncinate fasciculus increased after ketamine treatment. In addition, baseline FA values of the left cingulate tract and the upper longitudinal tract were significantly correlated with the effect of ketamine. In the study by Vasavada *et al.*,[10] patients who responded to ketamine had significantly greater FA in the cingulum and forceps minor at baseline compared to non-responders, with a complementary decrease in the radial diffusivity of these tracts.

2.2. Brain metabolism and hemodynamics

PET, a technology with moderate temporal and spatial resolution, can effectively detect brain metabolic levels. Carlson *et al.*[11] found that metabolism decreased in the right insula, habenula, and ventrolateral and dorsolateral PFCs after ketamine treatment. In addition, acute improvement in depression was significantly correlated with metabolic

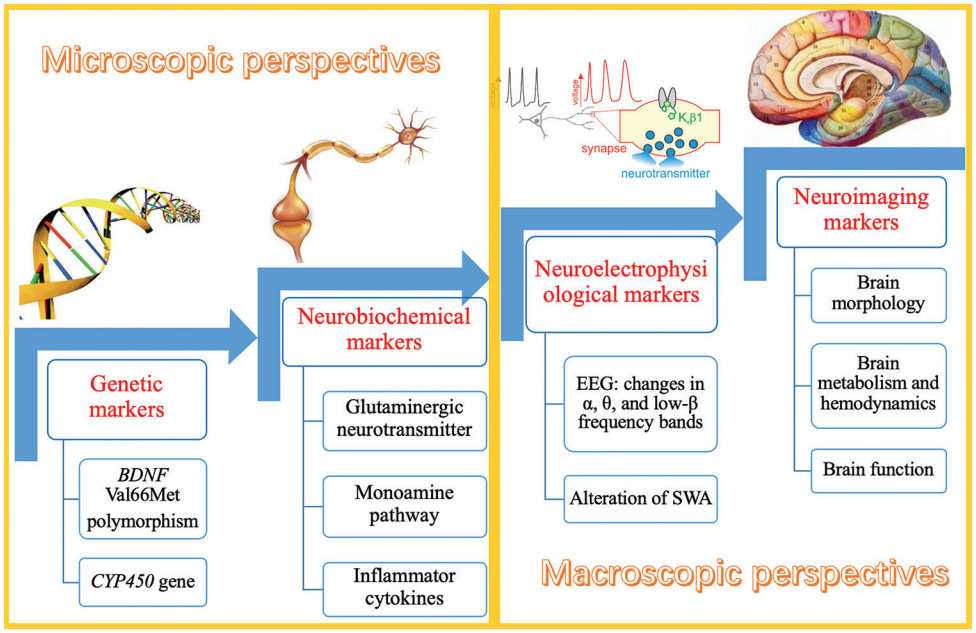

Figure 1. The neurobiological mechanisms underlying ketamine's rapid-acting antidepressant effects from micro- to macroperspectives
Abbreviations: BDNF: Brain-derived neurotrophic factor; CYP: Cytochrome enzyme P; EEG: Electroencephalogram; SWA: Sleep slow wave activity.

changes in the right superior and middle temporal gyri. Furthermore, increased metabolism in the sensory cortices was associated with dissociation symptoms. Nugent *et al.*[12] found that acute improvement in depressive symptoms post-ketamine therapy correlated with a corresponding increased metabolism in the right ventral striatum, and patients exhibited significantly lower glucose metabolism in the left hippocampus post-ketamine infusion compared to post-placebo infusion. Li *et al.*[13] observed increased glucose metabolism in the PFC after ketamine infusion, which was associated with alleviative depression within 2 h. Chen *et al.*[14] reported increased glucose uptake in the dorsal ACC 24 h after ketamine infusion in patients with treatment-resistant depression (TRD). Using ASL, Sahib *et al.*[15] reported increased cerebral blood flow (CBF) in the posterior cingulate cortex and visual association regions but decreased CBF in the bilateral hippocampus and right insula after serial ketamine infusion. Moreover, Gartner *et al.*[16] found that increased thalamic perfusion was associated with the efficacy of ketamine 24 h after infusion.

2.3. Brain function

Blood oxygen level-dependent (BOLD) fMRI is a technology used to measure brain activity. BOLD fMRI can be divided into resting-state fMRI and task-based fMRI based on whether a task is performed during the scan. Most studies investigating the relationship between brain function and ketamine use resting-state fMRI for its operational convenience. The default mode network (DMN) is the most prominent network in the resting state. Researchers have shown that after 2 weeks of ketamine infusion, functional connectivity decreases in the ventral limbic nodes but increases between subcortical and cortical nodes.[17] Compared to placebo, patients with depression exhibited increased functional connectivity between the DMN and the insula, as well as with the frontal, parietal, and occipital cortices 2 days after a single ketamine infusion.[18]

The pivotal hubs of the cognitive control network, such as the dlPFC and dorsal anterior cingulate cortex (dACC), showed decreased functional connectivity within the intrinsic network 48 h after a single dose of ketamine. In addition, the functional connectivity between bilateral dACC/dlPFC and the left superior parietal cortex significantly correlated with suicidal ideation.[19] The increased functional connectivity between the right central executive network and amygdala connectivity in patients was normalized 24 h after four serial ketamine infusions.[20] Researchers have also used resting-state fMRI to detect global brain connectivity regression (GBCr) in TRD patients at baseline and follow-up ketamine treatment. They found that TRD patients had reduced GBCr in the dlPFC compared with healthy controls, but GBCr significantly increased 24 h post-ketamine infusion.[21,22] These findings suggest that ketamine could improve the function of the cognitive control network.

The pivotal hub of the emotion control network, sgACC, manifested increased functional connectivity with the insula and caudate but decreased functional connectivity

with DMN 2 weeks post-ketamine treatment.[17] Remission in depressive patients after ketamine treatment has been associated with increased functional connectivity between the sgACC and the supplementary motor area, as well as the dlPFC.[23] Another study revealed that depression remission was related to decreased functional connectivity between the sgACC and the right amygdala,[24] a finding corroborated by a recent study.[25] Nugent *et al.*[26] reported decreased functional connectivity between the amygdala and the insula, as well as the temporal cortex, post-ketamine treatment, suggesting that ketamine could normalize this hyperactive signature of depression. Functional connectivity within the frontostriatal circuitry has also been associated with ketamine response. Decreased functional connectivity within the frontostriatal circuitry at baseline has been linked to subsequent improvements in depressive symptoms,[27] and frontostriatal connectivity increased 2 days after a single ketamine infusion.[28] In addition, increased frontostriatal connectivity was found to be associated with improvements in anhedonia.[29]

As a pivotal hub of the epithalamus, the habenula directly connects with limbic structures and the basal ganglia, playing a crucial role in regulating emotion, reward, and motivation. Studies have reported that increased functional connectivity between the habenula and the right dlPFC is associated with an improved antidepressant response following a single ketamine infusion.[30] Furthermore, increased functional connectivity between the right habenula and the occipital-temporal cortex, as well as the para-hippocampal gyrus, has been linked to subjective mood improvement.[31]

Relatively, few studies have employed task-based fMRI due to the stringent demands of research equipment. However, a double-blind controlled trial investigated the influence of ketamine on cognitive and emotional processing in patients with TRD.[32] This study applied implicit and explicit facial recognition tasks to examine how ketamine impacts brain activity. The results indicated that the pattern of brain activity after ketamine infusion resembled that of the control group following a placebo infusion, suggesting that ketamine may act as an antidepressant by normalizing brain function during mood processing.

3. Neuroelectrophysiological markers

Neuroelectrophysiological changes associated with the antidepressant effects of ketamine can be detected using magnetoencephalography and electroencephalography (EEG), two technologies known for their high temporal resolution. EEG analysis revealed significant changes in the α, θ, and low-β frequency bands during ketamine treatment. While the α band showed initial changes in the early stages of treatment but returned to baseline levels at treatment cessation, the θ and low-β bands exhibited significant changes after the end of treatment.[33] McMillan *et al.*[34] combined MRI and EEG to investigate the correlation mechanism between EEG and BOLD signals underlying the rapid-acting antidepressant effect of ketamine. They found that low β and high γ power time courses explained significant variance in the BOLD signal. This finding suggested that the decreased sgACC BOLD signal might be noise with no relation to the antidepressant response to ketamine.

A recent EEG study revealed increased long-term potentiation approximately 4 h after a single ketamine infusion, suggesting that ketamine could accelerate neural plasticity within the time frame of its antidepressant effects.[35] Sleep slow wave activity (SWA), measured using EEG, may be a marker of homeostatic sleep regulation as well as synaptic plasticity. Evidence shows reduced SWA in depressive patients.[36] Duncan *et al.*[37] observed increased SWA during the first non-rapid eye movement (REM) episode post-ketamine treatment compared with baseline in TRD patients. This alteration in SWA was significantly correlated with the changes in brain-derived neurotrophic factor (BDNF), a classical marker of neuronal plasticity, in patients who responded to ketamine. Another study revealed a relationship between a lower SWA ratio in the non-REM period and the antidepressant effect of ketamine.[38] Rantamaki and Kohtala[39] proposed the coding, consolidation, and reorganization hypothesis of depression, considering changes in SWA and synaptic strength as the underlying mechanisms of the rapid-acting antidepressant effects of ketamine.

4. Neurobiochemical markers

Several neurobiochemical hypotheses explain the antidepressant effect of ketamine. The most popular is the glutamatergic hypothesis, which has been the subject of extensive investigation. Moreover, evidence from research testing the energy metabolism hypothesis, immunoinflammatory hypothesis, and neurotrophic hypothesis has provided valuable insights. This section presents a review of the relevant investigations on these four hypotheses.

4.1. Glutamatergic neurotransmitters

Magnetic resonance spectroscopy (MRS) can be used to examine intracerebral glutamatergic levels. MRS studies have shown that the glutamate levels in the hippocampus, PFC, and ACC are decreased in depressive patients.[40-42] In addition, glutamate levels in the ACC are significantly correlated with anhedonia in patients.[43] Milak *et al.*[44]

found that patients' glutamate levels in the PFC increase rapidly after treatment with ketamine. Chowdhury *et al.*[45] reported that glutamate levels in the PFC increase rapidly after ketamine infusion in animal models. Research has reported that glutamate levels in the PFC are significantly correlated with the dosage of ketamine.[46] However, a negative correlation between ketamine and glutamate has been reported in another literature.[47]

Two main hypotheses for the antidepressant effects of ketamine (the disinhibition hypothesis and the direct inhibition hypothesis) are related to the N-methyl-D-aspartate (NMDA) receptor in the glutamate metabolic pathway. According to the disinhibition hypothesis, ketamine acts by binding to NMDA receptors to block inhibitory interneurons, thereby increasing the firing of excitatory pyramidal neurons.[48] In contrast, the direct inhibition hypothesis posits that ketamine inhibits NMDA receptors in the postsynaptic membrane, subsequently altering cellular signaling pathways that affect protein expression.[49] The endogenous coagonist of the NMDA receptor, d-serine, plays a key role in NMDA-induced neurotoxicity, long-term potentiation, neurotransmission, and plasticity. Moaddel *et al.*[50] applied ketamine to treat TRD patients and found that the plasma d-serine concentration at baseline in the remission group was significantly lower than that in the non-remission group. Moreover, a low level of d-serine at baseline indicated an improved antidepressant response. Another regulatory protein of the NMDA receptor, SHANK3, has also been reported to be involved in the pathophysiology of depression. Ortiz *et al.*[51] investigated the relationships between the volume and glucose metabolism of subcortical nuclei, ketamine efficacy, and SHANK3 levels. They found that a high level of SHANK3 at baseline could predict the response to ketamine, enhanced glucose metabolism in the amygdala and hippocampus, and increased amygdala volume.

Recent intensive research has revealed that the alpha-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid (AMPA) receptor plays a key role in the antidepressant effects of ketamine. As a target of multiple signaling pathways that regulate synaptic plasticity, the AMPA receptor is primarily responsible for rapid synaptic neurotransmission and signal transduction in the brain. The findings in this area are as follows:

(i) Long-term, low-dose ketamine injection increases the ratio of AMPA receptors in the hippocampus.[52]
(ii) A series of synaptic signaling proteins are activated 2 h after ketamine injection, subsequently activating the postsynaptic rapamycin target protein molecular pathway. This activation triggers synaptic protein synthesis, lasting until 72 h after ketamine injection. During this period, synaptogenesis is promoted, especially the maturation and increase in the number of neuronal dendrites.[53]
(iii) Conflicting evidence has shown that the antidepressant effects of ketamine disappear after the use of an antagonist of the AMPA receptor.[54]

Another metabolic glutaminergic receptor, mGluR5, was also examined by PET. The ligand binding of mGluR5 significantly decreased and lasted for 24 h after ketamine treatment.[55] This finding suggests that the availability of mGluR5 is modulated by glutamate released after ketamine injection, which is associated with the antidepressant effect of ketamine. A recent study confirmed this observation, demonstrating that ketamine alters the mRNA or protein expression of mGluR5.[56]

4.2. Monoamine pathway

The traditional development of antidepressants is based on the monoamine hypothesis, which posits that the depletion of 5-hydroxytryptamine (5-HT), norepinephrine, and dopamine underlies depression. In addition to affecting glutamate, ketamine has been shown to indirectly regulate monoaminergic neurotransmission. In rodent models, the antidepressant effect of ketamine can be blocked through the consumption of 5-HT by tryptophan hydroxylase;[57] ketamine can increase the levels of extracellular serotonin, dopamine, and norepinephrine in the PFC.[58] According to a PET study, ketamine can also enhance the binding strength of the 5-HT1B receptor and the 5-HT transporter.[59] Nevertheless, several studies have reported negative results, which suggest that the antidepressant effect of ketamine was not affected by 5-HT.[60]

Ketamine can effectively improve core symptoms of depression and anhedonia, which are usually not alleviated by traditional antidepressants.[28] Anhedonia is strongly associated with the dopaminergic reward circuit, suggesting a potential effect of ketamine on the dopamine pathway. In rodent models, the behavioral response to repeated administration of ketamine can be blocked by dopamine receptor antagonists.[61] A recent study demonstrated that ketamine could reverse stress-induced behavioral inhibition in mice, but this effect was blocked by inhibiting dopaminergic signal transduction.[62] Moreover, the expression levels of dopamine receptors in the PFC and hippocampus increased following high doses of ketamine in a mouse model of schizophrenia, with these increases positively correlated with the injection dose.[62] Iro *et al.*[63] reported that repeated administration of ketamine increased the firing activity of dopaminergic and noradrenergic neurons, but not serotonergic neurons.

However, Chang *et al.*[64] found that esketamine's effects were not blocked by dopamine receptor antagonists, suggesting that esketamine might exert its effects independently of dopamine.

4.3. Inflammatory cytokines

Inflammatory cytokines such as tumor necrosis factor-α, C-reactive protein, interleukin (IL)-1β, IL-6, and IL-8 are upregulated in both depressive animal models and human patients. Ketamine has been found to exert anti-inflammatory effects.[65,66] For instance, in a mouse model of ulcerative colitis, ketamine decreased IL-6 levels in the blood.[67] It also reduced the production of proinflammatory cytokines induced by lipopolysaccharide in mice, thereby reducing splenomegaly and cognitive impairment.[68] In addition, ketamine reversed high proinflammatory cytokine levels in female Wistar rats subjected to maternal deprivation.[69] *In vivo* studies have shown that depressed women with low IL-8 levels at baseline demonstrate enhanced responses to ketamine treatment.[70] These studies suggest that ketamine's ability to regulate immune inflammation might play a role in its rapid antidepressant effects. The neutrophil-to-lymphocyte ratio, a novel biomarker of peripheral blood inflammation associated with depression, is closely related to the efficacy of ketamine.[71] In addition, studies have confirmed a link between depression and elevated IL-6, but not between IL-6 and ketamine. Park *et al.*[72] examined eight cytokines and found that only soluble tumor necrosis factor receptor 1 was associated with depression; the other cytokines were unrelated to emotional changes or ketamine, suggesting that cytokines are not the primary mechanism of ketamine's antidepressant effects. In summary, the neurobiological mechanisms of depression are not necessarily identical to the underlying mechanisms of the ketamine response, but they can be used as indirect predictors of the response to ketamine.

5. Genetic markers

Animal research has shown similar transcriptional responses related to neuroplasticity and the circadian clock in the ACC of sleep-deprived mice after low-dose ketamine injection.[73] Cell culture research has indicated that ketamine alters the expression of clock genes associated with the internal clock.[74] Researchers believe that the effect of ketamine on synaptic plasticity is mediated by BDNF. Laje *et al.*[75] reported that the *BDNF* Val66Met polymorphism was associated with dysfunction of NMDA receptor transmission and hippocampal synaptic plasticity, suggesting that increased *BDNF* expression might be related to increased susceptibility to depression and poor response to ketamine. Niciu *et al.*[76] found that bilateral thalamic volume was positively associated with the antidepressant response 230 min after ketamine injection in *Val/Val* homozygous patients but negatively associated with the ketamine antidepressant response in met carriers.

Ficek *et al.*[77] applied genome-wide microarray techniques to analyze numerous genetic transcription profiles with altered expression in the brain following ketamine administration. These transcription profiles reflected the multitarget pharmacological properties of ketamine. Interestingly, this study revealed similarities in the transcriptional profiles of ketamine and monoaminergic antidepressants, suggesting a degree of convergence of their antidepressant effects on the downstream molecules.

Ketamine is metabolized through cytochrome enzyme P450 (CYP450) in the liver. Pharmacogenomic analyses of the effects of individual genetic variants of CYP450 on ketamine metabolism might provide evidence for individual variation in ketamine efficacy. However, evidence on the effect of *CYP450* gene variants on the ketamine response is still inconsistent. A recent study revealed that the activity of the liver CYP450 subtype contributed to the sustained antidepressant effects of ketamine,[78] while another study showed that *CYP450* polymorphisms could not predict the clinical response to ketamine.[79]

Recently, the effects of several glutamatergic polymorphisms on the therapeutic effects of ketamine and esketamine in TRD patients were investigated.[80] Unfortunately, no positive result was obtained.

6. Other markers

The main pathway of action of ketamine, the glutamate pathway, functions by increasing BDNF levels, which could promote synaptic protein synthesis and synaptogenesis, increase synaptic connectivity, and ultimately play a role as an antidepressant. Substantial evidence indicates that BDNF is involved in the rapid antidepressant response to ketamine. For instance, Haile *et al.*[81] reported that improvement in depression 4 h after ketamine infusion was associated with increased BDNF levels. Woelfer *et al.*[82] investigated the relationships among the ketamine response, BDNF levels, and resting-state functional connectivity in healthy volunteers. They reported that the plasma BDNF level in the ketamine group was greater than that in the placebo group after treatment and that alterations in BDNF levels after ketamine infusion were associated with increased functional connectivity of the dorsomedial PFC, reflecting the effect of ketamine on synaptic plasticity. Zheng *et al.*[83] discovered that baseline plasma BDNF could predict the antianhedonic effect of repeated doses of ketamine on patients with depression.

The kynurenine (KYN) pathway plays an important role in depression, according to many investigations.[84] KYN is a major regulator of glutamate and 5-HT. Both the metabolic enzymes and metabolites of KYN are involved in the antidepressant mechanism of ketamine. Moaddel *et al*.[85] applied ketamine to TRD patients and found that plasma KYN levels decreased 4 h after ketamine infusion in the remission group. Kadriu *et al*.[86] reported that ketamine could reduce the levels of KYN, a metabolizing enzyme, and a toxic metabolite of KYN, quinolinic acid, but increase the levels of a protective metabolite, kynureric acid, in depressed patients. They also found that proinflammatory cytokines at baseline were associated with alterations in the KYN pathway after ketamine treatment, suggesting that KYN might be involved in the immune inflammatory response to depression. A recent study also confirmed that ketamine could rapidly increase the serum kynurenic acid concentration in depressed patients, and the level of kynurenic uric acid at 24 h could predict the sustained antidepressant effects of ketamine at 13 and 26 days.[87] The above evidence suggests that the KYN pathway is involved in the immunological, monoaminergic, and glutamatergic mechanisms of depression. The key neuroactive factors in the KYN pathway, including metabolic enzymes and metabolites, can be used not only as new therapeutic targets to intervene in depression but also as biomarkers to detect the efficacy of ketamine.

Recent animal studies have reported a number of novel protein or molecular markers associated with ketamine. For instance, Klotho has been reported to be associated with the antidepressant effect of low-dose ketamine.[88] Higher vascular endothelial growth factor levels at baseline were associated with greater antidepressant and antisuicidal effects after ketamine infusion.[89] In addition, ketamine promoted the differentiation of oligodendrocyte precursor cells and increased myelin formation, contributing to its antidepressant role.[90]

Ma *et al*.[91] reported that ketamine acts as a special use-dependent trapping blocker (activity-dependent trapping blocker). It only blocks NMDA receptors that enter the open state, after which it remains in the NMDAR channel and dissociates at a certain rate. *In vivo*, ketamine dissociates gradually, and the retained dose is free from the action of metabolic enzymes, thereby blocking the channel for a long time and continuing to exert its inhibitory effects.

7. Conclusion

Psychiatry is gradually shifting toward a paradigm of early identification and intervention. As a result of this paradigm shift, the rapid-acting antidepressant ketamine has significantly influenced awareness of antidepressant treatments and greatly expanded the medication options for patients with TRD and depression at risk of suicide. Investigating biomarkers related to the rapid-acting antidepressant effects of ketamine will be extremely beneficial for early intervention, rapid onset of therapeutic effects, and predicting treatment outcomes in depression. In this review, we summarize a number of biomarkers (Table 1) that can predict and modulate ketamine efficacy. Although research in this area is still in its infancy, it is helpful for clinicians to identify TRD patients who are suitable candidates for ketamine treatment, thereby alleviating the burden on these patients and society.

To date, the majority of biomarkers are still in the preclinical exploratory stage, and existing findings are limited. To realize the clinical application of these biomarkers, future studies should combine different types of biomarkers to investigate their relationships and interactions. This approach could optimize clinical outcomes by enhancing the involvement of biological targets in new models. Cross-modal research on biomarkers has been carried out consecutively and is extremely valuable for optimizing neurobiological signals-assisted diagnosis and treatment.

Table 1. Neurobiological markers underlying ketamine's rapid-acting antidepressant effects

Neurobiological markers	Biomarkers and reference
Neuroimaging markers	
Brain morphology	Increase hippocampal volume[5,6]
	Reduce the volume of the left nucleus accumbens[6]
	Decrease the density of bilateral insula, right caudate, and bilateral dlPFC and increased density in the bilateral post-central gyrus, sgACC, thalamus, and cerebellum[7,8]
	Increase FA of the cingulum, forceps minor, and uncinate fasciculus[9,10]
Brain metabolism and hemodynamics	Decrease the metabolism of the right insula, habenula, ventrolateral, and dorsolateral PFCs[11]
	Increase metabolism of the right ventral striatum[12]
	Increase glucose metabolism in the PFC[13]
	Increase dorsal ACC glucose uptake[14]
	Increase CBF of the posterior cingulate cortex, thalamus and visual association regions[15,16]
	Decrease CBF in the bilateral hippocampus and right insula[15]

(Cont'd...)

Table 1. ***(Continued)***

Neurobiological markers	Biomarkers and reference
Brain function	Decrease FC in ventral limbic nodes[17]
	Increase FC between subcortical and cortical nodes[17]
	Increase FC between the DMN and the insula as well as with frontal, parietal, and occipital cortices[18]
	Decrease FC within the intrinsic cognitive control network[92]
	Decrease FC between bilateral dACC/dlPFC and left superior parietal cortex[92]
	Increase FC between right central executive network-amygdala connectivity[20]
	Increase GBCr in dlPFC[21,22]
	Increase FC of sgACC with insula as well as caudate, but decreased FC with DMN[17]
	Increased FC between sgACC and SMA as well as dlPFC[23]
	Decreased FC between sgACC and right amygdala[24,25]
	Decrease FC between amygdala and insula as well as temporal cortex[26]
	Increase frontostriatal connectivity[27-29]
	Increase FC between the habenula and right dlPFC[30]
	Increase FC between right habenula and occipital-temporal cortex as well as para-hippocampal gyrus[31]
Neuroelectrophysiological markers	EEG analysis revealed significant changes in α, θ, and low-β frequency bands during ketamine treatment[33]
	Increased long-term potentiation[35]
	Increase SWA[37-39]
Neurobiochemical markers	
Glutamatergic neurotransmitters	Elevate the glutamate levels in PFC[44-46]
	Increase the plasma d-serine (an endogenous co-agonist of the NMDA receptor) concentration[50]
	High levels of SHANK3 (a regulatory protein of NMDA receptor) at baseline could predict the response to ketamine[51]
	Increase the ratio of AMPA receptors in the hippocampus[52]
	Decrease the ligand binding of mGluR5, a metabolic glutamatergic receptor[55,56]
Monoamine pathway	Increase the levels of extracellular serotonin, dopamine and norepinephrine of PFC[58]
	Increase the binding force of the 5-HT1B receptor and 5-HT transporter[59]
	Increase the expression levels of dopamine receptors in PFC and hippocampus[62]
	Increase the firing activity of dopaminergic and noradrenergic neurons[63]
Inflammatory cytokines	Decrease IL-6 level in the blood[67]
	Low IL-8 levels at baseline responded better to ketamine treatment[70]
	Decrease the neutrophil-to-lymphocyte ratio[71]
Genetic markers	Alter the expression of the *clock gene*[74]
	BDNF Val66Met polymorphism[75,76]
	Ketamine has multi-target pharmacological properties and is similar to the transcriptional profiles of monoaminergic antidepressants[77]
	CYP450 gene[78]
Other markers	High level of BDNF[81,83]
	Increase FC of dorsomedial PFC associated with the alteration of BDNF[82]
	Decrease plasma KYN level[85,87]
	Increase serum kynurenic acid (a protective metabolite of KYN) and reduce the level of quinolinic acid (a toxic metabolite of KYN)[86]
	klotho gene[88]
	Vascular endothelial growth factor[89]
	Promote the differentiation of oligodendrocyte precursor cells and increase myelin formation[90]

Abbreviations: 5-HT: 5-hydroxytryptamine; AMPA: Alpha-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid; BDNF: Brain-derived neurotrophic factor; CBF: Cerebral blood flow; dACC: Dorsal anterior cingulate cortex; dlPFC: Dorsolateral prefrontal cortex; DMN: Default mode network; EEG: Electroencephalogram; FA: Fractional anisotropy; FC: Functional connectivity; GBCr: Global regression; IL: Interleukin; KYN: Kynurenine; NMDA: N-methyl-D-aspartate; PFC: Prefrontal cortex; sgACC: Subgenual anterior cingulate cortex; SMA: Supplementary motor area; SWA: Sleep slow wave activity.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: All authors
Writing – original draft: Yingying Yin
Writing – review & editing: Yonggui Yuan

Ethics approval and consent to participate

Not applicable.

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Availability of data

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ACCSCIENCE PUBLISHING

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PERSPECTIVE ARTICLE

Reviewing the art of safe prescription practices: A checklist for the use of psychotropic drugs during pregnancy

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Abstract

Half of the women diagnosed with a mental health condition requiring regular medication have previously given birth to children. A dilemma arises when deciding whether to continue medication to treat the mother's illness or potentially cease or replace medication in the interests of their child. This study endeavors to examine the challenges associated with prescribing psychotropic medications to pregnant women experiencing mental health disorders. Its primary objective is to furnish a checklist delineating essential considerations for prescribers in such cases. The investigation underscores the pivotal equilibrium required in addressing the mental health of the mother while mitigating risks to the developing fetus. The paper delves into the nuances of decision-making within this framework, highlighting the importance of a collaborative health-care approach coupled with personalized treatment strategies. These strategies may encompass modifications in medication regimens and the incorporation of non-pharmacological interventions. The prescription of psychotropic medications to pregnant women with mental health conditions presents complex challenges and demands consideration. Striking a critical balance is imperative, as it entails managing the mother's mental health while minimizing potential risks to the developing fetus. The decision-making process is nuanced, influenced by factors such as the teratogenic potential of specific medications, the risk of neonatal withdrawal syndrome, and the potential for adverse outcomes in maternal and fetal health if psychiatric conditions remain untreated. Pre-conception counseling and maternal-fetal medicine services are beneficial tools in navigating this balance. Predictors of the necessity for medication during pregnancy include the patient's diagnosis, severity of prior episodes, and responsiveness to treatment. The dynamic landscape of pharmaceutical research underscores the importance for prescribers to actively engage with evolving literature, ensuring the provision of accurate and up-to-date advice. Effective shared decision-making is of paramount significance in instilling confidence and assuring the patient.

Keywords: Psychotropic medication; Pregnancy; Prescribing; Prescribing safely; Checklist

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1. Introduction

Many women who take psychotropic medication may find themselves pregnant during their treatment.[1] According to Morgan *et al.*, half of women diagnosed with a mental health condition requiring regular medication have previously given birth to children.[2]

Often, this medication has been prescribed after pregnancy rather than during, when it may have been appropriate. Frayne *et al.* discussed that pregnant women possess a "dual role as both persons with a diagnosed mental illness but also new mothers, with many options causing conflict."[3(p385)] This assessment accurately captures the dilemma that arises when deciding whether to continue with medication to treat the mother's illness or potentially cease or replace medication in the interests of their child.[3] Psychiatrists, general practitioners, and other mental health professionals encounter challenges characterized by competing interests, varied agendas, and occasionally conflicting or evolving medical safety data. This complexity renders the risk-to-benefit assessment of prescribing decisions a challenging undertaking.[1-3] The burden of the mother's mental illness and depressive cognitions can further complicate this issue.

Prescribing anti-depressants and anti-psychotics during pregnancy is scarcely covered by Australian Medical Curricula.[4] A recent submission from the Medical Student Council of Victoria highlighted that "the proportion of teaching on mental health and its management is disproportionately low given the burden of disease it poses in Australian society."[4 (p1)]

Psychiatrists who regularly prescribe medications for pregnant patients demonstrate proficiency in the process. However, professionals in related fields or within medicine, which intersect with mental health, may derive advantages from a more systematic approach to underscore critical areas of concern that should not be overlooked. The prescribing landscape during pregnancy encompasses as many risks as benefits, with numerous uncertainties to navigate. Nevertheless, practitioners should possess the requisite knowledge to feel confident in sustaining the prescription of most medications throughout pregnancy.[3]

2. The balancing act: To prescribe or deprescribe?

Prescribing psychotropic drugs to pregnant patients is a complex and delicate undertaking that requires meticulous consideration of potential risks and benefits. The paramount concern for most medical practitioners when prescribing for pregnant patients revolves around teratogenic or other harmful effects on the fetus. Neonatal withdrawal syndrome, exemplified by its occurrence with selective serotonin reuptake inhibitor use, is also a significant issue, as is the use of drugs that cross the placental barrier. Furthermore, some psychotropics are associated with an increased risk of low birth weight or premature birth.[2] However, these risks must be carefully balanced against the possibility of relapse or exacerbation of the maternal mental health condition should effective psychiatric medication be altered or ceased.[3] Such changes can pose their own set of risks to both maternal and fetal health, which may potentially be more severe than those associated with continuing treatment. Abrupt discontinuation of psychotropic medication can precipitate withdrawal symptoms and an undesirable rebound of psychiatric symptoms, both of which can have deleterious effects on the pregnancy. Therefore, the decision to continue or modify psychotropic medication during pregnancy requires a careful assessment of these risks against the benefits of maintaining maternal mental health stability.

3. The art of prescribing

In cases where the benefits of continued treatment with psychotropics outweigh the potential risks, a psychiatrist may opt to maintain medication, sometimes adjusting dosages, to ensure optimal health and well-being for both the mother and the developing fetus. Interestingly, the therapeutic guidelines note that their recommendations are based on evidence of low-to-moderate quality and that data on psychotropic safety is limited to observational studies with substantial confounding factors.[5] This complexity further convolutes the process for the prescriber. There is no treatment that is risk-neutral or universally applicable for a pregnant patient with a mental health condition.

Childbirth can trigger a relapse of bipolar disorder in 37% of women with the condition. This figure rises to 66% if the women are unmedicated and 23% if they are on prophylactic medication.[6] In a recent Australian survey of pregnant women, 25% of participants screened positive for depression, 19% for moderate or higher-range anxiety, and 15.5% for stress.[7] There is a significant mental health burden among pregnant women not only in Australia but globally. There is a paucity of recent comparison data between child-bearing and non-child-bearing women. Nevertheless, it is essential to have a framework in place to assist in safely prescribing for the child-bearing demographic.

Accordingly, a 10-point checklist (Table 1) has been constructed to outline considerations and key risks for the prescribing practitioner to assess when deciding whether to prescribe psychotropic agents during pregnancy. This checklist does not explore the risks associated with specific agents, which should be researched individually when commencing prescribing.

4. Practical considerations

It is imperative to maintain awareness that each case is inherently unique, and this guide does not serve as a substitute for the clinical judgment of the treating

Table 1. A 10-point checklist of key considerations when prescribing/deprescribing psychotropic medications before or during pregnancy

No.	Consideration/risk description
1	Pre-pregnancy counseling: Balancing risks and benefits The primary concern when prescribing psychotropic drugs during pregnancy is finding a balance between managing the mental health condition and minimizing potential harm to the fetus. Leaving a mental health condition untreated can also have serious consequences for both the mother and the developing fetus.[3] Unplanned pregnancies in women taking psychotropic medications are common, resulting in fetal exposure during the first trimester.[8] Pre-pregnancy counseling, involving shared decision decision-making with the patient about the risks and benefits of proposed continuation, termination, or amendment of a current medication regimen, is preferable to having this first discussion during pregnancy.[3]
2	Potential risks to the fetus: • Teratogenicity: Some psychotropic drugs have been associated with increased teratogenicity when taken during specific stages of pregnancy. These have varying levels of risk. For example, mood stabilizers such as valproate and lithium have well-known teratogenic risks (e.g., neural tube defects and cardiovascular malformations, respectively),[9] while antidepressants (e.g., SSRIs and TCAs associated with heart defects) are considered low risk.[10] It is essential to examine the specific drug's safety profile. Second-generation antipsychotics may increase the risk of gestational diabetes. Lithium is contraindicated in breastfeeding and poses a risk of congenital heart defects. However, lithium is the gold standard treatment for bipolar disorder, with demonstrated efficacy in the prophylaxis of postpartum relapse, and should be considered for women with severe bipolar disorder.[11] If lithium is used during pregnancy, fetal echocardiography, and ultrasonography are recommended.[11] • Neonatal withdrawal syndrome: Certain psychotropic drugs, particularly selective SSRIs, can lead to withdrawal symptoms in newborns if taken during late pregnancy, as well as opioids.[12] Fetal exposure, particularly in the last trimester, may result in respiratory, motor, central nervous system, and gastrointestinal symptoms in about 10%–30% of newborns (Poor Neonatal Adaptation Syndrome).[13] **N.B.: Not all teratogens or drug interactions have been discussed –each medication in question should be individually reviewed by the treating practitioner.*
3	Maternal well-being Untreated mental health conditions during pregnancy can have adverse effects on the mother's well-being and health, potentially leading to difficulties with bonding, prenatal care, self-care, and an inclination to engage in dangerous behavior. Activities of daily life, including employment, social obligations, caring for other children, and other daily responsibilities, need to be considered, along with the previous dosage history and success. As discussed by Ward *et al*., "The patient's diagnosis, severity of previous episodes, the necessity for medication, and responsiveness to medication are strong predictors of the need for medication to maintain remission."[14 (p635]])] The patient's past level of function when not taking medication must be explored.[14] A comprehensive history should, at a minimum, include: • Previous psychiatric hospitalization(s), which likely suggest severe previous dysfunction[14] • Suicidality • Self-destructive thoughts or behaviors • Assessment of the patient's ability to meet home, educational, and occupational responsibilities[11] If there have been previous pregnancies, the pattern of prior dysfunction and symptoms present is greatly useful.[14]
4	Consultation/collaboration Prescribing psychotropic drugs during pregnancy should ideally involve a collaborative approach with a team of healthcare providers, including obstetricians, psychiatrists, and mental health specialists.[3,15] According to Coffman *et al*. "The first, most important thing to do is to change nothing; that is, do not recommend to your patient that they immediately stop or taper off [their] psychotropic medication."[15(p380)] This decision needs to be made in consultation with a psychiatrist and the deprescription needs to follow normal safety protocols. A specialist perinatal psychiatrist can be particularly helpful in making informed decisions.[3,15] There should be a conversation (preferably face-to-face) with the patient discussing the risks of continuing the psychotropic medication versus tapering off. Maternal-fetal medicine services, a subspecialty of obstetrics that focuses on identified high-risk pregnancies, can provide pre-conception counseling for high-risk patients, counseling for fetal complications, first-trimester ultrasounds, and other tests that may be relevant.[15] It is worthwhile considering if a high-risk patient satisfies referral criteria for their local service.
5	Medication selection The choice of medication is crucial. Some psychotropic drugs may be considered safer during pregnancy or have fewer side effects than others. Healthcare providers should carefully evaluate the risks and benefits of each drug and consider non-pharmacological treatments when appropriate. Additional care and attention are required in the case of polypharmacy and whether to continue or amend the existing medication regimen.[5,14]
6	Dose adjustment Adjusting the dosage of psychotropic drugs may be necessary during pregnancy. Pregnant patients may metabolize medications differently, and dose adjustments may help minimize potential risks while maintaining therapeutic benefits. Pregnancy is a hypermetabolic state; accordingly, drug doses may need to increase to achieve the same result before pregnancy.[12]

(*Cont'd...*)

Table 1. (*Continued*)

No.	Consideration/risk description
7	Monitoring Pregnant patients taking psychotropic drugs should receive close monitoring throughout pregnancy, including regular assessments of the mother's mental health and fetal development. Routine ultrasound scans and blood tests should be performed (as is the case for every pregnancy – offered at [18-20] weeks in Australia); however, additional or more frequent consultations to assess the effectiveness of prescribed medications and their level of symptom control is recommended. If an infant is suspected of being exposed to a psychotropic antenatally, consider the need for observation in the initial postpartum period.[13]
8	Patient education and informed consent Pregnant patients must receive comprehensive information about the potential risks and benefits of taking psychotropic drugs during pregnancy. They should be active participants in the decision-making process and provide informed consent.[3] For consent to be valid, it must be voluntary, informed, specific, current, and given by a person with capacity. To be informed, all relevant information must be discussed with the patient.[16] As per the case of Rogers v. Whitaker, a doctor has a duty to warn a patient of any material risk involved in a proposed treatment.[17] This principle of informed consent would be applicable to both new prescriptions and deprescribing. The High Court of Australia has considered the following factors in deciding whether a risk is "material," thus requiring discussion with a patient: • The nature of the matter: If harm is more likely or serious, it requires disclosure; • The nature of the proposed procedure/treatment: complex interventions require more information; • The patient's desire for information: patients who ask more questions or make their desire for information known should be informed; • The temperament and health of the patient: Patients with existing health issues or relevant circumstances that make a risk more important for them (e.g., pregnancy) may require more information; • The general surrounding circumstances[16,18] Consent should be appropriately documented.[19] Decision aids/written materials can be utilized where appropriate.
9	Timing of medication initiation and discontinuation In some cases, it may be advisable to adjust the timing of medication initiation or discontinuation to minimize fetal exposure during critical developmental periods. For example, possible teratogenicity caused by benzodiazepines in the first trimester.[20]
10	Consideration of alternative treatments Non-pharmacological treatments, such as psychotherapy, neurostimulation, and lifestyle modifications, may be explored as potential alternatives or complements to medication.[11] Psychotherapy and counseling interventions, often used without prescription or referral, may prevent the progression of symptoms or clinical presentation altogether.

Note: The checklist has been formulated by consulting Frayne *et al*., Desai *et al*., Alsdorf and Wyszynski, Tuccori *et al*., Boyce and Buist, Wang and Cosci, Jefferies, Ward and Zamorski, Coffman and Ash.[3,8-20]
Abbreviations: SSRI: Selective serotonin reuptake inhibitors; TCA: Tricyclic antidepressants.

practitioner. This checklist has been developed as an aide-memoire to prompt consideration of the myriad and intricate aspects associated with prescribing. Decisions pertaining to the prescription of psychotropic drugs during pregnancy must be tailored to the individual, encompassing factors such as the patient's medical and psychiatric history, the severity of their condition(s), and the range of available treatment options, which may extend beyond medication use.[5,11,15]

It is vital for psychiatrists to maintain open and honest communication with their pregnant patients and involve them in a shared decision-making process to ensure the best possible outcome for both mother and baby.[3,15] Frayne *et al.* discussed that decision-making among pregnant women, including those with "anxiety and depression, is most strongly influenced by health practitioners, family, and the internet."[3(p384)] Accordingly, there may be many more factors and elements outside of the doctor–patient relationship influencing the decision that shall require careful evaluation by the treating practitioner.

5. Conclusion

The prescription of psychotropic drugs to pregnant women diagnosed with mental health conditions entails multifaceted challenges and considerations. Striking a critical balance is imperative, as it involves managing the mother's mental health while minimizing potential risks to the developing fetus. The decision-making process is intricate, shaped by factors such as the teratogenic potential of specific medications, the risk of neonatal withdrawal syndrome, and the potential for adverse health outcomes in both maternal and fetal contexts if psychiatric conditions are left untreated.[12,13,20] It also emphasizes the importance of a collaborative approach involving various health-care professionals, informed patient consent, and individualized treatment plans that may include medication adjustments and consideration of non-pharmacological treatments.[14,15] Pre-conception counseling plays a very helpful role if it is an available option. The benefits of referring to maternal-fetal medicine services where appropriate can also prove advantageous. This paper is

limited, as while it recognizes and recommends the role of psychotherapy and counseling, and includes this in the checklist, it does not formally evaluate these methods, which warrant their own extensive review. The patient's diagnosis, severity of previous episodes, necessity for medication, and responsiveness to medication are strong predictors of the need for medication during pregnancy.[14] Evolving pharmaceutical studies are being frequently released, so it is essential for prescribers to remain engaged with the evolving literature to provide accurate and up-to-date advice. As considered by Frayne *et al.*, "the clinician needs to provide comprehensible and concise information, giving space for a woman's voice to be heard to guide them from a position of hesitancy to one of assurance."[3(p385)] Incorporating effective shared decision-making will assist in providing that assurance to the patient.

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This article does not constitute or replace legal advice and/or clinical judgment. If in doubt, please contact your medical indemnity insurer or legal representative.

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ACCSCIENCE PUBLISHING

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PERSPECTIVE ARTICLE

Categorization challenges in research on organ donation after euthanasia: Determining somatic or psychiatric origins of suffering

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Abstract

This perspective article discusses the classification challenges encountered in organ donation after euthanasia (ODE) among individuals with psychiatric disorders, as highlighted in our recent case series. In cases involving "somatic symptoms and related disorders," somatic symptoms are connected to excessive thoughts, feelings, and behaviors, causing distress or dysfunction. Conditions such as tinnitus and chronic pain often co-occur with psychiatric disorders. The recent Dutch guideline on ODE eliminated the requirement to distinguish between somatic and psychiatric causes of suffering. This updated guideline encourages a holistic approach to patient care, emphasizing the importance of addressing patients' overall suffering rather than specific categorizations. To avoid errors in classification, categorization in research on ODE should recognize the overlap between somatic and psychiatric diagnoses, thereby eliminating the risk of misclassification, avoiding the stigmatization of patients, and optimizing future treatment options.

Keywords: Euthanasia; Organ donation; Psychiatric disorder; Suffering; Organ donation euthanasia; Classification; Pain syndrome; Tinnitus

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1. Introduction

Physician-assisted dying, legally permitted in countries such as Belgium, the Netherlands, Luxembourg, Colombia, Canada, Australia, Spain, and New Zealand, allows patients to choose a peaceful death. In Belgium, the Netherlands, Canada, and Spain, patients can also donate their organs following euthanasia (ODE), particularly

those with neurodegenerative or psychiatric diseases. The combined procedure, guided by national ODE protocols, enables the donation of organs such as kidneys, lungs, and hearts. Annually, the incidence of ODE increases, with cases based on psychiatric suffering accounting for up to 50% of all ODE cases, reflecting its growing acceptance and implementation.

The case series conducted by van Dijk *et al.*[1] marked the first scientific insight into organ donation after euthanasia (ODE) among psychiatric patients. In this case series covering the first 10 years of ODE in psychiatric patients, it was revealed that some patients presented with both psychiatric and somatic disorders. Somatoform complaints were not primarily documented as a psychiatric disease, leading to a debate over whether some patients' suffering should be classified as psychiatric or somatic. Unfortunately, detailed specifics about the psychiatric disorders, treatment attempts, and the duration of both disorders and treatments were partly unavailable to the researchers. In addition, some details were deliberately withheld to protect the privacy of individual patients, curtailing the granularity of the information. While classifying ODE patients based on their conditions using the available information was generally straightforward, certain diseases posed challenges in categorization. While amyotrophic lateral sclerosis and myasthenia gravis distinctly fall under somatic conditions, disorders like depression, post-traumatic stress disorder, and personality disorders are unquestionably psychiatric. However, the classification of tinnitus or chronic pain syndrome, which may manifest alone or alongside other conditions, is less straightforward. This perspective article delves deeper into the classification challenges of these disorders in our ODE studies, exploring alternative perspectives and discussing their clinical and research implications. We aim to provide a more detailed description and exploration of a preliminary practical experience from previous research.

2. Different perspectives

At least two different perspectives on the relationship between tinnitus, chronic pain syndrome, and psychiatric disorders are evident. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5TR), the mentioned conditions fall under "somatic symptoms and related disorders."[2] Such a somatic symptom disorder (SSD) is characterized by one or more somatic symptoms, such as pain or phantom noise, accompanied by excessive thoughts, feelings, and/or behaviors causing significant distress and/or dysfunction, independent of any underlying medical condition. The second perspective suggests that pain or perception of sounds may be symptoms of an underlying psychiatric disorder such as post-traumatic stress disorder, obsessive-compulsive disorder, or psychosis.[3,4]

Tinnitus is defined as "the phantom perception of sound without the corresponding acoustic or mechanical correlates in the cochlea." It can be attributable to hearing loss, somatosensory system dysfunction, or auditory cortex dysfunction. Among these, hearing loss is the most common cause, scarcely accompanied by underlying severe pathologies[5]. Therefore, tinnitus is primarily viewed as a prevalent ontological disorder. In 2023, Hackenberg *et al.*[6] revealed a prevalence of 26.1% among the German adult population, consistent with diverse prevalence rates reported in the literature: 9 – 29% in Europe and 4 – 37% globally.

However, tinnitus commonly co-occurs with psychiatric comorbidities, particularly anxiety and depression.[7] The systematic review by Salazar *et al.*[8] included 28 studies that reported a mean depression prevalence of 33% (range 6 – 84%), consistent with findings by Meijers *et al.*,[9] who reported rates between 4.6 and 41.7%. The wide range of reported prevalence of depressive symptom scores is attributed to variations in questionnaires, definitions, and cut-off values used to measure and define depressive symptoms.[9] A 45% lifetime prevalence of anxiety disorders is reported among individuals with tinnitus. In addition, significant overlap is suggested in the associated (sub) cortical brain areas and cortico-subcortical networks involved in attention, distress, and memory functions.[10] Genome-wide association studies have demonstrated the polygenic nature of tinnitus susceptibility. Bhatt *et al.*[11] revealed common genetic links between tinnitus and neuropsychiatric disorders, with gene sets related to anxiety and stress being significantly associated with tinnitus-related distress. Psychological treatments, such as cognitive behavioral therapy and eye movement desensitization and reprocessing, are effective for tinnitus patients, regardless of the disorder's classification.[12,13]

Comparably, chronic pain disorder involves persistent and severe pain consuming the individual's attention, leading to significant distress or impairment. Conventionally, pain in the absence of an apparent anatomical or neurophysiological cause was labeled as psychopathological.[14] However; Katz *et al.*[14] described several unusual, clinically atypical, and previously unexplained physical phenomena for which pathophysiological explanations have been found more recently. Despite the absence of a uniform definition, chronic pain affects one in five adults in Canada.[14] Chronic pain may have a complex interplay with psychological factors and/or symptoms. The neural mechanisms underlying chronic pain are complex and

involve multiple brain regions. Chronic pain has been associated with altered activity and connectivity in limbic and cortical structures. These neural changes can lead to the amplification and persistence of pain perception, as well as the development of comorbid psychological symptoms such as anxiety and depression.[15-17]

The experience of chronic pain can lead to psychological distress, feeling helpless, anxious, and depressed, and such conditions can, in turn, worsen the perception and impression of pain. Comparable to tinnitus, chronic pain is thus highly linked to the occurrence of anxiety and depression.[14] Consequently, chronic pain management often requires a multidisciplinary approach involving health-care professionals from both physical and mental health disciplines.

In summary, physical health and mental health are intrinsically interconnected. Physical illnesses can elevate the risk of developing mental disorders, and conversely, mental disorders can increase the susceptibility to physical illness. To gain a deeper understanding of these relationships, it is essential to integrate diverse perspectives on the same matter.[15] Therefore, irrespective of whether a somatic or psychiatric perspective is applied to conditions such as tinnitus and chronic pain disorder, recognizing and addressing the associated somatic or psychiatric comorbidities and the resultant burden of disease for the patient is more pertinent than the mere categorization of the disease as either somatic or psychiatric in origin.

3. Misclassification potential

The recent DSM classification system has been critiqued for its criteria regarding SSDs. The DSM-5 may contribute to misdiagnosis, misclassification, and unnecessary stigma when applied to patients with tinnitus and chronic pain. Several authors have consequently proposed modified diagnostic criteria to reduce the likelihood of misclassification of a purely physical disorder for a psychiatric disorder.[18] At present, an increasing subset of the primary care population with medically unexplained symptoms is at risk of receiving the diagnosis of SSD, potentially associated with the misconceived bias that "physical disorders are considered genuine," while patients with SSD are "inappropriately accused of manufacturing their symptoms."[19]

Potentially, tinnitus and chronic pain may be incorrectly labeled as psychopathological. We made a deliberate effort to avoid misclassification in our previous study. In our first article on ODE,[1] where we compared patients suffering from an underlying somatic disorder with those suffering from an underlying psychiatric disorder, patients with tinnitus and chronic pain syndrome were categorized as suffering from somatic disorders. Only those patients formally diagnosed with a psychiatric disorder such as depression, in addition to tinnitus and chronic pain syndrome, were categorized as suffering from a psychiatric disorder. This distinction enabled us to detect incidence patterns between patient groups in our studies. We have not attempted to divide or distinguish the severity of their suffering. Consequently, the prior distinction between patients suffering from somatic and psychiatric disorders was relinquished in the Dutch guideline for ODE in January 2023.[20] To enable data comparison with other studies on ODE across different patient subgroups, future research should clearly acknowledge the rationale behind any categorization method used. A suggestion for categorization in future studies is to add an additional group alongside the psychiatric and somatic disorders, a group that highlights the overlap between these two categories of disorders.

4. Conclusion

Since 2012, over 130 ODE cases have been performed in the Netherlands. The classification of various medical conditions into distinct categories of somatic diseases and psychiatric disorders continues to pose significant challenges. Extensive evidence underscores the frequent co-occurrence of psychiatric symptoms alongside somatic illnesses. Given the scientific evidence and the updated Dutch guideline for ODE, the rigid categorization of these conditions has become less critical. As of January 2023, the updated ODE guideline applied universally to all patients, regardless of the nature of their underlying suffering, potentially enhancing patient care and research outcomes.

Future studies in this prospect should acknowledge the recent ODE guideline update, emphasizing that after confirming the patient's mental competence in their decision to undergo euthanasia, the focus should be on the patient's suffering rather than its categorization and classification as either somatic or psychiatric. Scientifically unraveling the psychological factors contributing to the patient's decision regarding ODE, considering their perspective and regardless of their underlying condition, is a promising direction for future research.

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ORIGINAL RESEARCH ARTICLE

Factors associated with depressive and anxiety symptoms among anophthalmic patients wearing ocular prostheses

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Abstract

This study aimed to investigate the prevalence of anxiety and depression among individuals with ocular prostheses and to identify factors associated with these psychological symptoms. A sample of patients who underwent monocular enucleation and socket implantation participated in the study, responding to digital questionnaires covering demographics, psychosocial factors, and aspects related to their ocular prostheses. Depressive and anxiety symptoms were evaluated using Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7), respectively. Optimal scale regression analysis was employed to explore factors linked to psychological symptoms in ocular prosthesis users. Results from 100 valid participants revealed a 51% prevalence of depressive symptoms and a 45% prevalence of anxiety symptoms. The mean PHQ-9 score was 4.91 ± 1.98, and the mean GAD-7 score was 4.99 ± 2.15. Factors such as undergoing right eye enucleation, longer duration of ocular prosthesis use, comfort with prosthesis wearing, and greater satisfaction correlated with milder depressive symptoms. In terms of anxiety, those who used ocular prostheses due to trauma or tumors were affected by more severe symptoms, while individuals who were comfortable with their prosthesis or using alumina-based prostheses reported fewer anxiety symptoms. In conclusion, ocular prosthesis users wrestle with significant challenges of depressive and anxiety symptoms. Factors including age, household registration, economic status, enucleation side, cause of anophthalmos, prosthetic material, and satisfaction and duration of prosthesis use were associated with depressive or anxiety symptoms. Long-term comprehensive care targeting these vulnerable individuals is imperative to alleviate depression and anxiety.

Keywords: Anophthalmos; Ocular prosthetics; Depressive symptoms; Anxiety symptoms

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1. Introduction

The eye and periocular area play a crucial role in interpersonal communication.[1] Ocular trauma, intraocular tumors, painful blindness, eyeball atrophy, or microphthalmia

may necessitate eyeball removal, which results in not only physical impairment but also substantial psychological distress.[2,3]

The loss of an eye leads to functional defects, facial deformities, and even significant psychological consequences.[1,4-7] Compared to individuals who have normal vision, those experiencing blindness often exhibit symptoms of anxiety and depression such as mental exhaustion, hypoactivity, and social withdrawal, especially in the first few months after their blindness. Appearance issues, temporary hallucinations, or ocular secretions may be the main reasons. Some other studies suggest that using ocular prosthesis may alleviate the psychological symptoms in blind patients.[7-9] However, the levels of depression and anxiety in these patients with ocular prosthesis still remain high, possibly due to a combination of factors including financial burden, prosthetic materials, and the time of ocular prosthesis use.[10,11]

At present, although several studies have examined depression and anxiety in patients with ocular prosthesis, most of these studies were of small sample size and only investigated a small number of influencing factors, which made their findings limited in scope and inconvincible. Hence, a more comprehensive and standardized study of the psychological symptoms and their related factors in these patients is warranted. This study was conducted aiming at thoroughly investigating the depression and anxiety symptoms and the associated factors among patients wearing ocular prosthesis.

2. Methods

2.1. Participants and procedure

This study was conducted from June 2022 to September 2022 on a network-based platform among patients with monocular enucleation eye socket implantation. Structured questionnaires were utilized in this survey, which was conducted on the Haodaifu Bulletin Board System (BBS) (https://bbs.haodaifu.com/). Haodaifu BBS, founded in 2006, is one of the Chinese leading Internet medical platforms that provide medical consultation, prescription, and follow-up services. As of October 2022, Haodaifu BBS has served more than 74 million patients.

In the present study, questionnaires were distributed and collected by doctors on the platform. The questionnaires included demographic, psychosocial, and ocular prosthesis-related factors. All participants were requested to give informed consent at the beginning of the survey. For the patients under 18, the informed consent from their guardians was obtained. In this study, patients who are as follows: (i) Haodaifu BBS users, (ii) recipients of monocular enucleation eye socket implant, (iii) able to read questionnaire written in Chinese, and (iv) volunteers for this survey, were included in the study. Exclusion criteria included: (i) individuals who are illiterate or semi-literate that cannot complete the survey independently, (ii) individuals who suffer from serious physical and mental illness, and (iii) individuals with erroneous or missing data. The study was approved by the Ethics Committee of Nanfang Hospital, Southern Medical University, and the study was conducted in accordance to the Declaration of Helsinki.

2.2. Instruments

Demographic, psychosocial, and ocular prosthesis-related data were collected in the survey using structured questionnaire. The demographic data included gender, age, household registration, education level, marital status, and economic status. Factors associated with ocular prosthesis included prosthetic material, time of wearing ocular prosthesis, cause of anophthalmos, and the satisfaction of ocular prosthesis wearing. The Patient Health Questionnaire-9 (PHQ-9) and the Generalized Anxiety Disorder-7 (GAD-7) were used to measure psychological symptoms.[12-15]

The PHQ-9 was conducted to assess depressive symptoms. The total scores were categorized into five severity levels: normal (0–4), mild depression (5–9), moderate depression (10–14), moderate to severe depression (15–19), and severe depression (20–27). Higher score indicated more severe depressive symptoms. The reliability and validity of the Chinese version of the PHQ-9 have been verified in a previous research.[16]

To assess patients' anxiety level, the GAD-7 was adopted. GAD-7 is a four-point Likert scale, in which higher scores indicate more severe anxiety symptoms. The total scores were categorized into five severity levels: normal (0–4), mild anxiety (5–9), moderate anxiety (10–13), moderate to severe anxiety (14–18), and severe anxiety (19–21). The reliability and effectiveness of the Chinese version of the GAD-7 have been validated to be high.[17]

2.3. Statistical analysis

In univariate analysis, Mann–Whitney *U*-test and Kruskal–Wallis univariate analysis were used to unravel factors that are able to distinguish patients with different levels of psychological symptoms. The factors that were significant in the univariate analysis were fed into further analysis. The optimal scale regression model was performed to analyze the association among psychological symptoms, demographic factors, and ocular prosthesis-related factors. All analyses were two-tailed with an alpha level set at

$P < 0.05$ and were performed using SPSS analytics software v.22.0.

3. Results

3.1. Demographic and ocular prosthesis-related characteristics

We obtained data from 100 participants, of which none were excluded before data analysis. The mean age of the participants was 32.3, with males constituting more than half of the sample. All demographic characteristics are presented in Table 1.

Regarding the characteristics related to participants' ocular prostheses, the majority of the participants underwent enucleation due to trauma. Hydroxyapatite was the most common chosen ocular prosthesis material. More than half of the participants (63%) reported to feel general comfort with wearing their ocular prosthesis. All ocular prosthesis-related characteristics are also shown in Table 1.

3.2. Depression and anxiety status of patients with ocular prosthesis

Based on the cutoff score of the PHQ-9, 49 (49%) participants exhibited no depressive symptoms, while 51 (51%) were found to have mild to moderate depressive symptoms. The mean PHQ-9 score was 4.91 ± 1.98. Furthermore, 45 (45%) participants displayed no anxiety symptoms, while the others exhibited mild to moderate anxiety symptoms. The mean score for GAD-7 was 4.99 ± 2.15 (Figures 1 and 2).

3.3. Results of univariate analysis

The univariate analysis revealed significant differences in the PHQ-9 and GAD-7 scores across variables such as age, household registration, marital status, economic status, material of ocular prosthesis, and the time of and the comfort of ocular prosthesis wearing. In addition, PHQ-9 scores differed significantly based on education level (Table 1).

3.4. Results of multivariate analysis

The results of multivariate analysis using the optimal scale regression model are presented in Tables 2 and 3. The adjusted R^2 for the optimal scale regression analysis of PHQ-9 was 0.721, and the adjusted R^2 for the optimal scale regression of GAD-7 was 0.704. The results indicated that depressive symptoms were negatively correlated with economic status, while anxiety symptoms were negatively related to age.

In regard of ocular prosthesis-related factors, participants who wore the prosthesis for longer time would have less severe depressive symptoms. In addition, feeling comfortable when wearing ocular prosthesis was found to be negatively associated with the severity of depressive symptoms. Participants who had undergone enucleation of the right eyes were found to experience more severe depressive symptoms compared to those who had their left eyes enucleated. Participants who had higher satisfaction with their ocular prosthesis would experience milder depressive symptoms.

Concerning anxiety symptoms, participants who wore ocular prostheses due to trauma or tumor exhibited more severe anxiety symptoms compared to those due to congenital conditions or other causes. Participants who wore ocular prostheses made of alumina experienced the least anxiety symptoms. In addition, the comfort of wearing ocular prosthesis was negatively associated with anxiety symptoms.

3.5. Results of mediating effects analysis

According to the correlation analysis, bias-corrected percentile bootstrap was used to test the mediating effect of satisfaction of wearing ocular prosthesis between ocular prosthesis material and depressive and anxiety symptoms. The results showed that 95% confidence intervals were −0.03, 0.20 and −0.02, 0.19, indicating that there is no mediating effect of satisfaction between prosthetic eye materials and depressive or anxiety symptoms.

The mediating effect of satisfaction of ocular prosthesis wearing was also analyzed between the time of wearing prosthetic eye and the depressive and anxiety symptoms. The results are shown in Tables 4 and 5. Direct effect was found between the time of prosthetic eye wearing and depressive symptoms ($t = -3.356$, $P < 0.01$), but not between the time of prosthetic eye wearing and anxiety symptoms ($t = -1.672$, $P = 0.098$). When other variables were adjusted, there was also neither direct effect between the time of prosthetic eye wearing and depressive symptoms ($t = -1.743$, $P = 0.085$). However, the time of prosthetic eye wearing could predict satisfaction of wearing ($t = 3.309$, $P < 0.01$), while satisfaction of wearing could also predict depressive symptoms ($t = -6.055$, $P < 0.001$) and anxiety symptoms ($t = -5.561$, $P < 0.001$). Therefore, indirect effect was found between the time of prosthetic eye wearing and depressive and anxiety symptoms through the satisfaction of prosthetic eye wearing, which meant satisfaction of prosthetic eye wearing was a complete mediator. The indirect effect size of path 1 (time of prosthetic eye wearing → satisfaction of wearing → depressive symptoms severity) was −0.223 −0.37, −0.09. The indirect effect size of path 2 (time of prosthetic eye wearing → satisfaction of wearing → anxiety symptom severity) was −0.244 −0.42, −0.09.

Table 1. Demographic and ocular prosthesis-related characteristics of the total sample (*N*=100)

	Total (*N*=100)	PHQ-9 score (mean±SD)	*P*	GAD-7 score (mean±SD)	*P*
Gender		4.910±1.975	0.082	4.990±2.153	0.144
Male	52 (52%)	4.596±1.912		4.673±2.194	
Female	48 (48%)	5.250±2.005		5.333±2.077	
Age (years)			<0.001		<0.001
16–25	25 (25%)	6.280±1.838		6.640±2.018	
26–55	71 (71%)	4.451±1.811		4.479±1.911	
>55	4 (4%)	4.500±2.082		3.750±2.062	
Geographical area of residence			<0.001		0.003
Rural	64 (64%)	5.422±1.991		5.516±2.175	
Urban	36 (36%)	4.000±1.604		4.056±1.788	
Education status			0.027		0.066
Junior or below	55 (55%)	5.327±2.152		5.473±2.356	
Senior	28 (28%)	4.750±1.713		4.607±1.853	
University or above	17 (17%)	3.828±1.286		4.059±1.478	
Marital status			0.001		<0.001
Married	59 (59%)	5.683±1.968		5.927±2.149	
Non-married	41 (41%)	4.373±1.809		4.339±1.917	
Economic status			<0.001		<0.001
Low	24 (24%)	7.083±1.840		6.833±2.120	
Middle	65 (65%)	4.431±1.403		4.677±1.706	
Upper middle	4 (4%)	3.500±1.291		3.500±2.381	
High	7 (7%)	2.714±1.113		2.429±1.272	
Enucleated eye			0.622		0.831
Left	45 (45%)	4.800±2.085		5.067±2.260	
Right	55 (55%)	5.000±1.895		4.927±2.080	
Cause of anophthalmos			0.933		0.923
Congenital malformation	11 (11%)	5.032±2.185		4.968±2.321	
Trauma	63 (63%)	4.727±1.737		5.182±2.359	
Tumor	11 (11%)	4.545±1.508		5.182±1.722	
Others	15 (15%)	4.800±1.568		4.800±1.656	
Materials of prosthetic eyes			0.001		0.001
Hydroxyapatite	64 (64%)	4.844±2.057		4.922±2.263	
Medpor	10 (10%)	3.400±0.966		3.500±1.269	
Alumina	2 (2%)	3.500±0.707		2.500±0.707	
Autologous issue	5 (5%)	5.000±1.871		5.000±1.581	
None	19 (19%)	6.053±1.580		6.263±1.593	
Time of wearing prosthetic eyes			<0.001		<0.001
<6 months	29 (29%)	6.724±1.486		6.724±1.980	
6 months–1 year	6 (6%)	4.333±1.366		4.167±0.753	
1–2 years	31 (31%)	4.677±1.904		4.742±2.033	
2–5 years	22 (22%)	3.545±1.371		3.955±1.759	
>5 years	12 (12%)	3.917±1.165		3.750±1.422	

(Cont'd...)

Table 1. (*Continued*)

	Total (*N*=100)	PHQ-9 score (mean±SD)	*P*	GAD-7 score (mean±SD)	*P*
Satisfaction of wearing prosthetic eyes			<0.001		<0.001
Uncomfortable	11 (11%)	8.455±1.214		8.273±1.737	
General comfortable	63 (63%)	5.079±1.371		5.286±1.570	
Very comfortable	26 (26%)	3.000±0.894		2.885±1.211	

Abbreviations: PHQ-9: Patient Health Questionnaire-9; GAD-7: Generalized Anxiety Disorder-7.

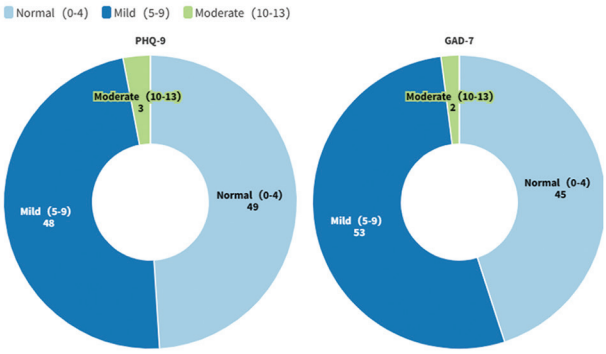

Figure 1. Composition of patients with varying degrees of depression and anxiety

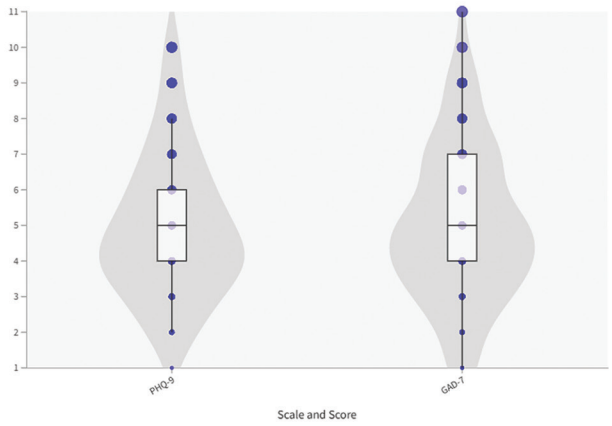

Figure 2. Violin charts of Generalized Anxiety Disorder-7 and Patient Health Questionnaire-9 scale score distribution

4. Discussion

Owning good-looking or even functional eyes are perceived as contributing hugely to one's interpersonal communication and esthetics. Consequently, the psychological implications of globe enucleation can be substantial and far-reaching in patients' lives. The previous studies have demonstrated that patients with globe enucleation suffered from increased psychological symptoms.[7] Although some studies suggested that wearing ocular prosthesis can mitigate depression and anxiety by improving patients' satisfaction, our study reveals that the prevalence of depressive and anxiety symptoms remains high among patients with ocular prostheses, which was 55% and 51%, respectively. This finding may indicate that the mental health concerns among globe enucleation patients tended to persist even after they wore ocular prostheses. Interesting, the total scores of PHQ-9 and GAD-7 were at low ranges in our study. This may imply that many patients with ocular prostheses would suffer from depressive and anxiety symptoms, which are subtler than depressive or anxiety disorders. Lighter interventions, such as psychotherapy or low dose of antidepressants, may be sufficient to treat these depressive and anxiety symptoms.

The issues surrounding the ocular prosthesis itself, or its use, are cited as a potential cause of the high prevalence of depressive and anxiety symptoms. Factors such as the type of ocular prosthesis material, the time of wearing ocular prosthesis, and the satisfaction with the ocular prosthesis were all found to be associated with psychological distress. These elements could generate unpleasant experiences when wearing ocular prostheses. Another possible reason may be about social interaction, body image, and self-esteem issues. In social contexts, patients with artificial eyes may be discriminated against, ultimately subjected to the negative impacts on their self-image and self-esteem.[1]

Participants residing in rural areas were found to experience more severe depressive symptoms than those living in urban areas. In comparison to urban areas, rural areas tend to have less comprehensive medical care services, which could lead to more complications with ocular prosthesis wearing.[18] Geographical area of residence has a great influence on one's income status, which is a crucial factor determining the quality of eye care products used. This can be exemplified by the struggles of patients from rural areas with affording high-quality prosthetic implants, or even just the basic cleaning and soothing drugs. Using low-quality products may raise the possibility of eye secretions, bacterial infections and other ocular health issues, which may lastly induce psychological distress.

The present study also found that patients with right-eye blindness were more likely to experience anxiety symptoms. Previous research showed that the majority

Table 2. Optimal scale regression statistical analysis results of PHQ-9 scale

	β	Quantification	F	*P*
Gender	0.078		1.860	0.177
Male		−0.961		
Female		1.041		
Age (years)	−0.107		1.694	0.191
16–25		−1.435		
26–55		0.325		
>55		3.203		
Geographical area of residence	0.122		2.600	0.111
Rural		0.750		
Urban		−1.333		
Education status	−0.050		0.245	0.622
Junior high or below		−0.905		
Senior high school		1.106		
University or above		1.106		
Marital status	0.083		1.831	0.180
Married		1.200		
Non-married		−0.834		
Economic status	−0.169		3.114	0.031
Low		−1.700		
Middle		0.425		
Upper middle		0.496		
High		1.602		
Enucleated eye	0.131		4.093	0.046
Left		−1.106		
Right		0.905		
Cause of anophthalmos	0.059		1.194	0.318
Congenital malformation		−0.630		
Trauma		2.313		
Tumor		−0.110		
Others		1.032		
Materials of prosthetic eyes	0.072		2.422	0.055
Hydroxyapatite		0.427		
Medpor		−1.872		
Alumina		−3.261		
Autologous issue		−2.333		
None		0.502		
Time of wearing prosthetic eyes	−2.16		3.802	0.027
<6 m		−1.556		
6 months–1 year		0.517		
1–2 years		0.517		
2–5 years		0.765		
>5 years		0.765		
Satisfaction of wearing prosthetic eyes	−0.504		26.375	0.001
Uncomfortable		−2.550		
General comfortable		0.014		
Very comfortable		1.046		

(Cont'd...)

Table 2. (*Continued*)

of the population in China is right-eye dominant.[19] The dominant eye plays a more crucial role in daily life, making the blindness in the right eye the cause of more physical and psychological challenges.

As expected, we found that the time of wearing ocular prosthesis was a significant factor positively associated with depressive symptoms. On the contrary, age was negatively correlated with anxiety symptoms. In the first 6 months of initial ocular prosthesis wearing, patients often experience severe depression due to adaptation challenges. Over time, however, patients' negative emotions typically decrease, while acceptability and happiness increase.[20] Furthermore, as patients grow older or wear ocular prosthesis for a longer time, their knowledge and skills in dealing with physical and psychological problems related to wearing ocular prostheses tend to increase.[20,21]

As for the reasons of ocular prosthesis wearing, patients who used ocular prostheses due to trauma or other causes exhibited more severe anxiety symptoms than those due to tumors or congenital malformations. Trauma patients may not only have ocular impairment but could also suffer from other physical disabilities at the same time. These comorbid conditions could aggravate their depression as they need to spend more money and time on treatment. Such disabled conditions may also reduce their quality of life and generate psychological problems.[22,23]

Interestingly, we found that patients wearing ocular prostheses made of alumina experienced milder anxiety and depressive symptoms. In contrast, patients not wearing prosthetic eyes reported the most severe anxiety symptoms. The same result comes from a previous research by Song *et al.*,[7] which identified that higher satisfaction was observed in patients with implants than those without. Compared to other materials, alumina offers the benefits of smoother surface, lower cost, and a lower tendency to extrude.[24] Thus, patients may consider ocular prostheses made of alumina more acceptable and preferable to use.

Another finding was that patients' satisfaction with wearing ocular prostheses was significantly negatively

Table 3. Optimal scale regression statistical analysis results of GAD-7 scale

	B	Quantification	F	*P*
Gender	0.079		1.790	0.185
Male		−0.961		
Female		1.041		
Age (years)	−0.311		8.619	0.001
16–25		−1.565		
26–55		0.404		
		0.423		
		0.423		
		2.448		
		2.448		
>55		2.607		
Geographical area of residence	0.107		1.742	0.191
Rural		0.750		
Urban		−1.333		
Education status	-0.162		1.957	0.166
Junior high or below		−0.905		
Senior high school		1.106		
University or above		1.106		
Marital status	0.056		0.608	0.438
Married		1.200		
Non-married		−0.834		
Economic status	−0.099		0.784	0.460
Low		−0.860		
Middle		−0.048		
Upper middle		−0.048		
High		3.424		
Enucleated eye	0.023		0.218	0.642
Left		−1.106		
Right		0.905		
Cause of anophthalmos	0.128		3.740	0.014
Congenital malformation		−0.222		
Trauma		2.699		
Tumor		0.015		
Others		−1.056		
Materials of prosthetic eyes	0.124		4.963	0.001
Hydroxyapatite		−0.132		
Medpor		−0.634		
Alumina		−3.965		
Autologous issue		−1.630		
None		1.624		
Time of wearing prosthetic eyes	0.080		0.221	0.640
<6 months		−0.369		
6 months–1 year		−0.369		
1–2 years		−0.369		
2–5 years		−0.369		
>5 years		2.708		
Satisfaction of wearing prosthetic eyes	−0.540		26.083	0.001
Uncomfortable		−2.119		
General comfortable		−0.192		
Very comfortable		1.363		

correlated with depressive and anxiety symptoms. Patients' satisfaction is associated with both the ocular prosthesis itself and the individuals' usage experiences. Adverse reactions, such as eye secretions and inflammation, can significantly affect the comfort of wearing prostheses and lead to depressive and anxiety problems. Moreover, the feelings of discomfort and perceived discrimination during social interactions may also influence patient satisfaction and psychological well-being.[7,25]

In summary, depressive and anxiety symptoms are still prevalent among patients with ocular prostheses. Understanding the associated factors, particularly those associated with ocular prosthesis wearing, can help us identify high-risk patients. Long-term comprehensive care is essential for the successful social and psychological rehabilitation of these patients to mitigate their depression and anxiety.

Several strengths of this study should be acknowledged. First, to the best of our knowledge, this is the first study that systematically investigates the impact of ocular prosthesis-related factors, including the cause of wearing and the materials used to make the prostheses, on depressive and anxiety symptoms. In addition, on top of the optimal scale regression model, standardized psychological measurement was conducted, yielding results that are more objective and compelling compared to previous studies.

This study is not without limitations. First, some factors, such as the appearance of the ocular prosthesis, were not investigated in this study. These factors should be taken into consideration in future research. Second, all participants recruited in this study were the users of the Haodaifu platform. Therefore, the generalizability of this study's findings is limited and less convincing. Third, psychological symptoms were evaluated using a self-rated scale, which may lead to self-report bias. Fourth, the PHQ-9 and GAD-7 could only measure the general depressive and anxiety symptoms rather than the exact symptoms caused by ocular prosthesis wearing, which may

Table 4. Mediating effect of satisfaction between the time of wearing prosthetic eyes and the degree of depression symptoms

	R	R^2	F	*P*	β	t	*P*
PHQ-9 (total effect)							
Time	0.771	0.5945	13.048	<0.001	−0.292	−3.356	<0.01
Sex					0.077	1.027	0.307
Address					−0.156	−1.876	0.063
Education					−0.117	−1.391	0.177
Age					−0.094	−0.996	0.322
Income					−0.328	−3.926	<0.001
Marriage					−0.211	−2.337	0.021
Eye					0.041	0.583	0.561
Reason					−0.073	−1.035	0.303
Material					−0.087	1.190	0.237
Satisfaction							
Time	0.725	0.526	9.855	<0.001	0.311	3.309	<0.01
Sex					−0.035	−0.426	0.671
Address					0.026	0.292	0.771
Education					0.035	0.377	0.707
Age					−0.109	−0.107	0.288
Income					0.413	4.572	<0.001
Marriage					0.259	2.653	<0.01
Eye					0.071	0.926	0.357
Reason					0.059	0.766	0.446
Material					−0.137	−1.721	0.089
PHQ-9 (direct effect)							
Time	0.845	0.714	19.949	<0.001	−0.136	−1.743	0.085
Satisfaction					−0.501	−6.055	<0.001
Sex					0.060	0.094	0.349
Address					−0.142	−2.032	0.045
Education					−0.991	−1.369	0.175
Age					−0.149	−1.852	0.067
Income					−0.121	−1.541	0.127
Marriage					−0.081	−1.024	0.309
Eye					0.077	1.279	0.205
Reason					−0.044	−0.731	0.467
Material					0.019	0.299	0.766

Abbreviations: PHQ-9: Patient Health Questionnaire-9; GAD-7: Generalized Anxiety Disorder-7.

also leading to some biases. Finally, the response rate of the survey conducted in this study is unknown due to the convenient sampling method utilized, thereby limiting the representativeness of the obtained results.

Table 5. Mediating effect of satisfaction between the time of wearing prosthetic eyes and the degree of anxiety symptoms

	R	R^2	F	*P*	β	t	*P*
GAD-7 (total effect)							
Time	0.732	0.536	10.295	<0.001	−0.155	−1.672	0.098
Sex					0.081	1.011	0.315
Address					−0.138	−1.563	0.122
Education					−0.146	−1.600	0.114
Age					−0.222	−2.197	<0.05
Income					−0.304	−3.403	<0.01
Marriage					−0.212	−2.202	<0.05
Eye					0.035	−0.458	0.648
Reason					−0.047	−0.619	0.538
Material					0.111	1.418	0.160
Satisfaction							
Time	0.725	0.526	9.855	<0.001	0.311	3.309	<0.01
Sex					−0.035	−0.426	0.671
Address					0.026	0.292	0.771
Education					0.035	0.377	0.707
Age					−0.109	−0.107	0.288
Income					0.413	4.572	<0.001
Marriage					0.259	2.653	<0.01
Eye					0.071	0.926	0.357
Reason					0.059	0.766	0.446
Material					−0.137	−1.721	0.089
GAD-7 (direct effect)							
Time	0.811	0.657	15.317	<0.001	0.001	0.016	0.987
Satisfaction					−0.504	−5.561	<0.001
Sex					0.064	0.916	0.362
Address					−0.125	−1.634	0.106
Education					−0.129	−1.624	0.108
Age					−0.277	−3.150	<0.01
Income					−0.096	−1.114	0.268
Marriage					−0.082	−0.945	0.347
Eye					0.001	0.017	0.987
Reason					−0.017	−0.263	0.793
Material					0.042	0.615	0.540

Abbreviations: PHQ-9: Patient Health Questionnaire-9; GAD-7: Generalized Anxiety Disorder-7.

5. Conclusion

Depressive and anxiety symptoms remain significant challenges among patients wearing ocular prosthesis. Factors such as age, geographical area of residence,

economic status, side of enucleation, cause of anophthalmos, materials of ocular prosthesis, and the time of and the satisfaction of ocular prosthesis wearing were found to be associated with depressive or anxiety symptoms. Long-term comprehensive care targeting these vulnerable patients is warranted to mitigate their depression and anxiety.

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Conflict of interest

The authors declare no conflicts of interest in this work.

Author contributions

Conceptualization: Ke Xiong, Yongzhi Zhao
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Writing – review & editing: Yongzhi Zhao

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Nanfang Hospital, Southern Medical University, and the study was conducted in accordance with the Declaration of Helsinki. In the present study, informed consent was obtained from all subjects and/or their legal guardian (if age is less than 18 years). Participants were guaranteed confidentiality of their private information and the right to withdraw at any time from the study.

Consent for publication

Online informed consent was obtained from the patients to publish their data in this article.

Availability of data

Datasets analyzed in this study are available on reasonable request from the corresponding author.

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ACCSCIENCE PUBLISHING

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ORIGINAL RESEARCH ARTICLE

Unraveling the biomolecular effects of Mongolian mind-body interactive psychotherapy on psoriasis: An exosome proteomic analysis

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Abstract

Psoriasis is a chronic inflammatory skin disease etiologically related to stress. Mongolian mind-body interactive psychotherapy (MMIP) is a group psychotherapy that integrates traditional Mongolian medicine theory with modern psychology. Exosomes are nanovesicles that carry biomolecules such as proteins, and the lipid bilayer protects cargo from degeneration. The present study was conducted to discern the effects of MMIP on psoriasis from a biomolecular perspective, particularly by performing an exosome proteomic analysis. Plasma exosomes were extracted from 15 samples, derived from psoriasis patients (n = 5, before and after MMIP) and healthy controls (HCs; n = 5). All patients had spent 60 days engaging with MMIP. Proteomic analysis was conducted using high-throughput mass spectrometry, and the differentially expressed proteins (DEPs) were analyzed. Further, validation test was done in serum samples of psoriasis (n = 56) and HC (n = 29). After the MMIP, the psoriasis area and severity index improved by 75%. Compared to HCs, psoriasis patients demonstrated alterations in 41 DEPs, with significant involvement of ribosome and apelin/APJ pathway. The recovery of psoriasis following the therapy was found to be associated with significant alterations in 16 DEPs, involving pathways of Fc gamma-mediated receptor phagocytosis, tight junction, and vascular smooth muscle contraction. Notably, one of the immunoglobulins that were reduced in psoriasis was significantly elevated after the MMIP. Validation results showed that the levels of serum elafin were higher in psoriasis than in HC but significantly decreased after MMIP. In conclusion, this study demonstrated that MMIP has a significant influence on the profiles of immunoglobulins and inflammatory molecules, as well as several pathways participating in the psoriasis recovery, providing insights into the pathophysiology of psoriasis and possible potential therapeutic targets of the disease.

Keywords: Psoriasis; Plasma exosome; Proteomic analysis; Mongolian mind-body interactive psychotherapy; Stress; Group psychotherapy; Biomarker; Inflammation

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1. Introduction

Psoriasis is a recurrent chronic autoimmune skin disease that affects the quality of life of patients.[1] Genetic predisposition, infection, endocrine environment, immunity, and metabolic disorders are etiologically related with psoriasis; however, the exact pathogenesis remains poorly understood.[1,2] It is known that 44% of psoriasis patients endure psychological stress before the disease onset, and 88% of them are subject to recurrent skin flares.[3] Relaxation, hypnosis, biofeedback, and behavioral and cognitive stress management therapies have been proven successful in treating patients with psoriasis.[4]

Abnormal proliferation of keratinocytes and immune dysregulation are the the main pathological manifestations of psoriasis.[5] At the cellular level, the skin lesions in psoriasis exhibit hyperproliferation and aberrant growth of keratinocytes as well as large-extent infiltration by immune cells such as neutrophils, macrophages, T-cells, and dendritic cells.[6,7] Keratinocytes may stimulate T-cells, respond to different stimuli, and play a pivotal role in the inflammatory lesions of psoriasis; aberrantly released cytokines and chemokines from keratinocytes can enhance migration or expansion of the inflammatory cells, including neutrophils. These disorganized interactions between skin-resident immune cells and keratinocytes cause persistent immune-mediated inflammatory responses in psoriasis.[8] Recently, exosomes have emerged as crucial mediators of intercellular communication.[9,10] Needless to say, exosomes, along with inflammatory cytokines, together play a role in promoting the development of skin inflammation in psoriasis by facilitating the interaction between immune cells and keratinocytes.[6]

Exosomes are lipid-bilayer vesicles derived from various cells, measuring 30 – 100 nm in diameter,[11] and found in various body fluids such as plasma, breast milk, urine, and saliva under pathological or non-pathological conditions.[12] Proteins associated with biogenesis (ALIX and SG101), tetraspanins (CD81, CD63, and CD9), heat shock proteins (HSP70 and HSP90), and major histocompatibility complex (MHC-I and MHC-II) are among the conserved proteins that are abundant in exosomes.[13] In addition to various proteins, exosomes also contain lipids and nucleic acids, including RNAs, miRNAs, lncRNAs, and circRNAs. These exosomes participate in intricate, physiologically significant intercellular communication between various cells.[14] The dysregulation of skin cell interactions associated with alterations in exosome cargoes might play roles in the complex pathogenesis of chronic inflammatory and autoimmune skin diseases.[15] During the development of skin diseases, the cargoes in circulating exosomes are transferred by blood flow to the skin cells, impacting their communications, thereby unfavorably resulting in lesions.[16] Therefore, exosomes are regarded as desirable diagnostic and therapeutic biomarkers for skin diseases. Furthermore, exosomes from psoriasis-like keratinocytes enhance the production of neutrophil extracellular traps formation and proinflammatory cytokine expression through activating the nuclear factor kappa B and p38 MAPK pathway.[17] Thus, exosome-mediated communication between activated keratinocytes and infiltrating immune cells contributes to the progression of psoriasis. Moreover, a previous study showed that the exosomes contain more intact proteins in culture supernatants of lipopolysaccharide-simulated THP-1 cells than those from non-stimulated cells.[18]

Proteomics refer to the large-scale systematic analysis of proteins, in terms of identity, quantity, and function. Biomarkers that have applications in the early and effective diagnosis, prognosis, and therapeutic outcome monitoring for psoriasis PS are urgently needed to optimize the diagnosis-prognosis-treatment axis of psoriasis management. Over the past two decades, proteomics has been widely employed in psoriatic research.[19] Using sera from six psoriasis patients, four individual parameters such as Zn-α2-glycoprotein, complement C3 (CO3), polymeric immunoglobulin receptor, and plasma kallikrein (KLK) were found to be differently expressed as compared to those from healthy individuals.[20] Proteomics analysis can also help with differentiating responders and non-responders to traditional Chinese medicine among psoriasis patients.[21] However, studies on exploring the therapeutic impact of plasma exosome-derived proteins on psoriasis patients are hitherto unavailable.

Mongolian mind-body interactive psychotherapy (MMIP) is a new kind of complementary therapy that combines modern psychology with traditional Mongolian medicine theory, which has been introduced in literature.[22] MMIP utilizes video or live group therapy approach (200 – 1000 people), through which the therapist lectures about knowledge of health, behavior, diet, mind, and psychology; patients present their own case of recovery or the significant therapeutic improvement their have attained; and the therapist offers feedback about their recovery course or treatment path. MMIP is a form of group psychotherapy that does not apply medicine or drugs, featuring the concept of homotherapy-for-heteropathy. This type of psychotherapy is less costly and associated with no side effects. Technically, MMIP utilizes narrative therapy, hypnosis therapy, music therapy, supportive therapy, cognitive psychotherapy, positive psychotherapy, *etc.*[22,23] Our previous study showed that patients with

esophageal cancer and insomnia experienced a better quality of life after MMIP.[22,24] Besides, MMIP has been found to significantly improve skin symptoms in psoriatric patients.[25]

MMIP can relieve skin symptoms and emotions such as anxiety and depression; however, their biomolecular effect remains unknown. A clinical prospective study investigating the clinical efficacy of MMIP in psoriasis is currently underway (ChiCTR1800015533). Among the enrolled 85 patients with psoriasis, 42% (n = 36) of them psoriasis area and severity index (PASI) 50, and 12% (n = 10) had PASI 75 after 60 days of MMIP (ongoing study, unpublished data). PASI 75 indicates a 75% or greater reduction in PASI scores from baseline and excellent disease improvement.[26] In this study, we screened for therapeutic molecules in five psoriasis patients with PASI 75 and pinpointed the pathways involved by analyzing their exosomes through proteomics means. To the best of our knowledge, this is the first report describing the identification of functional proteins in plasma exosome that respond to MMIP.

2. Materials and methods

2.1. Therapy details

MMIP is a group psychotherapy that integrates traditional Mongolian medicine theory with modern psychology. MMIP is practiced as a form of health education and can be used by anyone who needs it. MMIP involves group therapy (live or video, with around 200 – 1000 people at a time depending on the therapy room) and individual counseling. In each therapy (3 h in total), 6 – 10 cases presented their own diseases, symptoms, and recovery course. Participants reported how they overcame their symptoms after MMIP, followed by an experienced doctor commenting on their individual cases. The video-based group therapy entailed the playing of Mongolian songs, announcements, introduction of the treatment and the therapist, exercises, and presentation of cases, culminating with the playing of Mongolian songs (Figure 1 of reference Chagan-Yasutan *et al.*[22]). In group therapy, case report-based narrative therapy and hypnotic methods were primarily utilized, and it is recommended that people attending group therapy should begin with individual counseling. The case analysis and comments by the doctors were grounded in the theories of psychoanalytic, cognitive, behavioral, and supportive therapies. In MMIP, health education, case presentation, and the doctor's commentary are as psychological intervention.

The duration of the treatment was as follows: the patients had video-based group therapy for 3 h daily for a total of 60 days (treatment cycles might be split into two sessions over the duration of 6 months, nevertheless adding up to 60 days). Moreover, each of them attended four sessions of on-site live group therapy and one individual consultation.

2.2. Participants

Patients with psoriasis presented to our department between 2018 and 2020 were considered for recruitment. All the patients (n = 5) diagnosed with psoriasis vulgaris were confirmed by biopsy, and all patients did not receive any medication for 2 weeks before enrollment. Further, age- and sex-matched healthy controls (HCs) (n = 5) were chosen. Due to the small sample size, only those of the same ethnic background (Mongolian) and who were male were enrolled as controls. EDTA plasma samples were used for isolating exosomes, which were then subjected to proteomics analysis. Further, marker validation was done in serum samples of psoriasis patients (n = 56) and HCs (n = 29). All the samples from the patients were collected before and after the therapy and were aliquoted and frozen at -80°C until further use. Plasma samples were sent to Beijing Genomics Institute (BGI; Shenzhen, China) for exosome isolation, proteomics, and data analysis.

Moreover, the patient's basic information, including disease period, family history, PASI score, and hospital anxiety and depression scale (HADS), were obtained. The HADS is a patient-reported anxiety (HADS-A) and depression (HADS-D) measure that comprises seven questions for each subscale, with each item ranging from 0 to 3 points (totaling 0 – 21) and higher scores denoting more severe symptoms.[27] According to the report, on anxiety or depression can be classified based on the scores: normal (0 –7), mild (8 – 10), moderate (11 – 14), and severe (15 – 21).[28]

2.3. Exosome isolation and proteomics analysis

The isolation of exosomes from the plasma was performed using titanium oxide (TiO_2)-based technology (BGI, Shenzhen, China), as described previously,[29] with minor modifications. Briefly, 400 µL of plasma was diluted in the same volume of polybutylene succinate and mixed well; it was added to 20 mg of TiO_2 microspheres followed by incubation at 4°C for 10 min. After centrifugation, the pellets were obtained, followed by washing four times, and the obtained exosomes on the TiO_2 microsphere surface were treated with 20 µL of lysis buffer (2% sodium dodecyl sulfate and protease inhibitor cocktail), followed by heating at 95°C in a shaker at 1000 rpm for 15 min. Subsequently, the supernatant, denoted as the protein fraction, was collected by centrifugation (25,000 ×g at 4°C for 15 min). The obtained exosome samples were analyzed using proteomics analysis described below.[29] The experiment flowchart is shown in Figure 1A.

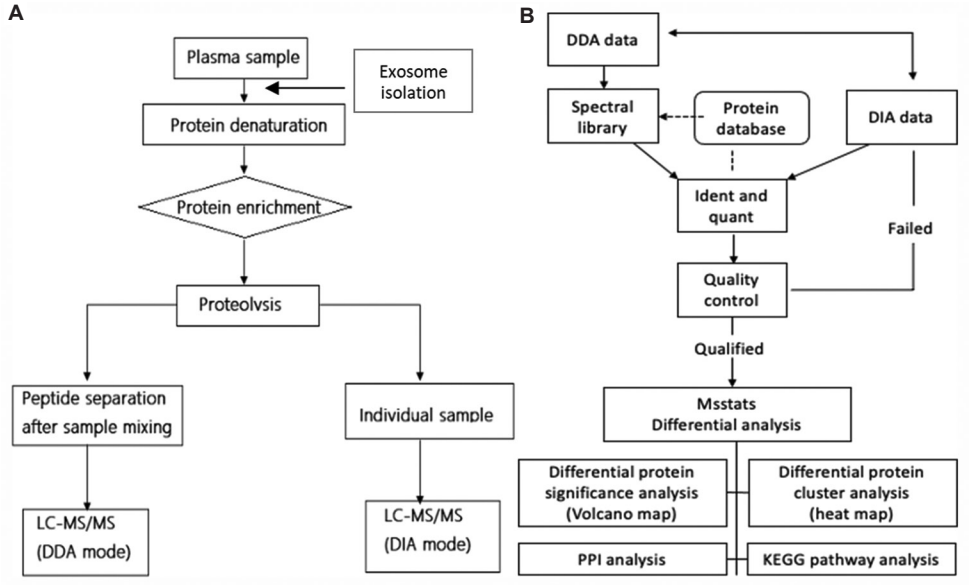

Figure 1. Proteomics experiment and analysis workflow. (A) Proteomics experiment workflow. (B) Proteomics data analysis workflow
Abbreviations: PPI: Protein and protein interaction; KEGG: Kyoto encylopedia of Genes and Genome.

2.4. Protein digestion

The obtained protein-containing solution was incubated at 37°C for 45 min after added with an appropriate amount of 10 mM dithiothreitol. Then, it was treated with 25 mM iodoacetamide and left in a dark room for 30 min at room temperature. After trypsinization, the solution was incubated for 14 – 16 h at 37°C. The digested peptides for spectral library generation were divided into ten fractions with a C18 StageTip. The Shimadzu LC-20AB HPLC system coupled with a Gemini high pH C18 column (5 m, 4.6 × 250 mm) was used. All peptides were frozen, dried, and desalted before liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis (BGI, Shenzhen, China).[30]

2.5. Data-dependent acquisition (DDA) and data-independent acquisition (DIA) analysis by nano-LC-MS/MS

The dried peptide samples were reconstituted with mobile phase A (2% acetonitrile [ACN], 0.1% formic acid [FA]), centrifuged at 20,000 ×*g* for 10 min, and the supernatant was taken for injection. Separation was carried out by a Thermo UltiMate 3000 UHPLC liquid chromatography. The sample was enriched in the trap column and desalted and then entered a tandem self-packed C18 column (150 μm internal diameter, 1.8 μm column size, 35 cm column length) and was separated at a flow rate of 500 nL/min by the following effective gradient: 0 – 5 min, 5% mobile phase B (98% ACN, 0.1% FA); 5 – 90 min, mobile phase B linearly increased from 5% to 25%; 90 – 105 min, mobile phase B rose from 25% to 35%; 105 – 110 min, mobile phase B rose from 35% to 80%; 110 – 115 min, 80% mobile phase B; 115 – 120 min, and 5% mobile phase B.

The nanoliter liquid phase separation was directly connected to the mass spectrometer (BGI, Beijing, China).[30] For DDA analysis, LC-separated peptides were ionized by nanoESI. They were injected into a tandem mass spectrometer Q-Exactive HF X (Thermo Fisher Scientific, San Jose, CA, USA) with DDA detection mode. The main settings were as follows: ion source voltage = 1.9 kV; MS scan range = 350–1,500 m/z; MS resolution = 120,000; maximal injection time (MIT) = 50 ms; MS/MS collision type = HCD; collision energy (nominal collison energy) = 28; MS/MS resolution = 30,000; MIT = 100 ms; and dynamic exclusion duration = 30 s. The start m/z for MS/MS was fixed at 100. A precursor for MS/MS had the following setting: charge range = 2+ to 6+; top 20 precursors with intensity over 2E4, and automatic gain control (AGC) = MS 3E6, MS/MS 1E5.

For DIA analysis, LC-separated peptides were ionized by nanoESI and injected into tandem mass spectrometer Q-Exactive HF X (Thermo Fisher Scientific, San Jose, CA, USA) with DIA detection mode. The main settings were as follows: ion source voltage = 1.9 – 2 kV; MS scan range = 400 – 1250 m/z; MS resolution = 120,000; MIT = 50 ms; and 400 – 1250 m/z was equally divided into a 45 continuous windows of MS/MS scan. MS/MS collision type was collision dissociation (HCD), while MIT was on auto mode. Fragment ions were scanned in Orbitrap, with MS/MS resolution = 30,000, collision energy in the distributed mode (22.5, 25, 27.5), and AGC = 1E6.

2.6. Bioinformatic analysis

Proteomics analysis was based on the sample data generated from a high-resolution mass spectrometer. DDA data were identified by the Andromeda search engine within MaxQuant, and identified results were used for spectral library construction.[31] The mProphet algorithm was used for large-scale DIA data to complete analytical quality control, thus obtaining numerous reliable quantitative results. The proteomics analysis was done by BGI (Shenzhen, China). MSstats software package was used to perform differential and functional analysis of the differentially expressed proteins (DEPs). The bioinformatics analysis process is shown in Figure 1B. The DEPs between comparison groups were identified based on fold changes >1.5 and a Q value <0.05. All volcano plots, heatmaps, venn diagrams, Kyoto Encylopedia of Genes and Genomes (KEGG) pathway, and protein-protein interaction (PPI) of the DEPs were illustrated using the Dr. Tom website provided by BGI (https://biosys.bgi.com).[32]

2.7. Elafin detection assay

The levels of elafin were detected in serum using an enzyme-linked immunosorbent assay (ELISA) kit (mlbio, Shanghai Enzyme-linked Biotechnology Co., Ltd. Shanghai, China) according to the manufacturer's instructions.

2.8. Statistical analysis

Statistical difference in ELISA results between pre- and post-MMIP among psoriasis patients was analyzed using Wilcoxon matched-pair signed rank test, whereas statistical difference between pre-MMIP and the HCs was analyzed using Mann–Whitney *U*-test. The age differences between psoriasis patients and HCs were compared using Mann–Whitney *U*-test. Gender differences between groups were analyzed with Fisher's exact test. $P < 0.05$ was considered statistically significant. These statistical analyses were performed using GraphPad Prism 8 software (GraphPad Software, San Diego, CA, USA).[33,34]

3. Results

3.1. Profiles of participants

The study was conducted using samples recruited in our department between July 2021 and May 2022. All the patients (enrolled in proteomics study) showed more than 75% improvement in their PASI scores after MMIP (Table 1). The mean ages of the patients and HCs were 32.8 ± 3.5 (Table 1) and 33.2 ± 3.5 (each was 32, 28, 33, 36, and 37) years old, respectively. The profiles of the enrolled patients are shown in Table 1. After the therapy, the higher anxiety and/or depression scores were reduced back to normal (patients no. 3, 4, 5). The exosomes were extracted from plasma, and proteomics analysis was carried out to compare between psoriasis and HCs, and between pre- and post-MMIP.

In the ELISA validation experiment, serum samples from MMIP-treated psoriasis patients (n = 56) and HCs (n = 29) were used. The mean ages of the MMIP and HC groups were 36 ± 9 and 35 ± 5 years old, respectively. The male prevalence was 48.2% and 37.9% in the MMIP and HC groups, respectively. There were no differences in age and gender between MMIP and HC groups. The median and range of PASI before and after the therapy were 9.3 (2.4 – 32.8) and 5 (0 – 25.7), respectively, in psoriasis patients.

3.2. Exosome proteomics profiles

This study used Q-Exactive HF X to acquire mass spectrometry (MS) data for 15 plasma-derived exosome samples in DIA mode. Consequently, 10,882 peptides and 770 exosomal proteins were identified in our samples. Among these 770 proteins, 41 kinds of DEPs were found in the exosomes of patients with psoriasis compared to HCs (Table 2), whereas 16 kinds of DEPs were identified after a comparison before and after MMIP in patients with psoriasis (Table 3).

3.3. DEPs in patients with psoriasis compared with HCs

Out of the 41 DEPs identified, 18 proteins were significantly decreased, and 23 proteins were significantly elevated

Table 1. Basic information of enrolled patients

ID	Age	Gender	Family history	Disease period	HADS				PASI before therapy	PASI after therapy	PASI improvement (%)
					Anxiety score before therapy	Anxiety score after therapy	Depression score before therapy	Depression score after therapy			
1	35	M	No	8 m	3	3	4	0	14.7	1.6	89
2	36	M	Yes	1 yr	1	1	0	1	16.6	0.3	98
3	27	M	No	17 yr	8	0	7	0	19.2	3	84
4	34	M	No	16 yr	1	0	6	2	21.2	5	76
5	32	M	No	10 yr	12	3	8	1	10.8	0	100

Abbreviations: HADS: Hospital anxiety and depression scale; m: Month; M: Male; PASI: Psoriasis area and severity index; yr: Year.

Table 2. List of exosomal proteins showing significant differences between psoriasis patients and healthy controls

S. No.	UniProt entry ID	Gene name	Protein name	Ratio (disease/health)	Q value	Up/ Downregulation
1	A2NYU9	N/A	Heavy chain Fab (Fragment)	0.12	0.04	Down
2	P05121	PAI1	Plasminogen activator inhibitor 1	0.15	0.03	Down
3	Q13835	PKP1	Plakophilin-1	0.26	0.04	Down
4	Q04695	KRT17	Keratin, type I cytoskeletal 17	0.27	0.01	Down
5	P35754	GLRX	Glutaredoxin-1	0.31	0.03	Down
6	Q6VFQ6	HBB	Hemoglobin beta chain	0.32	0.01	Down
7	P37840	SNCA	Alpha-synuclein	0.33	0.04	Down
8	P01860	IGHG3	Immunoglobulin heavy constant gamma 3	0.41	0.049	Down
9	A0A0C4DH68	IGKV2-24	Immunoglobulin kappa variable 2-24	0.44	0.01	Down
10	P22105	TENX	Tenascin-X	0.46	0.03	Down
11	B2R582	N/A	Highly similar to C-type lectin domain family 3, member B (CLEC3B)	0.47	0.03	Down
12	P01591	JCHAIN	Immunoglobulin J chain	0.49	0.02	Down
13	Q8NCL6	N/A	highly similar to Ig alpha-1 chain C region	0.50	0.02	Down
14	P01871	IGHM	Immunoglobulin heavy constant mu	0.53	0.04	Down
15	Q0ZCH6	N/A	Immunoglobulin heavy chain variable region	0.58	0.04	Down
16	Q0ZCF9	N/A	Immunglobulin heavy chain variable region	0.58	0.02	Down
17	B1N7B9	BMS1P20	Cryocrystalglobulin CC2 lambda light chain variable region	0.59	0.04	Down
18	P26572	MGAT1	Alpha-1,3-mannosyl-glycoprotein 2-beta-N-acetylglucosaminyltransferase	0.63	0.05	Down
19	P39060	COIA1	Collagen alpha-1(XVIII) chain	1.52	0.03	Up
20	Q13421	MSLN	Mesothelin	1.58	0.02	Up
21	P62753	RS6	40S ribosomal protein S6	1.59	0.03	Up
22	Q9Y509	VH3	VH3 protein (Fragment)	1.61	0.02	Up
23	P30086	PEBP1	Phosphatidylethanolamine-binding protein 1	1.62	0.03	Up
24	P04632	CPNS1	Calpain small subunit 1	1.63	0.04	Up
25	P01024	CO3	Complement C3	1.63	0.02	Up
26	O60282	KIF5C	Kinesin heavy chain isoform 5C	1.65	0.02	Up
27	P62244	RS15A	40S ribosomal protein S15a	1.67	0.02	Up
28	Q9HCU4	CELR2	Cadherin EGF LAG seven-pass G-type receptor 2	1.69	0.04	Up
29	P61247	RS3A	40S ribosomal protein S3a	1.84	0.00	Up
30	P62736	ACTA2	Actin alpha 2, aortic smooth muscle 2	1.90	0.04	Up
31	Q9Y577	TRI17	E3 ubiquitin-protein ligase TRIM17	1.94	0.049	Up
32	P62266	RS23	40S ribosomal protein S23	1.96	0.01	Up
33	Q6P387	CP046	Uncharacterized protein C16orf46	2.36	0.01	Up
34	Q01518	CAP1	Adenylyl cyclase-associated protein 1	2.46	0.03	Up
35	P50552	VASP	Vasodilator-stimulated phosphoprotein	2.55	0.02	Up
36	B4DRA0	N/A	Highly similar to RNA-binding region-containing protein 2	3.12	0.02	Up
37	O00233	PSMD9	26S proteasome non-ATPase regulatory subunit 9	3.16	0.02	Up
38	P37802	TAGL2	Transgelin-2	3.20	0.04	Up
39	P58166	INHB	Inhibin beta E chain	3.23	0.04	Up
40	Q6ZW64	N/A	Highly similar to Protein Tro alpha1 H, myeloma	6.18	0.04	Up
41	P19957	ELAF	Elafin	9.12	0.01	Up

Table 3. List of exosomal proteins showing significant differences between pre- and post-MMIP

S. No.	UniProt entry ID	Gene name	Protein name	Ratio (therapy/disease)	Q value	Up/Down-regulation
1	Q5T750	XP32	Skin-specific protein 32	0.11	0.034	Down
2	P23528	CFL1	Cofilin-1	0.24	0.023	Down
3	P19957	ELAF	Elafin	0.26	0.035	Down
4	O00233	PSMD9	26S proteasome non-ATPase regulatory subunit 9	0.36	0.049	Down
5	B4DRA0	B4DRA0	Highly similar to RNA-binding region-containing protein 2	0.36	0.039	Down
6	P14618	PKM	Pyruvate kinase PKM	0.43	0.037	Down
7	P81605	DCD	Dermcidin	0.43	0.033	Down
8	P50552	VASP	Vasodilator-stimulated phosphoprotein	0.48	0.034	Down
9	P62736	ACTA2	Actin, aortic smooth muscle	0.49	0.027	Down
10	P30086	PEBP1	Phosphatidylethanolamine-binding protein 1	0.52	0.005	Down
11	Q99972	MYOC	Myocilin	0.52	0.009	Down
12	Q92876	KLK6	Kallikrein-6	0.66	0.042	Down
13	P69905	HBA1	Hemoglobin subunit alpha	2.07	0.038	Up
14	Q0ZCH6	Q0ZCH6	Immunoglobulin heavy chain variable region (Fragment)	2.16	0.007	Up
15	Q01518	CAP1	Adenylyl cyclase-associated protein 1	3.56	0.025	Up
16	P60660	MYL6	Myosin light polypeptide 6	10.44	0.017	Up

Abbreviation: MMIP: Mongolian mind-body interactive psychotherapy.

(Figure 2A and Table 2). A cluster analysis chart was plotted based on these DEPs. The results showed the significantly different proteins between the patients and HCs (disease vs. health; Q value < 0.05; Figure 2B). Among the 41 DEPs, nine of them were immunoglobulins (Igs)-derived molecules such as IGHG3, IGKV2-24, JCHAIN, Q8NCL6 (no gene ID, instead of UniProt entry ID, same for others), IGHM, Q0ZCH6, Q0ZCF6, and IG-like proteins (A2NYU9, B1N7B9). Keratin 17 (KRT17) and plakophilin-1 (PKP1) were found to be decreased in patients with psoriasis compared to HCs (Figure 2B and Table 2). Further, four types of ribosomal protein (RS), namely, 40S ribosomal protein S6 (RS6), 40S ribosomal protein S23 (RS23), 40S ribosomal protein S3A (RS3A), and 40S ribosomal protein S15A (RS15A), which are proteins involved in the cellular process of translation, were observed to be increased in psoriasis patients compared with HCs (Figure 2B and Table 2). In addition, inflammation-related proteins, such as phosphatidylethanolamine-binding protein 1 (PEBP1), calpain small subunit 1 (CPNS1), complement C3 (CO3), vasodilator-stimulated phosphoprotein (VASP), 26S proteasome non-ATPase regulatory subunit 9 (PSMD9), and elafin (ELAF), were upregulated. Among these proteins, ELAF achieved the highest level of expression in psoriasis as compared to HCs (Table 2).

To gain further insight, we performed a KEGG pathway and PPI analysis (Figure 2C and D). The KEGG pathway analysis showed that two pathways of the ribosome (https://www.kegg.jp/dbget-bin/www_bget?map03010) and apelin signaling pathways (https://www.kegg.jp/dbget-bin/www_bget?map04371) were significantly involved in psoriasis (p <0.05). Subsequently, the DEPs were imported into the STRING database (STRING 11.0) to perform network interaction analysis of protein-protein relationships in the first 100 confidence intervals. As Figure 2D shows, actin alpha 2 (ACTA2) upregulation was associated with various ribosomal protein (RS) proteins and collagen alpha-1 chain (COLA1), which was also connected to cadherin EGF LAG seven-pass G-type receptor 2 (CELR2).

3.4. DEPs in psoriasis identified from comparison between pre- and post-MMIP

Comparative analysis of exosomal proteins before and after the MMIP unveiled 16 DEPs, as shown in Figure 3A and B. Among them, 12 of the proteins were significantly decreased, and four were increased. The levels of ELAF, PSMD9, VASP, ACTA2, PEBP1, and adenylyl cyclase-associated protein 1 (CAP1) in psoriasis patients decreased significantly and Ig of Q0ZCH6 was increased after the MMIP. Nine proteins were only observed in the group receiving the therapy. These proteins were skin, metabolic, or other function-related proteins, such as skin-specific protein 32 (XP32), cofilin-1 (COF1), dermcidin (DCD), myocilin (MYOC), KLK6, myosin light polypeptide 6 (MYL6), and pyruvate kinase (PKM) (Figure 3B and Table 3).

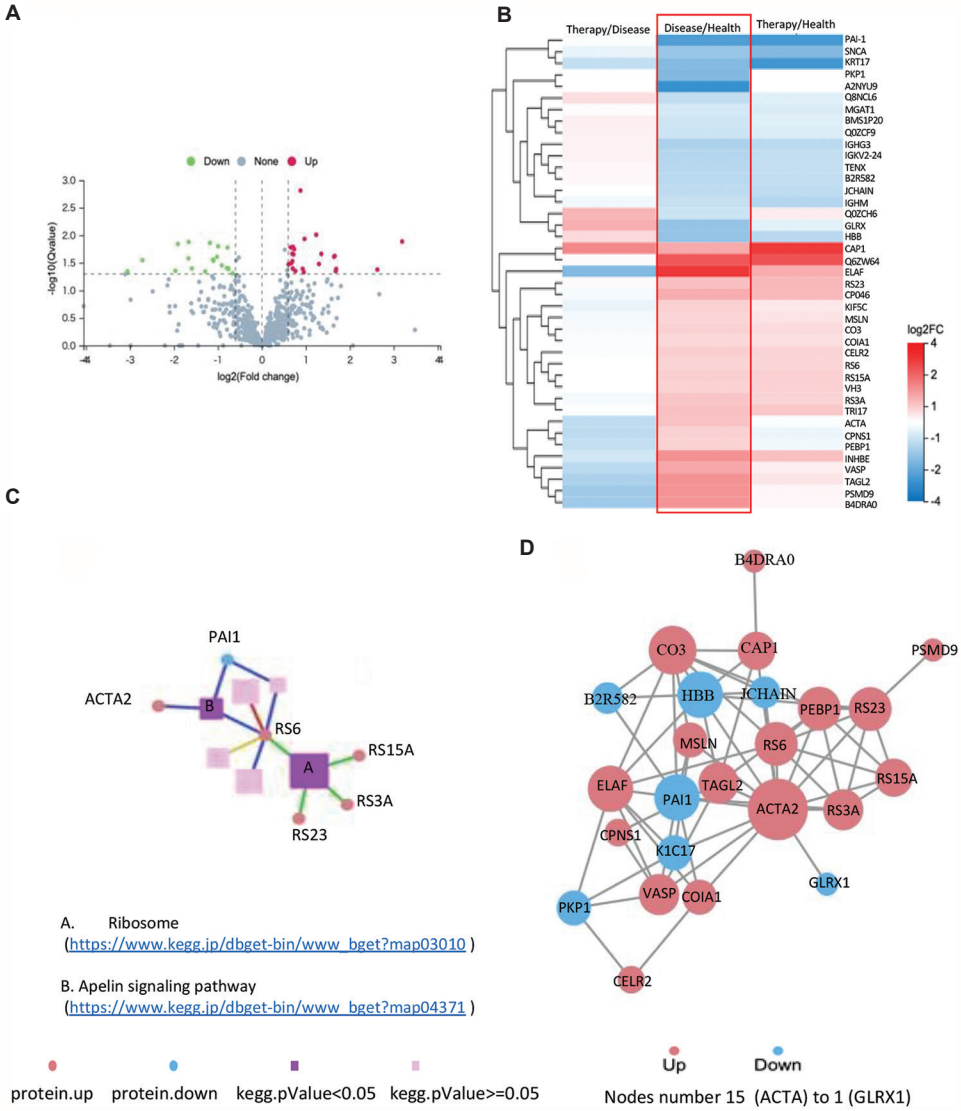

Figure 2. Differentially expressed proteins (DEPs) identified in proteomics analysis comparing protein profiles between patients with psoriasis and HCs. (A) Volcano plot shows significantly increased proteins (n = 23) and decreased proteins (n = 18) in patients with psoriasis. (B) Heatmap shows significantly altered proteins between patients with psoriasis (Disease) and HCs (Health). (C) KEGG pathway analysis unveils two pathways involved in psoriasis. (D) PPI figure shows the interaction of DEPs (Table 2 presents the full name of proteins).
Abbreviations: MMIP: Mongolian mind-body interactive psychotherapy; KEGG: Kyoto Encylopedia of Genes and Genomes; PPI: Protein-protein interaction; HCs: Healthy controls.

In the KEGG pathway analysis, the pathway of Fc gamma R-mediated phagocytosis (https://www.kegg.jp/dbget-bin/www_bget?map04666), tight junction (https://www.kegg.jp/dbget-bin/www_bget?map04530), and vascular smooth muscle contraction (https://www.kegg.jp/dbget-bin/www_bget?map04270) (Figure 3C) with the correlated exosomal proteins of COF1, VASP, MYL6, and ACTA2 was significantly involved in the recovery of patients with psoriasis by MMIP (Figure 3D).

3.5. Validation of elafin before and after therapy in psoriasis patients

The levels of ELAF were validated in serum samples of MMIP-treated (n = 56) psoriasis patients and HCs (n = 29). The levels of ELAF were significantly elevated in psorisis patients (before therapy), as compared to HCs ($P < 0.0001$), and significantly decreased after the MMIP therapy ($P < 0.01$) (Figure 4). However, there was no correlation between serum ELAF and PASI before and after the MMIP therapy.

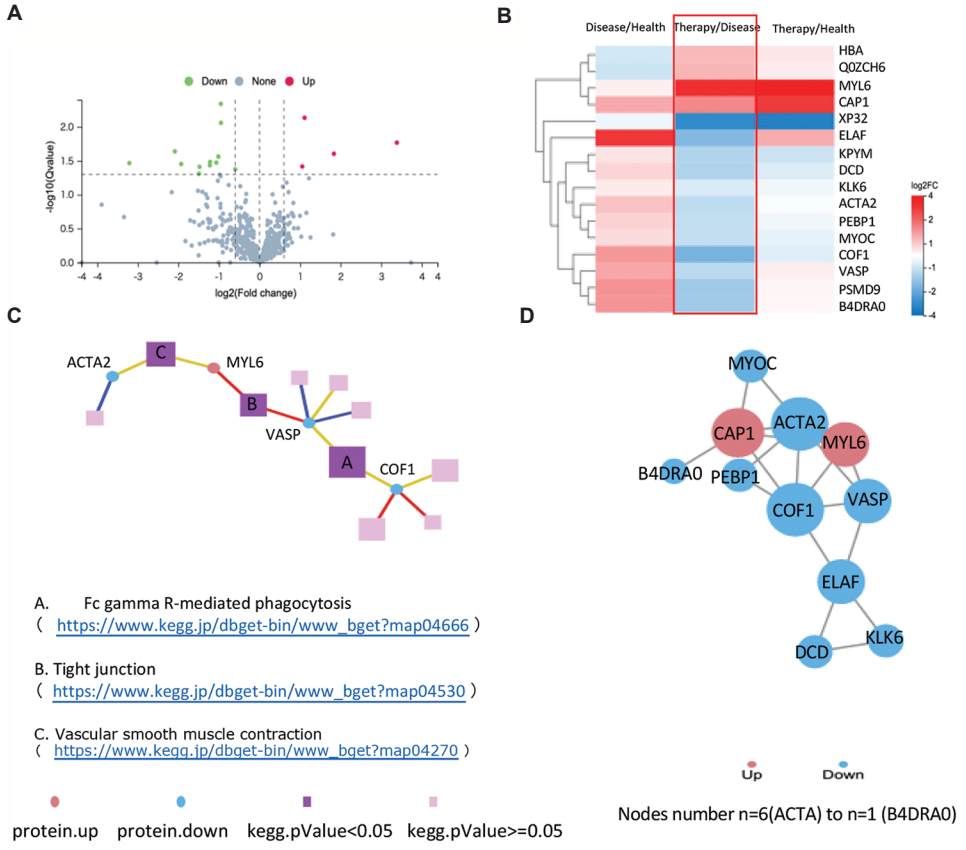

Figure 3. Differentially expressed proteins (DEPs) identified in proteomics analysis comparing protein profiles before and after MMIP. (A) Volcano plot shows significantly increased proteins ($n = 4$) and decreased proteins ($n = 12$) after therapy. (B) Heatmap shows significantly altered proteins after therapy (Therapy) and before therapy (Disease). (C) KEGG pathway analysis shows three significantly altered pathways after the therapy. (D) PPI figure shows the interaction of DEPs (Table 3 presents the full name of proteins).
Abbreviations: MMIP: Mongolian mind-body interactive psychotherapy; KEGG: Kyoto Encyclopedia of Genes and Genomes; PPI: Protein-protein interaction.

3.6. Venn diagram of proteomic analysis

Figure 5 shows a venn diagram of eight DEPs (Q0ZCH6, PEBP1, ACTA2, CAP1, VASP, B4DRA0, PSMD9, and ELAF) that were identified in both groups ([Disease vs. Health] & [Therapy vs. Disease]). Among these proteins, six of them significantly decreased after the MMIP, except Q0ZCH6 and CAP1 (Figure 3B and Table 3). The low Ig levels in psoriasis (nine types of Ig compared with HCs, Table 2) may be related to immune deficiency and/or enhanced ADCC activity against self-antigens through Fc receptors. Alternatively, the increase of Ig levels after therapy (Q0ZCH6) also suggests the recovery of immune status and/or the decrease of ADCC activity against self-antigens. In addition, the inflammatory markers of ELAF and PEBP1 were significantly elevated in patients with psoriasis and decreased after the therapy.

In summary, the results showed that the involvement of ribosome and apelin signaling is pathologically associated with psoriasis. MMIP therapy alters Fc receptor-mediated phagocytosis pathways, tight junction, and vascular smooth muscle contraction. In addition, our study showed that MMIP altered Fc receptor-mediated pathology in psoriasis. Further, we validated the changes of ELAF levels in the serum of psoriasis patients by ELISA.

4. Discussion

This is the first study of proteomics analysis of the exosomes derived from plasma of psoriasis patients. The exosome contains various cargos that are involved in cellular communications, and proteomics analysis of the exosome showed that molecular profile, which was pathologically altered in psoriasis, could be improved by MMIP. Comparisons were conducted based on disease status (between psoriasis patients and HCs) and MMIP treatment status (between pre- and post-MMIP among psoriasis patients).

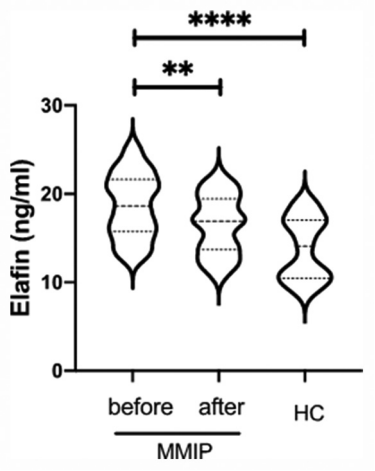

Figure 4. Significant differences in serum elafin between HCs and psoriasis patients and the changes in elafin level after MMIP. Statistical difference in elafin level before and after therapy was analyzed using Wilcoxon matched-pair signed rank test, wheras statistical difference in elafin level between HCs and psoriasis patients was analyzed using Mann–Whitney *U*-test (** $P < 0.01$; **** $P < 0.0001$).
Abbreviations: MMIP: Mongolian mind-body interactive psychotherapy; HCs: Healthy controls.

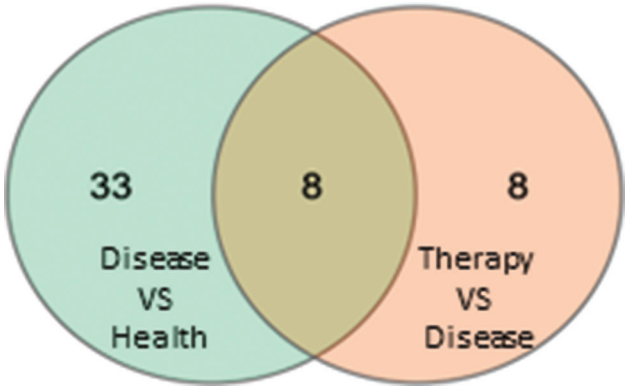

Figure 5. Venn diagram showing overlapping of differentially expressed proteins in plasma exosome between two study groups (Disease vs. Health; Therapy vs. Disease).

4.1. Comparative analysis of exosomal proteome between psoriasis patients and HCs

Comparing the exosomal proteome psoriasis patients and HC, we found that the levels of 41 proteins were altered in psoriasis patients. Among the four proteins that participate in skin function, KRT17 and PKP1 were downregulated, while COIA1 and CAP1 were upregulated in patients with psoriasis (Table 2 and Figure 2B). KRT17 is essential for lipid metabolism in keratinocytes and is beneficial for the homeostasis of the epidermal permeability barrier.[35] Another investigation revealed that PKP1 plays a key role in desmosome and tight junction function, and supports its role in growth control, which is essential for wound healing.[36] Downregulation of these proteins in the plasma-derived exosome may also indicate the deterioration of skin organization in psoriasis. Upregulation of COIA1 and CAP1 may alter skin organization in psoriasis because CAP1 was reported to inhibit endothelial cell proliferation and angiogenesis.[37] A study revealed that CAP1 controlled the actin cytoskeleton and its interactions with various actin-binding proteins in cellular processes.[38]

These data were fed into KEGG pathway analysis to decipher the functional and pathological roles of these changes. KEGG pathway analysis identified two pathways involved in psoriasis: ribosome signaling pathway (https://www.kegg.jp/dbget-bin/www_bget?map03010), and apelin signaling pathway (https://www.kegg.jp/dbget-bin/www_bget?map04371). The peptidase inhibitor-3K (PI3K)/Akt pathway acts downstream of the apelin pathway and regulates synthesis of osteopontin (OPN), which is known to be enhanced in psoriasis lesions and decrease after anti-TNF therapy.[39] OPN is a multifunctional protein synthesized by various immune-inflammatory cells, involved in diabetes, cardiovascular disease, and kidney disease, and often associated with psoriasis.[40] This finding is the first observation made with exosome proteomics analysis that the apelin signaling pathway is involved in psoriasis, further indicating that various metabolic pathways are altered in psoriasis.

Interestingly, PAI1 and ACTA2, which are reportedly involved in psoriasis, showed opposing alteration.[41,42] PPI analysis shed light on interesting PPI in psoriasis, showing that the ACTA2, one of six different actin isoforms, is involved in the contractile apparatus of smooth muscle, ACTA2 upregulation is associated with various RS proteins and COLA1, and COLA1 is related to CELR2. These three proteins were upregulated in patients with psoriasis, and the interaction of actin and cadherins was identified in the keratinocyte cell line.[43] Their upregulation was associated with a decrease of PKP1, a regulator of WNT signaling, and also known to play a prominent role in the desmosomes of keratinocytes in psoriasis.[44] It is necessary to obtain tissue and plasma simultaneously from the same patient and conduct a comparative study to understand its pathological roles. Moreover, the interaction of ELAF (a potent inhibitor specific for elastase and proteinase) and CO3 (complement 3) was identified. It is speculated that there is a circuit involving an increase in CO3 and an increase in elastase (which cleaves CO3), a concomitant increase in ELAF (which inhibits elastases),[45] and an elevation of ELAF in patients with psoriasis.[46] Thus, we and others confirmed an elevation of ELAF in PS and the interaction of these three molecules may be important in the pathogenesis of PS.

4.2. Comparative analysis of exosomal proteome in psoriasis patients before and after MMIP

Further, the expression levels of 16 proteins were altered significantly before and after the therapy in psoriasis patients. Among them, XP32 decreased after treatment, and it has been reported that XP32 is differentially expressed in non-lesional and lesional skin compared to healthy skin and may contribute to maintaining the non-lesional state.[47] DCD, which is a natural antibacterial peptide released by sweat glands and is usually transported to the epidermal surface by sweat, also reduces in level after therapy. It has been confirmed that DCD-derived polypeptide (86-103) could directly stimulate mast cells, trigger cytokine release *in vitro*, and cause a skin inflammatory response in wild-type mice, indicating its role in the onset and progression of psoriasis.[48]

KEGG pathway analysis showed that three pathways are involved in the recovery from psoriasis (Figure 3C). Involvement of exosomal proteins such as ACTA2 and VASP, as shown in the analysis results, could be by the exosomal proteins being the source of tested specimens. More meticulous study about the roles of these exosomal proteins in psoriasis development should be carried out. PPI analysis illustrated the interaction of the three KEGG pathways. The decrease of ACTA2 and COF1 is linked. Cofilin binds to actin, induces a twist in the filament, and critically contributes to phagocytosis.[49] The linked protein VASP may play a role in the phosphorylation and polymerization of actin.[50] It was found that a decrease in these proteins compared to before the therapy was involved in the recovery from psoriasis. In contrast, MYL6 and CAP1 increased after recovery. Phosphorylated MYL6 promotes actin assembly and contraction, while dephosphorylated MYL6 inhibits them.[51] Overexpression of CAP1 has been shown to decrease the level of phosphorylated cofilin, indicating that CAP1 facilitated actin depolymerization.[52] The above-mentioned findings indicate that the reduction in phagocytosis/antibody-dependent cellular cytotoxicity (ADCC) is associated with improvements in psoriasis.

The ADCC-mediated Fc receptor is known to be involved in psoriasis.[53] The low Ig levels in psoriasis, as shown in Table 2, may be related to immune deficiency and/or enhanced ADCC activity against self-antigens through Fc receptors. Alternatively, the increase of Ig after therapy (Q0ZCH6) also suggests the recovery of immune status and/or the decrease of ADCC activity against self-antigens.

Notably, several Igs (A2NYU9, IGHG3, IGKV2-24, JCHAIN, IGHM, Q0ZCH6, and Q0ZCF9) were found to be decreased in patients with psoriasis and apparently elevated after the therapy in this study (Figure 2B), and only Q0ZCH6 was significantly increased after the MMIP, indicating immune system was recovering after MMIP. It is known that hypogammaglobulinemia is a comorbidity of psoriasis, though the causative link remains unknown.[54] Intravenous immunoglobulin has been shown to exert a therapeutic effect on a patient with psoriasis associated with hypogammaglobulinemia.[55] The action of Ig on psoriasis is diverse, suggesting that it may be a double-edged sword.

In addition, the inflammatory markers such as ELAF and PEBP1 were significantly elevated in patients with psoriasis and decreased after the therapy. Recently, *PEBP1* has been reported as one of the ferroptosis-related genes that are altered in psoriasis.[56] The ligand of PEPB1, phosphatidylethanolamine, is captured by CD1 proteins on autoreactive human T-cells, which are involved in psoriasis. The metabolism of phospholipids in psoriasis also warrants investigation.[57]

4.3. Elafin in psoriasis patients and after MMIP

ELAF, also named PI3 or skin-derived antileucoproteinase, is an elastase inhibitor produced by keratinocytes and initially purified from the skin of patients with psoriasis in the 1990s.[58,59] It was reported that inflammatory mediators (interleukin-1β or tumor necrosis factor-alpha) secreted by dermal neutrophils stimulate elafin secretion and may be involved in the overexpression of ELAF in keratinocytes to protect the epidermis from degradation caused by dermal neutrophil infiltration.[60] The previous studies have shown that ELAF responds to cyclosporin A[58] and traditional Chinese Medicine.[21] These prior results align with our finding that serum ELAF became higher in psoriasis patients and decreased significantly after the MMIP, suggesting that this form of therapy can reduce inflammation of neutrophil infiltration in psoriasis. Therefore, ELAF is one of the therapeutic markers of MMIP in the context of psoriasis. Furthermore, our proteomics analysis also revealed that the neutrophil KLK6 that was elevated in psoriasis patients, significantly decreased following the MMIP. These findings demonstrate the effectiveness of MMIP at molecular level, unveiled by exosome proteomics analysis.

Furthermore, skin proteomes from three out of five patients showed that ELAF was significantly decreased after receiving the therapy (unpublished data). Exosomes act as carriers transferring proteins from skin to blood or vice verse, contributing to pathogenesis of psoriasis, and ELAF stands as a indicator of response to MMIP, indicating that the extent of inflammation suppressed by MMIP in psoriasis or MMIP maintains the homeostasis of skin barrier system. The previous studies also showed that the levels of ELAF in blood and skin could reflect the severity of psoriasis.[60,61]

4.4. Stress and therapy in PS patients

Our previous study showed that the skin symptoms of patients with psoriasis significantly improved after the MMIP.[25] Nowadays, studies have demonstrated that 37 – 88% of patients with psoriasis believe that their disease is caused or exacerbated by stress.[62] Furthermore, the related psychological problems can affect daily social activities and work; it causes embarrassment, lack of self-esteem, anxiety, and an increased prevalence of depression.[1] Therefore, psychological interventions like relaxation therapy could decrease disease severity and improve psoriasis patients' quality of life.[63] In this study, we demonstrated for the first time that the proteomics analysis of the exosomes is helpful at analyzing the therapeutic effect of MMIP.

The limitation of the study was the small size of the patients and healthy individuals enrolled. In the future, plasma-derived exosomes and therapeutically effective exosomal proteins need to be further analyzed and verified in a large-scale population study to understand the pathogenesis of psoriasis and determine the therapeutic targets. Here, we examined the effect of MMIP on exosomal proteome in selected patients with PASI 75; however, the clinical effect of MMIP on psoriasis needs to be confirmed by a randomized controlled study in the future. Nevertheless, the present study, for the first time, showed the biomolecular effect of MMIP and provided novel insights into the pathophysiology of PS.

5. Conclusion

In this study, we conducted comparative proteomics analysis of the exosomes derived from the plasma of MMIP-treated psoriasis patients and HCs. The results showed that the involvement of apelin signaling and ribosome pathways is pathologically associated with psoriasis. The potential involvement of a circuit comprising complement, protease, and its inhibitor is postulated. MMIP therapy attenuates the activation of actin-mediated inflammatory pathways and alters Fc receptor-mediated phagocytosis pathways as well as the pathways of tight junction and vascular smooth muscle contraction. In addition, nine types of immunoglobulins were decreased in psoriasis, and one of them significantly increased after the MMIP. Further, validation study revealed that the levels of serum ELAF were higher in psoriasis patients than in HCs and significantly decreased after MMIP. Thus, MMIP can heighten immunity and suppress inflammation in psoriasis patients at the biomolecular level. Through proteomics analysis of plasma-derived exosomes, new insights into psoriasis pathology and therapeutic targets in MMIP are unveiled.

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Conflict of interest

The authors declare no conflicts of interest.

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Ethics approval and consent to participate

The study was conducted according to the code of ethics of the World Medical Association (Declaration of Helsinki) and approved by the Ethical Committee Review Board of the International Mongolian Medicine Hospital of Inner Mongolia (2018-002). Written informed consent was obtained from all of the participants.

Consent for publication

Written informed consent was obtained from all participants to publish their data. Moreover, the effort has been made by authors to conceal any identifying information of the participants that appear in the paper.

Availability of data

Data are available from the corresponding author on reasonable request.

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ACCSCIENCE PUBLISHING

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ORIGINAL RESEARCH ARTICLE

Assessment of depressive symptoms among medical students and doctors using PHQ-9

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Abstract

Medical students and doctors are at increased risk of experiencing depression. Doctors exhibit varying severity of depression symptoms at different stages of their careers. This study aimed to evaluate the prevalence of depressive symptoms among medical students and doctors using the Patient Health Questionnaire-9 (PHQ-9). We conducted a cross-sectional study in Lithuania from February to March 2024, using an anonymous online questionnaire that collected demographic data and included the PHQ-9. A score of ≥10 indicated criteria for depression. The questionnaire was completed by 146 respondents, comprising 77 medical students and 69 doctors or resident doctors. Overall, 40% of respondents met the criteria for depression, including 48% of medical students and 32% of doctors. Medical students had a higher mean PHQ-9 score compared to doctors, and the difference in PHQ-9 scores between students and doctors was significant (P = 0.045). No significant differences were found in PHQ-9 scores between genders (P = 0.430) or among respondents living in different city sizes (P = 0.780). Our data align with the literature findings that medical students exhibit higher depression scores than doctors. The study underscores the importance of regularly monitoring the emotional well-being of medical students and doctors and implementing interventions to improve their emotional health.

Keywords: Medical students; Doctors; Residents; PHQ-9; Depression; Prevalence

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1. Introduction

The World Health Organization reports a global prevalence of depression among adults at 5%, with women being 50% more likely to experience depression than men.[1] Depression and anxiety contribute significantly to lost work time, costing the world economy about US$1 trillion annually, a figure projected to rise to US$16 trillion by 2030.[2] Studies indicate that the prevalence of depression among medical students, residents, and doctors is higher than in the general population.[3-5] During medical studies, the prevalence of depression increases, with reported symptoms varying widely from 1.4% to 73.5% among students.[6] Medical students experience numerous challenges, including intense academic rigor, financial difficulties, lack of sleep, lack of control, constant exposure to sickness and death, inappropriate behavior during studies, and/or other challenges.[7] Research revealed that doctors generally have better mental health ratings than medical students. For example, a study involving 1417 medical students, residents,

and doctors discovered that almost half of the students exhibited symptoms of depression, while about a third of doctors and residents did. However, despite doctors having better mental health ratings compared to students, their mental health remains poorer than that of the general population.[8] Factors such as being single, longer weekly working hours, an increased average number of on-call days per week, lower levels of expertise,[9] and personality traits such as perfectionism[10] significantly risk the emotional health of doctors. At work, doctors mostly deal with human health and constantly encounter a multitude of intense emotions in their interactions with patients. Some doctors employ strategies such as depersonalization and acquiescence to cope with negative emotions such as anger, frustration, and guilt, stemming from the tension between professional ideals of expertise and the realities of organizational constraints and self-preservation. These coping mechanisms may contribute to the deterioration of doctors' relationships with their work, posing a significant threat to the health system.[11]

Growing research underscores the significant impact of poor mental health among doctors on the health-care system, which includes lower quality of communication and/or care, increased errors, poorer overall outcomes, and/or higher costs.[12] The specifics of doctors' work often involve uncontrollable stress, unpredictability, and low work control. Research indicates that such uncontrollable stress directly disrupts the function of the prefrontal cortex, causing neuronal connections in this brain region to deteriorate, which explains the psychological difficulties experienced by doctors and the decline in their work efficiency when subjected to prolonged, chronic stress.[13] The decreased work productivity and errors among doctors lead to patient morbidity and mortality and pose an economic burden. For example, annually in England, there are 237 million medication errors, with 66 million potentially clinically significant. These avoidable adverse drug events cost the National Health Service £98,462,582 annually.[14] Despite global progress in reducing the harm caused by adverse effects of medical treatment (AEMT), the overall incidence and prevalence of AEMT remained largely unchanged.[15]

Considering the high rates of depression among medical students and professionals, the lack of studies, and depression's burden on the healthcare system, we have decided to investigate the symptoms of depression among medical students and doctors in Lithuania using the Patient Health Questionnaire-9 (PHQ-9). Our goal is to raise awareness about this critical population, stimulate further research, deepen understanding, and advocate for interventions aimed at improving mental health.

2. Methods

2.1. Study design and population

Between February and March 2024, we conducted a cross-sectional study involving medical students and doctors (including resident doctors) in Lithuania. The survey was conducted in Lithuanian and utilized an anonymous online survey consisting of the PHQ-9 and demographic questions. The distribution of the survey was carried out via social media platforms, specifically closed groups on Facebook dedicated to medical students and doctors.

We opted for a cross-sectional study design for two main reasons: Firstly, there is a lack of recent studies examining the prevalence of depression symptoms among doctors and medical students in the scientific literature, especially in Lithuania. Secondly, we intend to pursue further research aimed at implementing interventions to improve the mental health of medical students and doctors. The results of this research will guide our decision-making regarding which group — whether medical students or doctors — should be prioritized for these interventions.

2.2. PHQ-9

The severity of depressive symptoms was assessed using the Lithuanian version of the PHQ-9. The PHQ-9 is a self-administered instrument that is used for screening depressive symptoms and their severity in the general population. The PHQ-9 is a reliable and valid screening tool, demonstrating high sensitivity and specificity in detecting major depression.[16,17] So far, the PHQ-9 has been widely used in various scientific studies,[18] as well as in the screening for depression in doctors,[19] making it a valuable instrument for comparative analysis of results.

The questionnaire consists of nine questions and an additional patient-rated difficulty item assessing symptom-related impairment. Each answer is rated by the respondent on a 4-point Likert scale, ranging from 0 ("not at all") to 3 ("nearly every day"), reflecting experiences over the previous 2 weeks. Total scores range from 0 to 27, with higher scores indicating greater severity of depressive symptoms. The summed-item scoring method with a threshold of ≥ 10 is favored, as it seems to be a better option than the PHQ-9 algorithm in identifying major depression. When comparing a PHQ-9 cutoff of ≥10 to semi-structured interviews, sensitivity and specificity (95% confidence interval [CI]) were 0.88 (0.82 – 0.92) and 0.86 (0.82 – 0.88), respectively.[20] For major depression screening, we used a cut-off score ≥10. Also, we presented the results by categorizing PHQ-9 scores into the following categories: none (0 – 4), mild (5 – 9), moderate (10 – 14), moderately severe (15 – 19), and severe (20 – 27). Our

survey did not include an additional patient-rated difficulty item.

As we proceeded with our discussion, evaluating the prevalence of depression symptoms compared to data from other countries on doctors' depression, we included a paragraph detailing studies that specifically used the PHQ-9 questionnaire to make comparisons more significant.

2.3. Sociodemographic variables

The questionnaire included demographic data such as gender, age, city size, and group. When selecting gender in the questionnaire, options included female, male, non-binary, or choosing not to say. When comparing PHQ-9 scores between genders, we compared them between men and women, as only two individuals chose non-binary, and one chose not to say. City size options included large cities (>250,000 inhabitants), medium cities (50,000 – 250,000), small cities (<50,000), and rural areas. The average PHQ score was compared between individuals living in large cities and others (medium cities, small cities, and rural areas). The group question allowed selections from medical students, doctors, and others. In the introductory text, we noted that the definition of doctor includes resident doctors.

2.4. Statistical analysis

The statistical analyses were conducted using MS Excel and SPSS v29 software. Given the non-normal distribution of the data, the Mann–Whitney U test was employed to assess differences in the PHQ-9 scores among the two groups. Statistical significance was defined as $P < 0.05$.

3. Results

A total of 146 respondents answered the questionnaire, with 77 identifying as "medical students," 69 as "doctors," and none selecting "other." Among the respondents, 117 (80.1%) were female, 26 (17.8%) were male, two (1.4%) chose the non-binary option, and one (0.7%) preferred not to disclose their gender. The median age of respondents was 24 ± 8.26 (range: 18 – 70 years). Regarding residency, 124 individuals reported living in a large city (more than 250,000 inhabitants), six in a medium-sized city (50,000 – 250,000 inhabitants), nine in a small city (<50,000 inhabitants), and seven in a rural area. The overall mean PHQ-9 score was 9.60 ± 5.93. Table 1 provides an overview of the demographic characteristics of medical students and doctors in this study.

3.1. PHQ-9 scores

A total of 59 (40.4%) respondents scored ≥10, meeting the criteria for depression. Among them, 37 (48.1%) were medical students, and 22 (31.9%) were doctors. The mean PHQ-9 score was 10.49 ± 5.89 for medical students and 8.46 ± 5.52 for doctors, revealing a statistically significant difference between the groups (mean rank: 80.12 vs. 66.11; $P = 0.045$). For gender differences, the mean PHQ-9 was 9.78 ± 6.01 for women and 8.46 ± 4.60 for men. There was no statistically significant difference between genders (female mean rank = 73.29; male mean rank = 66.21; $P = 0.430$). Among medical students, the mean PHQ-9 score for women was 10.86 and for men was 8.69, with no statistically significant difference found between genders (mean rank 39.98 vs. 31.35, $P = 0.198$). Similarly, among doctors, the mean PHQ-9 score for women was 8.52 and for men was 8.23, with no statistically significant difference observed (mean rank = 33.65 vs. 35.46; $P = 0.762$). Regarding residency, 124 individuals answered that they live in large cities and 22 in other areas. No statistically significant difference was found in the PHQ-9 scores between people who live in large cities and those in other areas (mean rank = 73.91 vs. 71.18; $P = 0.780$). Correspondingly, no differences in PHQ-9 were found when comparing medical students ($P = 0.577$) and doctors ($P = 0.181$) living in different locations. Table 2 presents the detailed data on PHQ-9 scores between groups.

Table 1. Demographics of medical students and doctors

Demographics	Medical students	Doctors
Gender, *n* (%)		
Female	63 (81.8)	54 (78.3)
Male	13 (16.9)	13 (18.8)
Non-binary	1 (1.3)	1 (1.4)
Chose not to say	0 (0.0)	1 (1.4)
City size, *n* (%)		
Large city	62 (80.5)	62 (89.9)
Medium city	4 (5.2)	2 (2.9)
Small city	6 (7.8)	3 (4.3)
Rural area	5 (6.5)	2 (2.8)
Median age, years (min – max)	21 (18 – 24)	29 (25 – 70)
PHQ-9 (mean±*SD*)	10.49±5.89	8.46±5.52

Abbreviations: PHQ-9: Patient Health Questionnaire-9; SD: Standard deviation.

4. Discussion

Our study revealed that nearly half of medical students and a third of doctors met the criteria for depression. If we lower the threshold to include scores from five upwards instead of using a cut-off of ≥10, the prevalence would be even higher. These findings are similar to previous research conducted in Lithuania. For example, a study conducted in 2019 discovered that 36% of medical residents and

Table 2. PHQ-9 scores among medical students and doctors

Depression severity	Medical students (*n*=77)	Doctors (*n*=69)
None – minimal (0 – 4), *n* (%)	12 (15.6)	20 (29.0)
Mild (5 – 9), *n* (%)	28 (36.4)	27 (39.1)
Moderate (10 – 14), *n* (%)	18 (23.4)	13 (18.8)
Moderately severe (15 – 19), *n* (%)	11 (14.3)	5 (7.2)
Severe (20 – 27), *n* (%)	8 (10.4)	4 (5.8)
Depression (≥10), *n* (%)	37 (48.1)	22 (31.9)

26% of doctors in Lithuania have depressive symptoms, i.e., a PHQ-9 score ≥10.[21] Our findings are also similar to a study conducted in Lithuania during the COVID-19 pandemic period (December 2020 – February 2021), which reported that 41.6% of medical students and residents had depressive symptoms with a PHQ-9 score ≥10,[22] although our study identified a higher prevalence among medical students. Looking at the 2019 population data in Lithuania, the proportion of people experiencing symptoms of depression was 18.1%. The highest prevalence of depressive symptoms in Lithuania is observed among people aged 75 and over (35%), and the lowest prevalence is among people aged 35 – 44 (11%). The prevalence of depression among people aged 15 – 34 is around 15%.[23] The aforementioned study assessed depressive symptoms using the PHQ-8. Research indicates that there is no difference in the operational attributes between the PHQ-8 and PHQ-9 for distinguishing major depressive disorder.[24] Both PHQ-9 and PHQ-8 exhibit comparable overall scores, with a slight decrease in sensitivity observed with the PHQ-8. However, their specificity remains similar.[25] Nevertheless, it is difficult to draw conclusions due to methodological differences in the studies, as well as the fact that our research was conducted during a different time than the data we presented for the general population of Lithuania. However, we can observe a tendency toward poorer mental health among health-care professionals compared to the general population.

Symptoms of depression among medical students, assessed using PHQ-9 with a cutoff of 10 or higher, vary widely across different countries, ranging from approximately 15 – 64%,[26-29] with the lowest prevalence in Nigeria and the highest prevalence among medical students in Iraq. No gender differences were found in studies conducted in Nigeria, whereas in Nepal, symptoms of depression were more common among women. Our findings are similar to those from European Union countries, such as Poland, where about 50% of medical students exhibited depressive symptoms in 2020,[30] and a study in Greece in 2021 reported a prevalence of 45%, with significantly higher rates among women.[31] Regarding doctors, a similar prevalence to our study was observed in a study conducted in Latvia in 2020, where 25% of doctors exhibited symptoms of depression using the PHQ-9 questionnaire.[32] Similarly, using the same cut-off of ≥10, a study in Malaysia published in 2021 reported that 25% of residents have depression.[33] In contrast, a study conducted in Romania in 2022 reported exceptionally high depression scores among residents, with a prevalence of 73% using the ≥10 cutoff. If we consider depression scores >5, all residents would meet the criteria for depression. In the same study, depression scores for radiologists and infectious disease specialists were 34%. It should be noted that the sample sizes in the mentioned study were small, with only 15 residents surveyed and 35 doctors.[34]

Most of our reviewed cross-sectional studies consisted of research conducted in 2020 – 2021, a similar timeframe to the COVID-19 pandemic. Systematic reviews and meta-analyses conducted during similar periods indicate a lower depression rates among doctors compared to our research. For example, a systematic review and meta-analysis that analyzed the prevalence of depression among doctors globally during COVID-19, including studies conducted until March 2021, found that the pooled prevalence of depression was 21%. One of the conclusions drawn was that while symptoms of depression during COVID-19 are high, they may not be higher than pre-pandemic levels.[35] The lowest score was found among imaging doctors, with a prevalence of depression using the PHQ-9 being <7%. It is important to note that this study excluded doctors with diagnosed mental disorders, which may have contributed to the low prevalence of depression found.[36] The highest prevalence of depression was found among emergency medical doctors. Based on a Hospital Anxiety and Depression Scale score of 11 or higher, the prevalence was 74%.[37] Another systematic review and meta-analysis, which analyzed the prevalence of depression in healthcare workers from December 2019 to September 2020, found that 24% of medical doctors had depression.[38] In this systematic review and meta-analysis, the highest prevalence was found among doctors in China, with a rate of 45% using the Self-Rating Depression Scale.[39] The lowest prevalence was among pediatricians, at 8% using the 21-item Depression Anxiety Stress Scale, but the authors excluded mild depression scores. In the original article, we found that the prevalence is 17% when using a cut-off of ≥10.[40] There is a lack of more recent studies that would have collected data on doctors' depression in 2023 or 2024. Our research shows slightly higher rates of doctor depression than those mentioned in the systematic reviews and meta-analyses during the COVID-19 pandemic period.

Our study revealed that female medical students exhibit slightly higher depression scores compared to males; however, this difference was not statistically significant. In addition, we did not observe a significant disparity in PHQ-9 mean scores between genders within the doctor population. It is important to note that our study involved a small sample of men, which could have influenced the results. Data from the general population often exhibit higher estimates of depression in women.[1] This difference is not unambiguous among doctors. There are studies showing a significant link between female gender and depression in medical students and doctors. For example, a study conducted in Saudi Arabia from December 2021 to January 2022 among 1st- and 2nd-year medical students found statistically significantly higher levels of depression among female medical students.[41] A study conducted in 2019 in China, assessing emergency doctors, also discovered that women were more likely to suffer from depression.[42] In the scientific literature, we can also find results showing no gender differences in depression or a higher prevalence of depression among men than among women. A study conducted in 2020 found no difference in the prevalence of depression between Moroccan male and female medical doctors.[43] A study conducted in Nepal reported higher depression rates among male medical students and proposed that female students' increased involvement in extracurricular activities might have contributed to better stress management, overall mental well-being, and lower depression rates.[44] Further research is needed to better understand the prevalence of depression among genders and related factors.

Specific environmental factors of urbanization, such as social deprivation, air pollution, street networks, and urban land-use density, are positively correlated with poorer mental health.[45] Previous studies indicated that in developed countries, depression is more prevalent in urban areas than in rural ones, while this is not the case in developing countries.[46] In contrast, a study in the United States of America (US) reported that people living in larger urban areas had significantly lower rates of depression.[47] Another study from the US did not find any differences in rates of psychiatric diagnosis between people from rural and urbanized areas.[48] Studies assessing doctors' mental health based on the size of the city in which they live are lacking. Our study showed that doctors living in larger cities were more depressed, although the difference was not statistically significant. However, it would be meaningful to further investigate this aspect in future studies, as there is limited literature on mental health in relation to city size.

Doctors appear to experience depression more often than the general population; yet, the exact causes and barriers to seeking help remain unclear. Out of 316 Pakistani medical students, 44% had a negative attitude toward seeking professional help. When students were asked about barriers to seeking help, social stigma was the most frequently mentioned factor.[49] Beliefs about confidentiality, the impact on career progression, and other convictions can also hinder seeking help.[50] Research indicates that doctors with high rates of anxiety, depression, and stress are more prone to having negative attitudes towards seeking help for their mental health.[51] It is important to find ways to help doctors access mental health services when they feel their mental health is deteriorating. Furthermore, it could be helpful to develop and implement screening models that are not only effective but also acceptable to clinicians. Artificial intelligence could also be used for this purpose; e.g., studies reported that accurate voice recognition of depression can be as high as 90%.[52]

It would be important to further investigate the risk factors for depression among doctors. For instance, a study reported that shorter sleep duration is significantly associated with higher depression and suicidal ideation scores.[53] A study conducted in Egypt reported that 22% of doctors had been diagnosed with psychiatric disorders, with no significant difference in depression prevalence across almost all specialties. They also indicated that doctors with fewer academic degrees tended to exhibit more symptoms of depression.[9] In another study, younger age and employment at a primary care hospital were identified as risk factors.[54] Factors such as longer working hours,[55] living with family members aged ≤16 or ≥65 years,[56] higher work demands, and lower recovery experience[57] could also have an impact on worsened mental health. It is also important to evaluate the risk factors using a cultural lens. For example, a risk factor like neuroticism may be a risk factor in the US population, but it may not increase the risk of depression in the Chinese population.[58] Race/ethnicity can also affect doctors' mental health. In a study examining US doctors, the Hispanic/Latinx, non-Hispanic Black, and non-Hispanic Asian incidence of occupational burnout was lower compared to non-Hispanic White doctors. However, no disparities by race/ethnicity were observed in terms of depressive symptoms or career satisfaction.[59] The exploration of the risk factors for depression among medical students and doctors remains one of the most important directions for further research.

Protective factors should be an area of further research. One study reported that students who initially had high levels of self-efficacy, resilience, and cognitive self-regulation were more likely to be classified as non-depressed.[60] Resilience was also identified as an important factor in addressing depression in another

study conducted with doctors. Researchers found a negative correlation between total resilience scores and depression.[52] Long years of service, specifically more than 20 years of service, are indicated as one of the protective factors in one of the studies.[54] Biological markers, such as telomere length, could serve as helpful tools for identifying stress in health-care professionals. The study reported that during the internship, telomere length significantly shortens, and this shortening is six times greater than typical telomere shortening in other populations. Greater telomere shortening among doctors is associated with longer working hours, a stressful family environment, and neuroticism.[61] The biological and cultural aspects should not be excluded from further research on doctors' health.

It is known that depression rates tend to increase globally. For example, a study conducted in Norway comparing the well-being of medical students in 2015 to those who studied at the same faculty from 1993 to 1999 found that the well-being of students in 2015 was significantly worse.[62] In Lithuania, there is also a trend of increasing depression symptoms, with rates rising from 12.4% in 2014 to 18.1% in 2019.[23] During the COVID-19 pandemic, more cases of depression have emerged globally.[63] To better understand the prevalence of depression among healthcare professionals and compare it with the general population of other countries, it would be important to conduct international studies during the same period and use the same screening instruments.

It is essential to implement effective interventions to improve emotional well-being in medical study programs and healthcare systems. Various educational and skill-building interventions can have a positive impact. One such example is an intervention like the 8-week mindfulness course for doctors, which has been shown to improve patient safety and reduce errors compared to a group of doctors who did not undergo this mindfulness training.[64] Special mobile apps also show a positive effect on the mental health of healthcare professionals. For example, researchers conducting a randomized trial found that a mobile app designed to reduce burnout significantly reduced burnout scores compared to the control group.[65] Future studies should investigate the benefits and effectiveness of implementing interventions aimed at medical students and doctors, as well as combinations of various interventions.

This study encountered several limitations. It is important to acknowledge that the PHQ-9 functions primarily as a self-report screening tool rather than a diagnostic instrument. Therefore, scores exceeding validated thresholds may not always indicate clinically significant depression. Furthermore, the small sample size and the non-random sampling method employed in our study suggest that our data may not fully represent the entire target population. In future studies, it would also be important to categorize and analyze medical students based on their academic years of study. In addition, it would be necessary to separately analyze residents, and it would also be valuable to analyze groups of doctors based on their specialization or age.

5. Conclusion

Half of medical students and one-third of doctors exhibited symptoms of depression. Regular screening for mental health among health-care professionals, along with interventions aimed at improving mental well-being, holds paramount importance within medical education and practice. Recognizing and addressing barriers within the medical community that discourage seeking help and engaging in preventive initiatives are crucial steps toward improving doctors' mental health outcomes and ensuring high-quality care.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: All authors
Formal Analysis: Kamile Pociute
Investigation: All authors
Methodology: All authors
Writing – original draft: Kamile Pociute
Writing – review & editing: Sigita Lesinskiene

Ethics approval and consent to participate

Ethics board approval was deemed not necessary for this study since participation was voluntary, and the research posed no health risks to participants.

Consent for publication

Not applicable.

Availability of data

Data used in this work are available from the corresponding author on reasonable request.

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ORIGINAL RESEARCH ARTICLE

The effect of high-definition transcranial direct current stimulation on pain in somatic symptom disorder with predominant pain: A randomized single-blind sham-controlled crossover study

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Abstract

Somatic symptom disorder with predominant pain (SSD-P) is a commonly encountered disorder, yet treatment options often yield unsatisfactory outcomes. Transcranial direct current stimulation (tDCS) has proven useful in chronic pain conditions and may hold potential for treating somatoform pain. High-definition tDCS (HD-tDCS) offers more precise cortical stimulation than conventional tDCS. However, this modality has not been extensively studied in SSD-P. Consequently, this study aims to assess the effects of a novel HD-tDCS protocol on pain and other associated variables in patients with SSD-P. The Institute Ethics Committee approved the study, which was also registered in the Clinical Trials Registry of India. A single-blind, sham-controlled, crossover study design was employed. Thirty right-handed patients with DSM-5 diagnosis of SSD-P, aged 18 – 60 years and receiving stable treatment, were enrolled through consecutive sampling. After simple randomization, two repeated, short-interval sessions (2 mA, 20 min each) of either active or sham HD-tDCS were administered, followed by a washout period of 7 days and a subsequent crossover. Assessments were conducted at baseline, week 1, and week 2. Participants in active and sham arms were comparable on all baseline parameters. At the end of the 1st week, patients in the active group showed significant improvement in the study variables compared to the sham group. By week 2, all participants, irrespective of being in the active or sham arm, demonstrated a statistically significant difference (Cohen's $d > 0.8$) in pain and associated parameters such as depression, anxiety, pain-related interference, burden, and disability ($P < 0.01$). Transient mild local side effects such as burning, pain, and itching were noted, with no cognitive side effects reported. In conclusion, this novel HD-tDCS protocol is effective in reducing pain in patients with SSD-P, with sustained effects up to 1 week.

Keywords: High definition transcranial direct current stimulation; HD-tDCS; Chronic pain; Somatic symptom disorder; Crossover study, Sham-controlled study

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1. Introduction

Pain can be defined as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.[1] Inadequately explained pain can be classified under the category of somatoform disorders. Somatic

symptom disorder (SSD), as per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), consists of somatic symptoms that are distressing or result in significant disruption in daily life, persisting beyond 6 months.[2] Somatic symptom disorder with predominant pain (SSD-P), a specifier for SSD, has replaced the previous DSM-4 diagnosis of pain disorder, removing the requirement that symptoms should be medically unexplained.[2,3] Although the exact prevalence of SSD-P is not precisely known, it is estimated to affect about 4% of the population and is associated with a significant burden.[4,5] Treatment options for SSD-P are limited and unsatisfactory with regard to effectiveness and convenience.[6] SSD-P is considered difficult to treat due to the challenges associated with existing treatment modalities.[5]

Transcranial direct current stimulation (tDCS) has been utilized to treat various neurological and psychological conditions, including chronic pain.[7,8] tDCS has shown effectiveness in managing chronic pain across different diagnostic categories, with anodal stimulation of the dominant motor cortex or prefrontal cortex being common targets.[7] This effectiveness supports the proposed pathophysiology of pain, which suggests that pain perception and its emotional impact are influenced not only by tissue damage but also by central cortical processing.[9] The choice of cortical targets for tDCS is guided by their accessibility, ease of localization, and the proposed mechanisms of their involvement in painful conditions.[9] Therefore, it is likely that tDCS could be beneficial in most chronic painful conditions, including SSD-P.

There is a lack of consensus in existing protocols, with most studies utilizing conventional tDCS with variable and multiple sessions.[7,10] The effect of a single tDCS administration on chronic pain conditions has been assessed in a few studies and shown to provide significant pain relief.[11-14]

High-definition tDCS (HD-tDCS) is considered an improvement over conventional tDCS due to its more focused application of current and precise targeting of underlying brain regions. However, only a limited number of studies have examined the effect of HD-tDCS on chronic pain,[15,16] and none have studied its impact on SSD-P. In this study, we followed a novel protocol involving a single session of two administrations of HD-tDCS delivered within a 30-min interval. This protocol is a modification of single-session protocols, where it has been observed that delivering two sessions within a short interval (within-session repeated tDCS) results in longer-lasting effects due to increased excitability-induced plasticity.[17] Thus, this proposed protocol may represent a viable treatment modality.

The current study aimed to investigate the feasibility of this protocol on pain and other associated variables such as burden, interference, and disability in SSD-P when compared to sham stimulation.

2. Methods

2.1. Study design and setting

In this study, we employed a single-blind, sham-controlled, crossover design, which is advantageous compared to the parallel-group design because patients act as their own controls. This study design allows for a lower number of participants and greater homogeneity among study subjects. The treatment periods were separated by a washout period of 7 days. The study subjects were recruited from November 2020 to May 2021 from the outpatient clinic of the Department of Psychiatry and Neurology at a tertiary care hospital in North India. Approval was obtained from the Institute Ethics Committees where this study was conducted (INT/IEC/2020/SPL-481). The study was registered in the Clinical Trials Registry of India (CTRI/2020/10/028752). Figure 1 presents the flowchart of the study design.

2.2. Inclusion criteria

Right-handed patients of either gender, diagnosed with SSD-P as per DSM-5, aged 18 – 60 years, who provided written informed consent and were already receiving any form of stable treatment (defined as no change in treatment over the preceding 3 months), were approached for inclusion in the study. Patients who consented were included after obtaining written informed consent. The HD-tDCS sessions were an add-on to existing treatment, and no other changes were made to the treatment being received for the duration of the study.

2.3. Exclusion criteria

Patients who did not consent to participate in the study, those diagnosed with Parkinson's disease, organic brain syndrome, intellectual disability or dementia, head injury, uncontrolled epilepsy, encephalopathy due to any cause, substance dependence disorder other than tobacco dependence, presence of other cross-sectional or lifetime comorbid psychiatric disorders (except for a cross-sectional diagnosis of an anxiety or depressive disorder), and pregnant females were excluded from the study.

In view of the crossover design and as per the available data on the analgesic benefit of tDCS,[18] it was calculated that a total of 36 participants (18 per group randomized to the active tDCS or the sham tDCS conditions) would be needed to detect an effect (alpha = 0.05, effect size $f = 0.25$, correlation among repeated measures = 0.5) with adequate

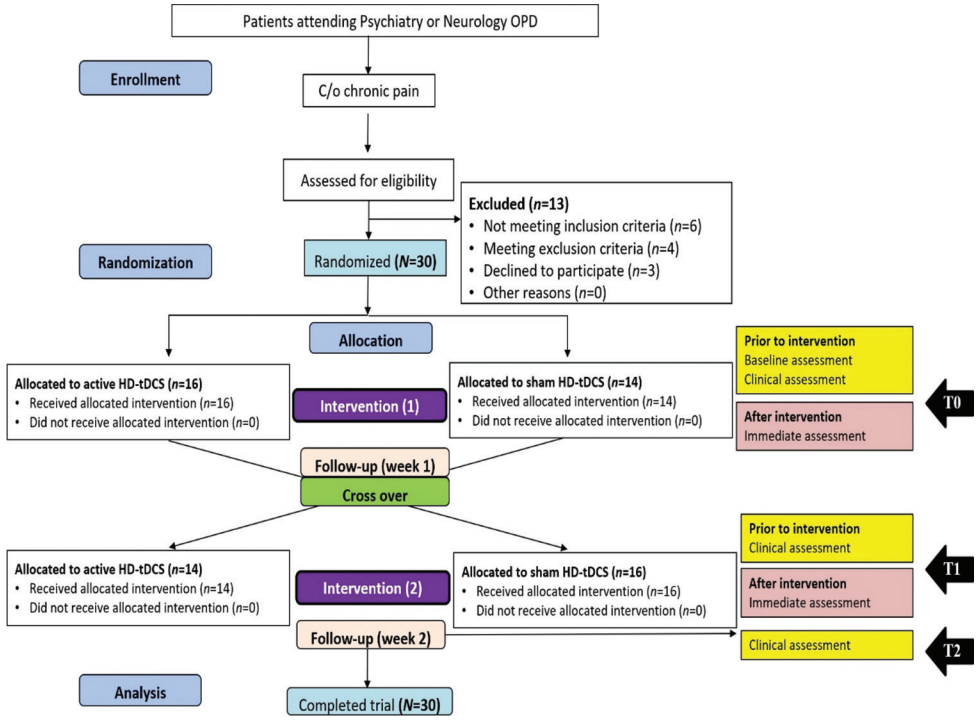

Figure 1. Flow diagram of the participant recruitment process. T0, T1, and T2 represent the times of measurements at baseline, week 1, and week 2, respectively

Abbreviations: C/O Chronic pain: Complaints of chronic pain; HD-tDCS: High-definition transcranial direct current stimulation; OPD: Outpatient department.

power (1-β = 0.95). Due to the COVID-19 pandemic and lockdown, we could only recruit a sample size of 30 patients. The corrected sample size was approved by the Institute Ethics Committee.

2.4. Assessments

A baseline assessment was conducted at the point of entry into the study. It consisted of sociodemographic and clinical profiles, and handedness determined by the Edinburgh Handedness Inventory.[19]

Clinical assessments were performed immediately before the commencement of the HD-tDCS session. These assessments included (i) pain evaluation using the numerical rating scale (NRS)[20] and the Brief Pain Inventory-Hindi version (BPI-H),[21] (ii) assessment of depressive and anxiety symptoms using the Patient Health Questionnaire-9 and Generalized Anxiety Disorder 7 Scale,[22] (iii) assessment of burden and disability due to pain on Somatic Symptom Scale-8[23] and Pain Disability Index 7,[24] and (iv) cognitive functions assessment using the Mini–Mental State Assessment.[25] Furthermore, the Clinical Global Impression (CGI) and Patient Global Impression of Change (PGIC) scales were applied to assess overall severity and improvement after the intervention.[26] These assessments were conducted at three-time points: at baseline (week 0 or T0), at the end of week 1 (T1), and at the end of week 2 (T2).

An immediate assessment was conducted to assess the perception of active or sham stimulation received and to monitor side effects using the tDCS side effect checklist.

2.5. Intervention

The intervention consisted of a single session with two administrations of HD-tDCS, each lasting 30 min and separated by a 30-min interval. Patients entering the active first stage received repeated active HD-tDCS administrations or vice-versa. A 1×4 montage was employed, with one anode positioned in the center and four cathodes placed two inches from the anode in a ring pattern. The anode was placed over F3 using the 5 cm rule (5 cm anterior to the motor hotspot detected by a single pulse of transcranial magnetic stimulation). We used a transcranial magnetic stimulator (Rapid^2, Magstim, United Kingdom) with an air-cooled, air-film, figure-of-eight coil for the transcranial magnetic stimulation. The point of the motor hotspot was defined as the region on the scalp that, when stimulated, would lead to a visible contraction of the abductor pollicis brevis muscle of the right hand. The intervention was carried out using the Soterix 1 × 1 tDCS stimulator (Soterix Medical Inc., United

States) with a 4 × 1 adaptor. An adult HD cap was used to hold the electrodes in place. The proprietary HD-tDCS electrodes (1.2 cm external diameter) fitted in the HD electrode holders supplied with the device were used for the interventions.

In the active phase, a 2 mA current was delivered after a ramp-up time of 30 seconds. In the sham phase, there was a brief period of stimulation in which the patient would have a sensation of current flowing, but no actual current flow would occur. The intervention consisted of one session of repeated active or sham HD-tDCS administration, followed by a washout period of 1 week. After this period, the patients entered the sham or active phase of the study, respectively. Thus, each patient received both active and sham stimulation by the end of 2 weeks.

2.6. Randomization

A consecutive sampling technique and simple randomization were utilized. Eligible patients were randomized in a 1:1 allocation ratio by computer-assigned random allocation to one of two treatment arms: active or sham HD-tDCS and concealed in sealed envelopes. The random allocation sequence was generated by one of the authors, while another author was responsible for enrolling participants and assigning them to the treatment sequence. Patients were blinded to the treatment sequence. Due to the reduction in sample size, 16 patients were allocated to the active followed by the sham treatment arm (Group A), and 14 patients were allocated to the sham followed by the active treatment arm (Group B).

2.7. Analysis

Descriptive analysis in terms of frequencies, means, and standard deviations, as well as Chi-square tests for ordinal data and *t*-tests for normally distributed data, was employed. Repeated measures analysis of variance (ANOVA) was employed to test the hypothesis regarding the effect of HD-tDCS on the pain scores, with treatment order (active-sham versus sham-active), treatment condition (active versus sham), and time (baseline, immediately after stimulation, and at follow-ups) as the independent variables. Analysis of covariance (ANCOVA) was applied to test the interaction of order and treatment group. ANCOVA test was chosen as it has been considered to increase the statistical power of crossover studies, as in this case. ANCOVA improves precision and avoids bias in the widest set of circumstances.[27] In addition, our scores were measured across three-time points. Statistical analysis was conducted using SPSS software version 21.

3. Results

3.1. Sociodemographic and clinical profile

Table 1 presents the sociodemographic and clinical profile of the participants in the study, comparing those entering the active arm first to those entering the sham arm first. The two groups were largely comparable.

Overall, a majority of the participants were female (~70%) and had moderate-to-severe somatic symptoms. Comorbid physical conditions were observed in one-fourth of the patients, with the most common being hypertension, followed by diabetes and hypothyroidism.

Males and females across the two groups were statistically comparable on baseline sociodemographic

Table 1. Sociodemographic and baseline clinical profile of Group A (active followed by sham) and Group B (sham followed by active)

Variable	Group A (*n*=16)	Group B (*n*=14)	*P*-value
Age (years)	40.44 (8.93)	39.29 (11.18)	0.75
Education (years)	11.00 (5.81)	10.64 (7.26)	0.88
Gender			0.41
Male	3 (18.7%)	5 (35.7%)	
Female	13 (81.3%)	9 (64.3%)	
Duration of illness (years)	8.44 (5.27)	8.71 (7.28)	0.90
DSM-5 severity of somatic symptoms			0.56
Mild to moderate	11 (68.8%)	9 (64.3%)	
Severe	5 (31.2%)	5 (35.7%)	
Comorbid physical diagnosis	4 (25.0%)	4 (28.6%)	0.90
Comorbid substance use (alcohol)	0 (0%)	3 (21.5%)	0.05
NRS	7.50 (1.97)	8.42 (1.65)	0.44
BPI-H (average pain)	7.00 (1.75)	7.71 (2.02)	0.87
BPI-H (interference)	6.10 (2.22)	7.09 (1.63)	0.34
GAD-7	12.12 (6.30)	12.71 (4.97)	0.64
PHQ- 9	13.12 (6.37)	14.28 (4.76)	0.23
SSS- 8	17.56 (8.79)	17.14 (8.06)	0.44
PDI-7	38.31 (11.92)	41.35 (18.78)	0.23
MMSE	29.62 (0.81)	29.85 (0.53)	0.63
CGI-S	4.06 (0.77)	4.07 (0.83)	0.45

Notes: Results are expressed in frequency (%) or mean (SD); Significant level was set at $P<0.05$.
Abbreviations: BPI-H: Brief Pain Inventory-Hindi version: CGI-S: Clinical Global Impression-Severity: GAD-7: Generalized Anxiety Disorder 7 Scale: MMSE: Mini-Mental State Assessment; NRS: Numerical Rating Scale; PDI-7: Pain Disability Index 7; PHQ-9: Patient Health Questionnaire 9; SSS-8: Somatic Symptom Scale-8.

and clinical scores. Pain was often widespread, involving more than one region. The most commonly reported sites were the head (60%), lower limbs (73.3%), back (50%), neck (40%), upper limbs (46.7%), and shoulders (33.3%). The distribution of patients between the two groups was statistically similar.

3.2. Comparison of active versus sham stimulation

The outcome of active stimulation compared to sham stimulation (N = 30) is summarized in Table 2. The mean pain scores demonstrated statistically significant differences between the active and sham groups on NRS and BPI. Measures of interference due to pain, anxiety, depressive symptoms, burden, and disability due to pain also showed statistically significant differences between the active and sham groups. However, there was no difference in cognitive function scores between the groups. The study was not powered to analyze the differential impact of the intervention across different regions of maximum pain. The improvement in pain scores persisted for at least 1 week, as seen in Figure 2 (at T2 in the patients in Group A). We also could not find the differential impact of the intervention on any specific pain region.

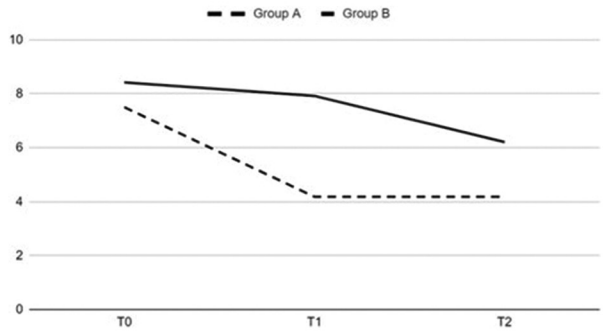

Figure 2. The outcome of pain on a numerical rating scale of groups A (active first) and B (sham first). T0, T1, and T2 represent the times of measurements at baseline, week 1, and week 2, respectively.

3.3. Side effect profile

Table 3 summarizes the side effects observed in both groups. Statistically significant differences were found between active and sham stimulation for burning and pain, but not for itching. No severe side effects, such as insomnia, acute mood changes, or changes in visual perception, were noted.

3.4. Impact of intervention order on the effects of stimulation

A one-way ANCOVA was conducted to examine the interaction of the order of intervention (active followed by sham and sham followed by active) on the pain outcome on the NRS at T2. The error of variance across the groups was equal as per Levene's test of equality, meeting the homogeneity of variances assumption. The impact of the order of intervention by treatment group interaction was not statistically significant ($F^{[1}$,55] = 2.136; P = 0.150), indicating that the order in which the patients entered the study did not affect the outcome at T2.

As shown in Table 4, when the entry status of active and sham stimulation was considered, there was no statistically significant difference between T0 and T2 scores in both Groups A and B on the NRS. However, there was a statistically significant difference between T0 and T1 scores in group A only and between T1 and T2 in group B

Table 2. Outcome of pain and other associated scores in active versus sham groups

Outcome variables	Paired differences				*t*-value	*P*-value
	Mean (*SD*)	*SE* of mean	95% confidence interval of the difference			
			lower	upper		
NRS	−0.80 (0.99)	0.182	−1.172	−0.428	−4.397	<0.01*
BPI-H (average pain)	−0.56 (0.93)	0.171	−9.159	−0.217	−3.319	<0.01*
BPI-H (interference)	−0.56 (0.77)	0.135	−0.845	−0.288	−4.171	<0.01*
GAD-7	−1.53 (2.43)	0.444	−2.441	−0.625	−3.454	<0.01*
PHQ-9	−1.66 (2.88)	0.526	−2.742	−0.591	−3.169	<0.01*
SSS-8	−2.00 (3.02)	0.553	−3.131	−0.869	−3.617	<0.01*
PDI-7	−3.03 (4.15)	0.758	−4.585	−1.481	−3.997	<0.01*
MMSE	0	0	-	-	-	-

Note: *P<0.05.

Abbreviations: BPI-H: Brief Pain Inventory-Hindi version; CGI-S: Clinical Global Impression-Severity; GAD-7: Generalized Anxiety Disorder 7 Scale; MMSE: Mini–Mental State Assessment; NRS: Numerical Rating Scale; PDI-7: Pain Disability Index 7; PHQ-9: Patient Health Questionnaire 9; SSS-8: Somatic Symptom Scale-8.

Table 3. Frequency and types of side effects experienced after active versus sham stimulation

Side effects checklist	Active stimulation (*N*=30)	Sham stimulation (*N*=30)	Chi-square value (*P*-value)
Itching at the stimulation site	9 (30.0%)	6 (20.0%)	0.813 (0.371)
Burning at the stimulation site	25 (83.3%)	12 (40.0%)	11.915 (<0.01)*
Pain at the stimulation site	16 (53.3%)	7 (23.3%)	5.711 (0.016)*

Note: The results are expressed as frequency (%); *P<0.05.

Table 4. Outcome of pain on the NRS of Group A (active first followed by sham) and Group B (sham first followed by active)

Group	Mean (*SD*)			Repeated measures ANOVA	T0 versus T2		T0 versus T1		T1 versus T2	
	T0	T1	T2	*P*	Mean difference (*SE*)	*P*	Mean difference (*SE*)	*P*	Mean difference (*SE*)	*P*
A (*n*=16)	7.50 (1.97)	4.18 (2.29)	4.18 (2.29)	<0.01*	3.313 (0.405)	<0.01*	3.313 (0.405)	<0.01*	0 (0)	-
B (*n*=14)	8.42 (1.65)	7.92 (2.02)	6.21 (2.22)	<0.01*	2.214 (0.334)	<0.01*	0.500 (0.292)	0.331	1.714 (0.194)	<0.01*

Notes: *P<0.05; T0, T1, and T2 represent the times of measurements at baseline, week 1, and week 2, respectively.
Abbreviations: η_p^2: Partial eta-squared; MD: Mean difference; NRS: Numerical rating scale; N: Total number; p: *P*-value; SD: Standard deviation; SE: Standard error; T0: Baseline value; T1: Week 1 value; T2: Week 2 value; ANOVA: Analysis of variance.

only. The same pattern was observed for all other outcome measures on repeated measures ANOVA.

The outcome at T2 was comparable in groups A and B, owing to the persistence of changes in Group A patients. This finding indicates that the intervention caused benefits that persisted for at least 1 week following active HD-tDCS administration.

Notably, we could not find any differential effect of gender on changes in scores across different time points.

3.5. Global improvement

Clinician-rated global improvement on the CGI-Efficacy Index at T1 showed a statistically significant difference between active and sham stimulation but no statistically significant difference at T2. Similarly, patient-rated global improvement on PGIC at T1 showed a statistically significant difference between active and sham stimulation but no statistically significant difference at T2.

4. Discussion

To our knowledge, this study is one of the first studies investigating the effects of HD-tDCS on pain in SSD-P. Patients were on a stable dose of pharmacological treatment for at least 3 months before recruitment for HD-tDCS as an add-on therapy. Although our primary focus was on the effect on pain, a host of secondary outcomes such as interference due to pain, burden due to somatic symptoms, depressive symptoms, anxiety symptoms, disability due to pain, and cognitive features was also assessed using standard rating scales, providing a holistic approach to pain.

A crossover study design was employed, which is recommended and commonly utilized in trials on pain treatment and is known to reduce between-patient variability.[28] Moreover, permuted block randomization was conducted to rule out any potential bias due to the order of active or sham stimulation.[29] In addition, a one-way ANCOVA with order as a covariate showed no interaction of order and group. Blinding was ensured, as patients were unable to discern above chance (P = 0.20) whether they had received active or sham stimulation. The ramp-up and ramp-down at the beginning and end, respectively, of sham stimulation simulate active stimulation, making the patient perceive the sensation of current flowing.[30] There was no statistically significant difference between patients blinded to the active and sham groups at entry on any of the sociodemographic or clinical parameters, eliminating any possible confounder bias between the groups at their entry into the study.[29]

Differences between the groups as per entry status at T0 versus T1 in the first active group and T1 versus T2 in the first sham group show that only active intervention had any impact on reducing pain scores when given first or second, irrespective of order. Sham stimulation given either as the first or second session showed no significant differences in the outcome parameters. This finding could also indicate that in the group receiving active stimulation, there was no carryover effect when sham stimulation was provided.

Apart from the use of HD-tDCS, focal stimulation was also ensured by single-pulse transcranial magnetic stimulation-aided marking of the left motor cortex. When two within-session repeated HD-tDCS administrations

were delivered, we observed sustained effects that lasted for 1 week. This effectiveness was demonstrated in other studies, which showed that sustained effects could be observed only with short interval within-session repeated tDCS but not with longer intervals (beyond 2 – 3 h)[31] or with the use of higher amplitudes (3 mA).[32] The sustained effects are said to be due to stimulation-timing-dependent plasticity regulation in the cortex.[33] We observed a high Cohen's *d* of 0.85 for the reduction in pain and other associated variables, indicating that our protocol is effective.

Patients experienced short-lasting side effects of mild-to-moderate intensity, similar to other studies on tDCS.[34] No cognitive or other serious side effects were observed. The specialized electrodes used in HD-tDCS ensure precise control of contact conditions, unlike conventional tDCS, indicating that HD-tDCS is well tolerated.[16]

Our study offers several significant reference values for future studies. As mentioned earlier, this study is among the first to investigate the effects of HD-tDCS on pain in SSD-P. A simple protocol of two repeat sessions of HD-tDCS was administered. A holistic approach, using standard assessment rating scales, was employed to evaluate pain and its associated variables. The study was feasible, as it was completed within a 1-year period, and there were no dropouts, thus demonstrating its acceptability. Potential biases due to blinding, allocation, baseline patient characteristics, order effect, or carryover effect were ruled out.

However, the use of a crossover study design, although recommended for trials of pain treatment, may introduce bias. The study's limitations include a small sample size, which was further reduced due to the COVID-19 restrictions and lockdown, and the use of single blinding.

5. Conclusion

The study demonstrates that two within-session repeated HD-tDCS administrations are effective and tolerable for reducing pain and other associated variables in SSD-P, with effects sustained for a week. There is a need for studies exploring multiple single-session protocols and comparing them to develop an optimal protocol. Formulating maintenance protocols that extend plasticity for longer periods, thereby improving quality of life, would benefit patients. In addition, more studies evaluating parameters other than pain are required to obtain a holistic understanding of the effectiveness of neuromodulation.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Shubh Mohan Singh, Abhishek Ghosh
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Ethics approval and consent to participate

Approval was obtained from the Institute Ethics Committees where this study was conducted (INT/IEC/2020/SPL-481). The study was registered in the Clinical Trials Registry of India (CTRI/2020/10/028752). Patients who consented were included after obtaining written informed consent.

Consent for publication

The patients gave consent to publish their data in this study.

Availability of data

Data used in this work are available from the corresponding author upon reasonable request.

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ACCSCIENCE PUBLISHING

Journal of Clinical and Basic Psychosomatics

CASE REPORT

Hashimoto's thyroiditis presenting solely with psychotic symptoms: A case report

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Abstract

This case report highlights the infrequent occurrences of myxedema psychosis and pituitary hyperplasia as secondary complications of Hashimoto's thyroiditis. The subject of interest is a 16-year-old female patient who displayed persistent symptoms of delusions, auditory hallucinations, and depression without any discernible cause. The physical examination did not reveal any notable abnormalities. Despite a continuous 4-week treatment regimen involving antipsychotic and antidepressant medications, the patient experienced a deterioration of psychotic symptoms, which resulted in substantial impairment in social functioning. Cranial magnetic resonance imaging scan detected an enlarged pituitary gland and laboratory tests indicated abnormal thyroid function and the presence of specific thyroiditis autoantibodies. Combined with these results, thyroid ultrasound findings revealed features that were consistent with Hashimoto's thyroiditis. Consequently, the patient was prescribed levothyroxine sodium replacement therapy, as well as low-dose antipsychotic and antidepressant medications, which led to a gradual amelioration of their psychotic symptoms. Following 6 months of treatment, the patient was ordered to stop taking the antipsychotic and antidepressant drugs but continue with levothyroxine sodium replacement therapy exclusively. The results of the 1-year follow-up demonstrated the restoration of thyroid function to normal levels, the normalization of pituitary size and structure, and the absence of any psychotic symptoms. These findings provide evidence for a diagnosis of myxedema psychosis and secondary pituitary hyperplasia caused by hypothyroidism associated with Hashimoto's thyroiditis. This emphasizes the significance of supplementary tests in the diagnostic procedures carried out by psychiatrists.

Keywords: Hashimoto's thyroiditis; Myxedema psychosis; Secondary pituitary hyperplasia; Hypothyroidism; Psychotic symptoms

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1. Introduction

Hashimoto's thyroiditis is an autoimmune disease characterized by a gradual onset and slow progression, leading to hypothyroidism. While the mental health implications of hypothyroidism, such as depression and cognitive impairments, are well documented, the presence of positive symptoms is rarely reported. Myxedema psychosis (MP), a rare complication of Hashimoto's thyroiditis associated with hypothyroidism, can

present with psychotic symptoms, such as delusions, changes in drive and activity, formal thought disorders, and perceptual abnormalities. These symptoms may be misdiagnosed as schizophrenia.[1-4] In addition, elevated levels of thyroid-stimulating hormone (TSH) in individuals with Hashimoto's thyroiditis can lead to the proliferation of TSH-releasing cells, resulting in secondary pituitary hyperplasia associated with primary hypothyroidism (PHPH). This rare complication of hypothyroidism, stemming from Hashimoto's thyroiditis, poses difficulties in radiological assessments used to differentiate it from pituitary adenoma.[5] The atypical clinical presentations of both MP and PHPH further complicate the diagnostic process.

2. Case presentation

This case involves a 16-year-old female adolescent who began experiencing symptoms of sensitivity and paranoia, accompanied by auditory hallucinations, approximately 2 months before seeking medical consultation in the Department of Psychosomatic and Psychiatry, Zhongda Hospital, School of Medicine, Southeast University, China. The patient perceived that her classmates at school targeted her due to jealousy of her talents, manifesting their animosity through behaviors such as coughing and spitting. Subsequently, the patient reported hearing multiple voices discussing her actions and predominantly criticizing her with malice. The hallucinations experienced by the patient were accompanied by a pervasive feeling of being under surveillance, resulting in increased levels of anxiety and nervousness. It is noteworthy that the patient did not attribute these symptoms to psychosis. Despite persisting for a period of 2 months, the patient's delusions and auditory hallucinations did not show obvious improvement. In addition, the patient displayed the onset of depressive symptoms, such as a depressed mood, reduced interest and pleasure, decreased appetite, and insomnia. Consequently, the individual's parents sought medical intervention for her condition.

The psychiatrist in the outpatient unit thoroughly evaluated the potential diagnosis of schizophrenia, considering the lack of pre-existing psychiatric or chronic medical conditions, as well as the absence of any history of substance abuse. Despite receiving consistent outpatient care with lurasidone (40 mg/day) and sertraline (50 mg/day) for the past 4 weeks, the patient did not manifest improvement in psychotic symptoms. In addition, new symptoms have emerged, such as a heightened perception of public surveillance and home monitoring through electronic devices. These symptoms significantly hindered her ability to engage in academic pursuits, resulting in her admission as an inpatient.

A comprehensive clinical assessment demonstrated normal findings, with no abnormalities noted in the skin or mucous membranes. The cranial nerves were intact, showing no signs of dysfunction. The neck exhibited normal flexibility without any evidence of rigidity. Cardiopulmonary auscultation revealed unremarkable results. There were no observed cases of limb edema, and muscle strength and tone were maintained. Physiological reflexes were within expected ranges, suggesting the absence of pathological signs. The psychiatric evaluation revealed intact consciousness, full orientation, the presence of significant auditory hallucinations involving a group of people commenting and criticizing the subject's behaviors and speech, delusions related to interpersonal interactions and victimization, along with symptoms suggestive of depression. In accordance with the International Classification of Diseases 11th Revision (ICD-11), the initial diagnosis upon admission was 6A20.0: schizophrenia, first episode. Following the cranial magnetic resonance imaging (MRI) scan, it was observed that the pituitary gland had enlarged, measuring 1.4 × 1.4 × 1.5 cm, and exhibited superior protrusion with T1 high signal intensity in the neurohypophysis, indicating a high probability of pituitary adenoma. The assessment of thyroid function revealed notably reduced levels of FT3 and FT4, accompanied by TSH levels surpassing 100 μIU/mL. Furthermore, there was a significant elevation in thyroglobulin antibody, thyroid peroxidase antibody (TPOAb), and thyrotrophin receptor antibody (TRAb). The thyroid ultrasonography results revealed heterogeneous thyroid echogenicity with multiple nodules categorized as C-TI-RADS category 3. All measured parameters, including plasma cortisol, serum prolactin levels, ACTH rhythm test results, and growth hormone measurements, fell within the normal range. Moreover, blood, urine, and stool analyses, along with biochemical indices, as well as electrocardiogram and electroencephalogram examinations, exhibited no abnormalities. In addition, both the humoral immune-specific protein tests and the 13-item antinuclear antibody panel did not detect any anomalies.

In light of the findings described above, the endocrinologist considered Hashimoto's thyroiditis as the potential diagnosis and recommended the initiation of levothyroxine sodium replacement therapy without adjusting the dosages of lurasidone and sertraline. After 4 weeks of treatment, the patient showed improvement in both psychiatric symptoms and thyroid function, which led to a decision to discharge the patient from medical care through mutual agreement between the patient and psychiatrist. In accordance with the ICD-11, the discharge diagnosis encompassed the following: (1) 6E61: Secondary psychotic syndrome? The patient initially presented with

Hashimoto's thyroiditis (5A03.20) and pituitary hyperplasia secondary to hypothyroidism (5A61.Y). Subsequent follow-up assessments revealed a progressive amelioration in thyroid function and pituitary morphology, which led to the remission of psychotic manifestations. The levels of thyroid-related antibodies exhibited a gradual decline but did not attain the standard range. At that time, the patient had achieved complete restoration of thyroid function, and the dimensions and configuration of their pituitary gland had reverted to baseline. The maintenance therapy of levothyroxine sodium was being continued, while the medications lurasidone and sertraline were discontinued after 6 months of initial treatment due to the absence of psychotic symptoms. The final diagnosis, according to ICD-11, includes: (1) 5A03.20: Hashimoto's thyroiditis; (2) 6E61: secondary psychotic syndrome-myxedema psychosis; and (3) 5A61.Y: other specified hypofunction or disorders of the pituitary gland-pituitary hyperplasia secondary to hypothyroidism (PHPH). Table 1 presents the thyroid function and MRI results during treatment and follow-up, along with the corresponding thyroid hormone dosage. In addition, Figure 1 illustrates the changes in pituitary MRIs before and after levothyroxine sodium replacement therapy.

3. Discussion

The initial treatment plan for the patient involved a 4-week regimen of combination therapy using antipsychotic and antidepressant medications. However, this period saw a deterioration of psychotic symptoms, characterized by delusions of victimization and a further decline in social functioning. Given the patient's condition, hospitalization was considered a more advantageous approach to facilitate thorough evaluations and determine a definitive diagnosis.

The patient was admitted to the hospital and diagnosed with Hashimoto's thyroiditis after undergoing pertinent examinations. During the initial outpatient consultation, this patient was exclusively treated with antipsychotics and antidepressants for a period of 4 weeks. Nevertheless, her psychotic symptoms deteriorated under this treatment regimen. Consequently, levothyroxine sodium replacement therapy was initiated in conjunction with the same therapeutic dosage of antipsychotics and antidepressants. As a result, the patient exhibited significant improvement in psychotic symptoms alongside enhanced thyroid function, leading to complete remission. Furthermore, the lack of relapse post-discontinuation of psychotropic medication suggests a strong correlation between thyroid hormone levels and the presentation of psychotic symptoms. Given its prevalence as a causative factor for psychiatric impairments in individuals with Hashimoto's thyroiditis, Hashimoto's encephalopathy assumes considerable importance as a crucial differential diagnosis. Hashimoto's encephalopathy typically presents with a range of neurological manifestations, including ataxia, myoclonus, aphasia, tremor, seizures, and abnormal electroencephalography findings, which are observed in approximately 98% of patients. It is worth noting that patients with this condition do not typically respond to levothyroxine sodium replacement therapy but instead show improvement when treated with steroid therapy.[6] In this case, the patient displayed no clinical manifestations consistent with Hashimoto's encephalopathy, had a normal electroencephalogram, and showed improvement after receiving levothyroxine sodium replacement therapy. As a result, the diagnostic criteria for Hashimoto's encephalopathy were not fulfilled.

Subsequently, the patient's psychiatric symptoms were attributed to MP after excluding Hashimoto's encephalopathy. The initial report of MP was documented by Asher in 1949, encompassing manifestations such

Table 1. Thyroid function, thyroid hormone doses, and MRI findings at diagnosis and during follow-up

Variable	At diagnosis	Time interval			Last visit
		3 m	6 m	12 m	
TSH (mIU/L)[a]	>100	>100	5.77	2.57	0.35
FT4 (pmol/L)[b]	1.70	9.90	16.3	20.2	21.6
FT3 (pmol/L)[c]	1.04	2.92	4.17	4.46	4.48
TGAb (IU/mL)[d]	333	274	-	279	-
TPOAb (IU/mL)[e]	>600	529	-	525	-
TRAb (IU/L)[f]	>40	>40		-	
Thyroxine treatment (μg)	12.5	100	100	100	100
Pituitary MRI (cm)	1.4×1.4×1.5	-	0.9×0.8×0.9	Normal	Normal

Notes: [d]0 – 115 IU/mL; [e]0 – 34 IU/mL; [f]0 – 1.75 IU/L.
Abbreviations: FT3: Free triiodothyronine; FT4: Free thyroxine; MRI: Magnetic resonance imaging; TGAb: Thyroglobulin antibody; TPOAb: Thyroid peroxidase antibody; TRAb: Thyrotrophin receptor antibody; TSH: Thyroid-stimulating hormone.

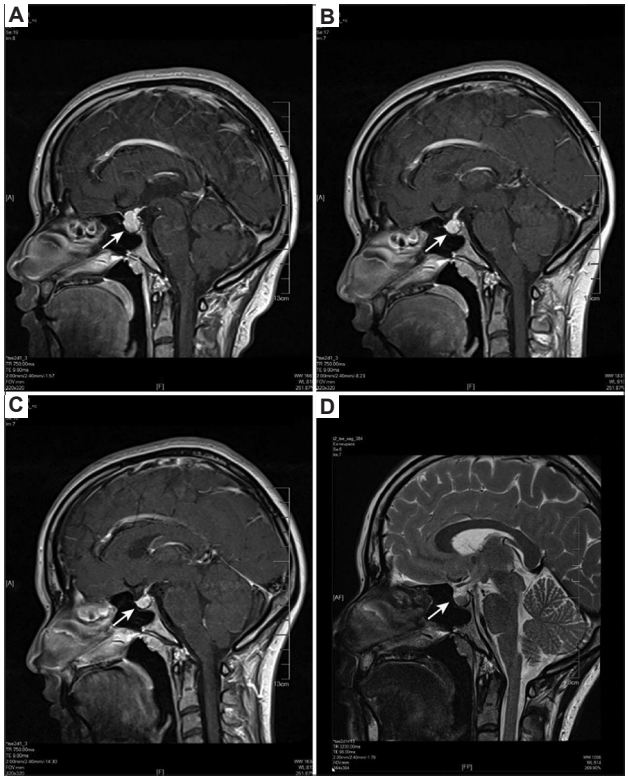

Figure 1. Sagittal brain magnetic resonance imaging (MRI) in patients before and after treatment. (A) Pre-treatment pituitary MRI scan with contrast enhancement. (B) Pituitary MRI scan with contrast enhancement after 6 months of levothyroxine sodium replacement therapy. (C) Pituitary MRI scan with contrast enhancement after 1 year of treatment. (D) MRI scan of the pituitary gland during the final visit.

as delusions, visual and auditory hallucinations, loose associations, and paranoia.[7] Despite significant advancements in our understanding of hypothyroidism diagnostics and treatment, our knowledge regarding the optimal management strategies for patients with MP has stopped expanding since Asher first described the proper treatments for this group of patients. At present, the complete understanding of the pathophysiological mechanisms linking MP and Hashimoto's thyroiditis remains elusive. Potential factors contributing to this association include dysregulation of tyrosine hydroxylase in the anterior lobe of the blue-spot, upregulation of T3 receptors in the amygdala and hippocampus, disturbances in serotonin-mediated neurotransmission, as well as compromised regional cerebral blood flow and glucose metabolism in Hashimoto's thyroiditis patients.[8,9] It is important to note that while MP may be associated with hypothyroidism, many patients with MP do not display the typical physical manifestations of hypothyroidism in the clinical context. After examining 71 case reports of MP published from 1980 to 2019, a recent study found that only 25% of MP cases displayed non-indented peripheral edema and approximately 26 – 37% exhibited no somatic symptoms.[10] This lack of typical symptoms can potentially lead to misdiagnosis.

The patient's MRI revealed an enlarged pituitary gland, suggesting a pituitary adenoma. Among adenomas, prolactinomas represent the most prevalent type, characterized by elevated prolactin (PRL) levels (>200 ng/mL). Patients with pituitary prolactin adenomas may present with hypothyroidism, but their TSH levels remain unaltered despite reduced plasma FT3, FT4, T3, and T4. In this particular instance, the patient exhibited normal PRL levels yet displayed notably elevated TSH levels in conjunction with heightened TPOAb and TRAb levels. The thyroid ultrasonography revealed heterogeneous echogenicity and the presence of multiple nodules. Consequently, these current findings strongly suggest that the abnormal thyroid function is more indicative of hypothyroidism caused by Hashimoto's thyroiditis. After the initiation of levothyroxine sodium replacement therapy, a progressive normalization of pituitary size was observed in conjunction with enhanced thyroid function, providing additional evidence of a significant relationship between pituitary hyperplasia and Hashimoto's thyroiditis. The enlargement of the pituitary gland may be linked to primary hypothyroidism as a rare complication of Hashimoto's thyroiditis.

The initial diagnostic imaging report indicated the potential presence of pituitary adenoma in our patient; nevertheless, we cast doubt on this diagnosis based on their neuroendocrine findings. Subsequent follow-up and administration of levothyroxine sodium replacement therapy ultimately confirmed the inaccuracy of the initial diagnosis of pituitary adenoma. The enlarged pituitary gland should be regarded as PHPH based on the patient's imaging, endocrine examination, and treatment follow-up findings. Adult PHPH was first recognized by Niepce in 1851, and similar cases were subsequently reported, but it is uncommon in children, with only relevant 18 cases reported thus far. MRI findings of PHPH typically show an enlarged pituitary gland with prominent uniform enhancement on scans.[11] Hashimoto's thyroiditis is the most common cause of hypothyroidism in children and adolescents. PHPH is a consequence of reduced thyroid hormone levels in hypothyroidism, resulting in diminished negative feedback from the thyroid hormone to the hypothalamus. This leads to excessive secretion of thyrotropin-releasing hormone and proliferation of TSH-secreting cells.[12] The clinical manifestations of PHPH encompass various symptoms associated with hypothyroidism such as fatigue, cold sensation, and myxedema, along with menstrual disorders, galactorrhea, infertility, and other symptoms caused

by elevated PRL levels. However, these specific clinical signs were not observed in this patient's case, increasing the possibility of misdiagnosis. Misidentifying PHPH as a pituitary tumor followed by surgical intervention can have significant adverse consequences including lifelong hormone replacement therapy requirement and substantial deterioration in the patient's quality of life. Therefore, it is crucial to conduct a comprehensive assessment that incorporates clinical presentation evaluation alongside neuroendocrine and imaging examinations while monitoring the patient's response to treatment for achieving an accurate differential diagnosis.

In a systematic review of 52 patients with myxedema psychosis,[13] it was found that brain imaging was conducted for a mere 16 individuals, uncovering pathological findings in only five instances. This review also identified several neurological conditions in the patient population, including white matter lesions (3.85%),[14] cerebral atrophy (1.9%),[15,] and a combination of both conditions (3.85%).[16] At present, there is a scarcity of case reports documenting the co-occurrence of myxedema psychosis and PHPH. In addition, it should be noted that the initiation of thyroxine replacement therapy in the 1st week may worsen psychotic symptoms, thus underlining the potential use of short-term adjunctive antipsychotic medication. Furthermore, the majority of myxedema psychosis patients (more than 90%) experienced complete resolution of psychotic symptoms through oral thyroxine replacement therapy and temporary use of antipsychotics during the follow-up period.[13,17] Similarly, it has been observed that PHPH typically reverts to its normal state within a span of one to months after initiating thyroxine replacement therapy.[18] In our case study, the patient exhibited a positive prognosis after receiving a combination therapy comprising low-dose lurasidone, sertraline, and sodium thyroxine replacement therapy for a short duration.

4. Conclusion

The co-occurrence of myxedema psychosis and PHPH is a rare clinical phenomenon. In the context of thyroid disorders presenting with diverse symptoms, there is a high chance of misdiagnosis and inadequate treatment if the diagnostic process is solely symptomatology-based without involving additional testing. The majority of patients diagnosed with myxedema psychosis or PHPH exhibit a favorable prognosis after receiving thyroxine replacement therapy. Therefore, it is imperative to consistently prioritize organic etiology as the principal differential diagnosis when assessing psychotic symptoms to prevent adverse outcomes. Precise diagnosis and treatment are pivotal for effective management, as emphasized in this case report.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Author contributions

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Ethics approval and consent to participate

Verbal consent was obtained from the patient. This study was approved by the Research Ethics Review Board (Approval ID: LCH-LW-2023013) of the Linyi Central Hospital.

Consent for publication

Verbal consent was obtained from the patient for publishing her data in this paper.

Availability of data

The data used in this work are presented in the text and original data can be obtained from the corresponding author following a formal request.

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ACCSCIENCE PUBLISHING

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CASE REPORT

Anxiety and depression in a patient with an implantable cardioverter defibrillator for early repolarization syndrome: A case report and clinical discussion

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Abstract

Early repolarization syndrome (ERS) was initially thought to be a good prognostic manifestation detectable by electrocardiogram. In recent years, with the gradual deepening of research and understanding, ERS is considered to possess malignant tendency and related to ventricular fibrillation (VF) and sudden cardiac death (SCD). Implantable cardioverter defibrillator (ICD) is currently the first choice of treatment used to reduce the risk of potentially life-threatening arrhythmias and SCD in patients at high risk for ERS. The stress of living with an implanted device and receiving ICD shock has been noted to exert a psychological toll on patients, especially those who have previously experienced VF and syncope. The current case report describes symptoms and signs of a patient with ERS, and discusses the changes of psychological condition after ICD implantation. Moreover, we explored a targeted treatment approach for anxiety and depression in an individual with an ICD for ERS, which combined medication, cognitive behavioral therapy, and physical exercise. We believe that the psychological experience of ICD recipients, which is a critical component in designing the biopsychosocial therapeutic approach for this growing patient population, is worthy of more attention.

Keywords: Cardiology; Early repolarization syndrome; Implantable cardioverter defibrillator; Ventricular fibrillation; Anxiety; Depression

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1. Background

Early repolarization syndrome (ERS) is a diagnosis of exclusion, following the exclusion of other common factors that may cause malignant arrhythmias, cardiac arrest, and sudden cardiac death (SCD), and electrocardiogram (ECG) can indicate early repolarization pattern (ERP).[1] At present, the pathogenesis of ESR remains unclear but is possibly related to the increase of transient outward potassium current (Ito). The ERP ECG is defined as the elevation of J point which was not less than 0.1 mv, the formation of J wave, and the elevation of ST segment in a bow-back downward pattern.[1] Antzelevitch and Yan have categorized ERP into three types according to the leads of J wave in ECG (Type 1: I, V4 – V6; Type 2: II, III, aVF; Type 3: I, V4 – V6, II, III, aVF) and proposed that type 3 is associated with the highest risk of electrical storm occurrence.[2]

However, the ECG manifestations tend to be spontaneous, intermittent, and dynamic, usually occurring when vagal activity is predominant. Moreover, the diagnosis of ERS can only be established by reviewing after the occurrence of clinical events.

The currently available treatments for ERS entail conservative measures for asymptomatic patients, including fever management and infection prevention. Isoproterenol is used in the patients in acute phase, and quinidine is utilized in chronic phase to control the episodes of ERS-related ventricular fibrillation (VF). It is currently believed that implantable cardioverter defibrillator (ICD) can be used for the primary and secondary prevention of fatal arrhythmia events and SCD in patients with ERS.[3] However, such implantable electronic devices are not without risks, and patients may experience surgical and post-operative complications during ICD implantation. In addition, ICD automatically delivering shocks after the identification of ventricular arrhythmic events also has a negative impact on the mental health of patients. ICD shocks, either appropriate or inappropriate, have been shown to be associated with anxiety and depression disorders in both patient populations with congenital and acquired heart diseases.[4] Anxiety and depression are considered to be associated with an increased risk of death and VF in patients with ICD, independent of traditional risk factors.[5]

In this case report, we present a middle-aged man exhibiting early repolarization, as indicated by ECG, who had been implanted with ICD for secondary prevention due to resuscitation after cardiac arrest. The patient developed anxiety and depression after frequent ICD shocks. In this paper, we discuss the psychological state of the patient implanted with ICD for shock therapy and the corresponding treatment measures employed to reduce anxiety and depression experienced by the patient.

2. Case presentation

A 49-year-old male with episodic syncope lasting 5 years was admitted to the Wuxi People's Hospital, China, and closely monitored for 1 day. In April 2017, the patient suffered from a sudden syncope without any triggers, accompanied by limb convulsions and loss of consciousness, and woke up spontaneously after 5 min. After that incident, the patient experienced syncope for an additional three times. In the latest syncope incident, the patient lost consciousness when he was being sent to the emergency department of the hospital. The emergency ECG monitoring showed that the patient had VF. Cardiopulmonary resuscitation, electrical defibrillation, and tracheal intubation were subsequently applied. The patient was reexamined using ECG, which indicated bradycardia (Figure 1A). A range of blood tests were conducted, showing low serum potassium level, elevated levels of cardiac enzymes and troponin I, and brain natriuretic peptide level at 1829.00 pg/mL. Cardiac color Doppler ultrasound showed that the size and function of each cardiac chamber were normal (Table S1).

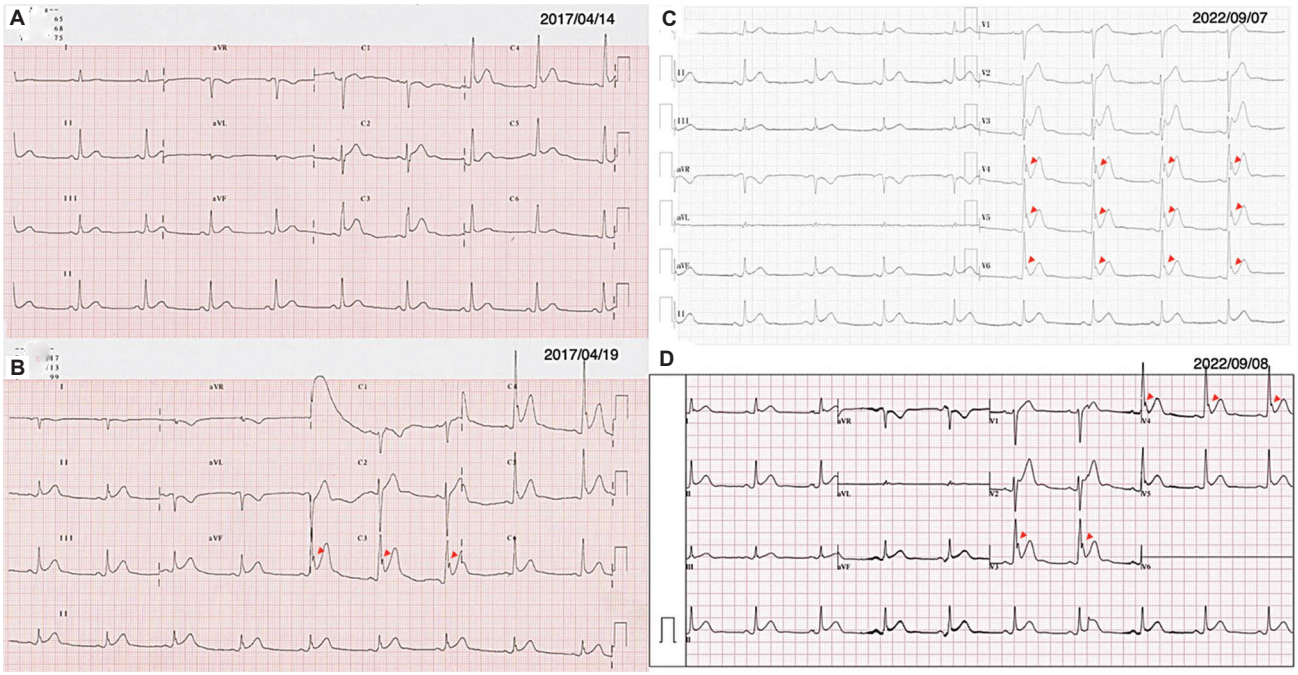


Figure 1. Multiple electrocardiogram manifestations. Red arrow points to area where J point is visible, followed by oblique elevation of the ST segment.

According to the findings from Holter monitor, the 24-h total heartbeat was 68637, the fastest heart rate was 74 bpm, the slowest heart rate was 42 bpm, the average heart rate was 53 bpm, and the longest R-R interval was 1.5 s, suggesting sinus bradycardia, occasional atrial premature, and ST-segment elevation (Figure 2). Coronary artery angiography was performed to exclude coronary heart disease, and separately, no arrhythmia was induced by intracavity electrophysiological study (Table S2-S3). During hospitalization, the patient was reexamined using ECG, which suggested early repolarization (Figure 1B), and thus, ICD implantation was recommended for secondary prevention, but the patient refused and requested conservative treatment using medications.

Over the next 5 years, the patient had endured multiple episodes of syncope coupled with transient loss of consciousness, each lasting from tens of seconds to minutes before the patient regained consciousness spontaneously. Repeated ECG revealed saddle ST-segment elevation in leads V2 – V6 (Figure 1C and D). The patient had a history of congenital cleft lip and palate, and his immediate family members had never experienced syncope and SCD events. To avoid recurrence of VF, the patient eventually agreed to receive ICD implantation. During postoperative follow-up, the patient experienced recurrent VF, and ICD therapy, mainly electric shock therapy, was prescribed.

Within 3 months after ICD implantation, the patient felt palpitation and chest tightness and had experienced multiple episodes of shocks. ICD follow-up revealed a total of four episodes of VF within the 3 months following ICD implantation, all of which were cardioverted by means of ICD shock therapy (Figure 3). After the second shock treatment, the patient developed persistent palpitation and an inability to raise the left arm after ICD implantation. The inability to raise the arm after ICD implantation may be related to electrode displacement, joint adhesion, muscle atrophy, muscle weakness, and peripheral nerve damage in the arm, but these conditions had never occurred in this case. Owing to frequent VFs, the patient took quinidine orally, but despite the drug treatment, he continued to experience recurrent VFs and ICD shocks. Four episodes of VF attack and ICD shock treatment had adversely affected the mental status of the patient; he began to fall into a state of insomnia and suffered from early awakening, overthinking, emotional agitation, and negative thoughts. On multiple occasions, he had expressed to the doctor that he felt uncomfortable and experienced suicidal thoughts.

After excluding the possible causal factors of fever, infection, electrolyte disturbance, and myocardial injury, the somatization symptoms, anxiety, and depression of the patient were evaluated using self-rating scales: SSS score = 44; GAD-7 score = 18; PHQ-9 score = 10 (Figure 4, Table S4-S6), which collectively indicate severe anxiety and moderate depression. Upon realizing these results, the physician consoled the patient through smart phone. Parts of the messages are given in the following: "with ICD protection, there is no need to be too nervous. If the palpitation or sudden syncope occurs, the ICD will not induce shock after the heartbeat returns to normal, unless the irregular heartbeat cannot stop by itself." "Aside from the heartbeat problems, other conditions of yours are well controlled. The usage of defibrillator plus quinidine will deliver ample protection to you, so there is no need to be depressed." "We are unable to intervene therapeutically if your condition is complicated by gene mutations, but we can address other external factors to improve your condition." The patient was prescribed lupentixol melitoxin tablets (delanxin) for controlling anxiety and depression. During the follow-up, the patient showed no recurrence of syncope, and the symptoms of palpitation and chest tightness were comparatively improved. The patient also reported no new episodes of VF and shock treatment complications under ICD programming.

3. Discussion

ERS and Brugada syndrome are collectively referred to as J-wave syndromes.[2] ERS has been considered an ECG manifestation with a good prognosis in the past decades. With the gradual development of research and understanding, ESR is found to increase the risk for malignancy and related to the occurrence of VF and SCD.[3] According to the HRS/EHRA/APHRS Expert Consensus,

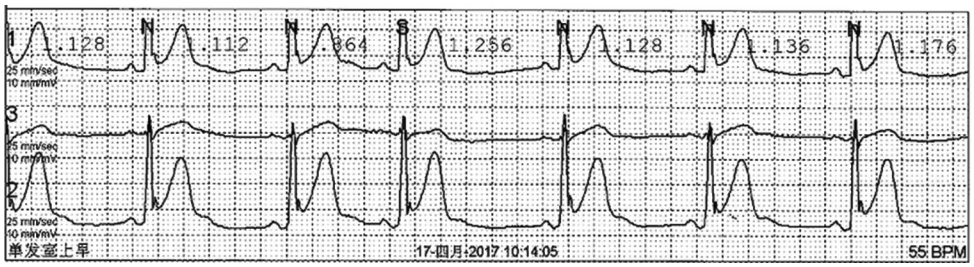


Figure 2. ST-segment elevation as shown on the Holter monitor. The ST segment was elevated in a bow-back downward pattern.

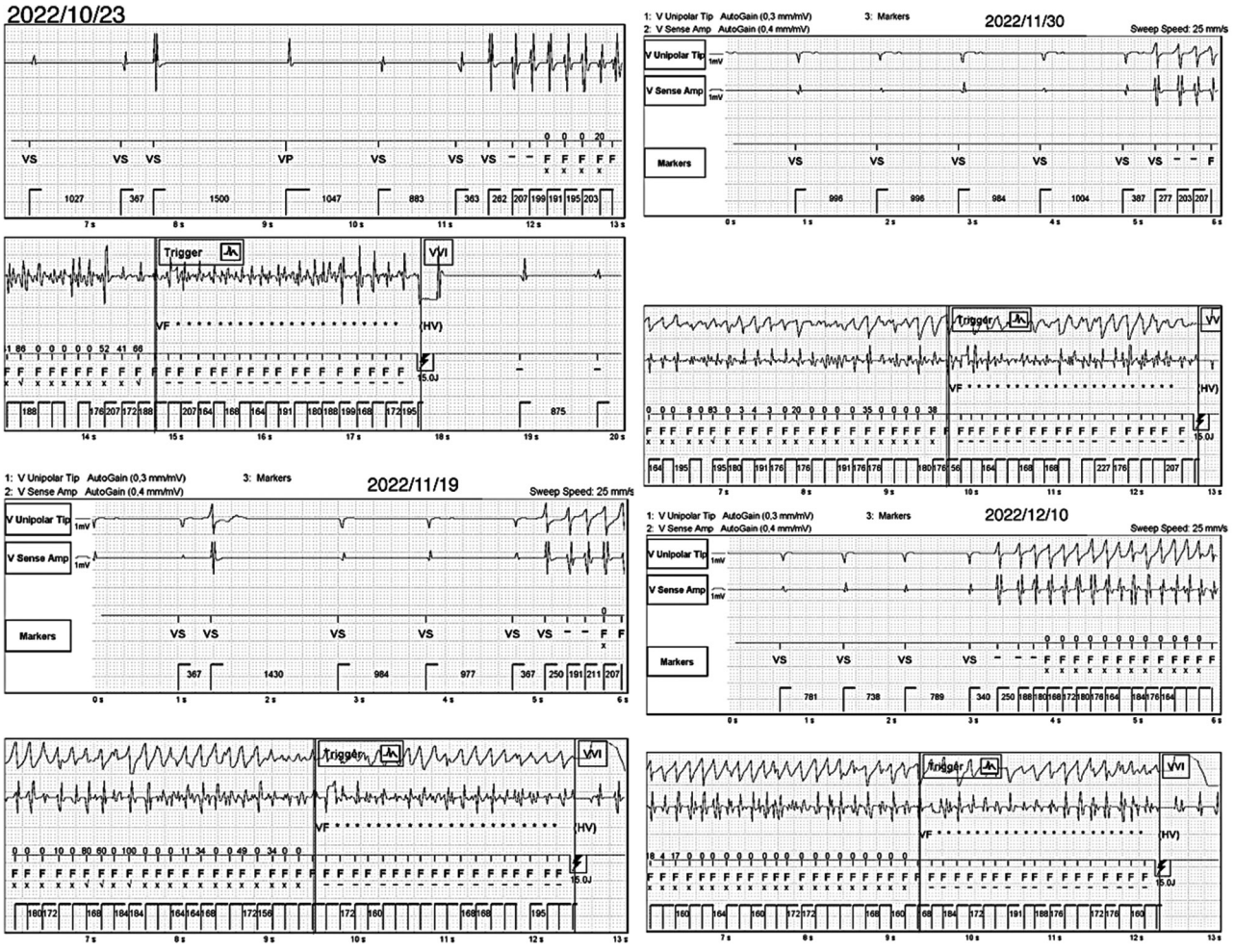
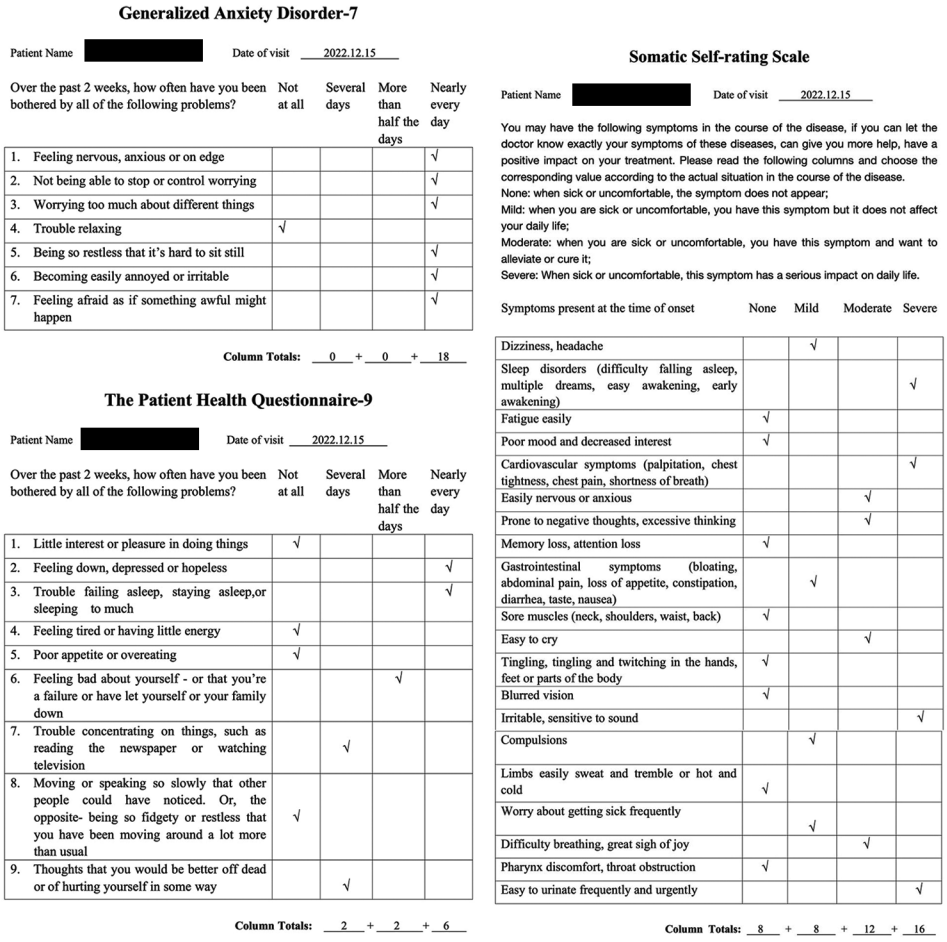


Figure 3. Ventricular fibrillation (VF) events in patients reviewed at the time of ICD programming. On October 23, 2022, one episode of VF lasting about 12 s (heart rate = 324 bpm) was detected, and the sinus rhythm was restored following one "shock" triggered by ICD implanted. On November 19, 2022, November 30, 2022, and December 10, 2022, the patient separately experienced episodes of VF that was terminated with ICD shock therapy.

ICD implantation is a recommended therapeutic strategy to prevent SCD for ERS patients who have experienced cardiac arrest. ICD implantation is also considered for symptomatic family members of ERS patients, who manifest ST elevation ≥1 mm in two or more inferior or lateral leads and have a history of syncope. For asymptomatic ERS patients, ICD implantation is also recommended if they exhibit high-risk ECG (such as a high-amplitude J wave, horizontal or descending ST segment) and have strong family history of sudden juvenile death (regardless of the disease-causing gene mutations).[6]

Patients with ICD implantation are often accompanied by more conspicuous physiological and psychological issues compared with general heart disease patients. Some of the main clinical symptoms attributable to the physiological and psychological issues are as follows: (1) anxiety and depression; (2) behavioral confrontation and suicide; (3) sexual dysfunction; (4) forced braking and limb weakness on one side of the device; and (5) frequent ventricular tachycardia attacks.[7] After analyzing the emotional symptoms of ICD-implanted patients, Ghezzi *et al.* found that 22.58% of the patients had clinically relevant anxiety (95% CI: 18.26 – 26.91), 15.42% of the patients had depression (95% CI: 11.90 – 18.94), and the prevalence of post-traumatic stress disorder was 12.43% (95% CI: 6.90 – 17.96). ICD-implanted patients who experienced shock were more likely to experience clinically relevant anxiety and depression (anxiety: odds ratio = 3.92 [95% CI: 1.67 – 9.19]; depression: odds ratio = 1.87 [95% CI: 1.34 – 2.59]).[8] The MADIT-RIT study, which followed patients with ICD implantation for 9 months, found that ≥2 appropriate or inappropriate ICD shocks and ≥2 appropriate antitachycardia pacing treatments were associated with more anxiety at 9 months of follow-up.[9] At



Generalized Anxiety Disorder-7

Patient Name [redacted] Date of visit 2022.12.15

Over the past 2 weeks, how often have you been bothered by all of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge				√
2. Not being able to stop or control worrying				√
3. Worrying too much about different things				√
4. Trouble relaxing	√			
5. Being so restless that it's hard to sit still				√
6. Becoming easily annoyed or irritable				√
7. Feeling afraid as if something awful might happen				√

Column Totals: 0 + 0 + 18

The Patient Health Questionnaire-9

Patient Name [redacted] Date of visit 2022.12.15

Over the past 2 weeks, how often have you been bothered by all of the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	√			
2. Feeling down, depressed or hopeless				√
3. Trouble failing asleep, staying asleep,or sleeping to much				√
4. Feeling tired or having little energy	√			
5. Poor appetite or overeating	√			
6. Feeling bad about yourself - or that you're a failure or have let yourself or your family down			√	
7. Trouble concentrating on things, such as reading the newspaper or watching television		√		
8. Moving or speaking so slowly that other people could have noticed. Or, the opposite- being so fidgety or restless that you have been moving around a lot more than usual	√			
9. Thoughts that you would be better off dead or of hurting yourself in some way		√		

Column Totals: 2 + 2 + 6

Somatic Self-rating Scale

Patient Name [redacted] Date of visit 2022.12.15

You may have the following symptoms in the course of the disease, if you can let the doctor know exactly your symptoms of these diseases, can give you more help, have a positive impact on your treatment. Please read the following columns and choose the corresponding value according to the actual situation in the course of the disease.
None: when sick or uncomfortable, the symptom does not appear;
Mild: when you are sick or uncomfortable, you have this symptom but it does not affect your daily life;
Moderate: when you are sick or uncomfortable, you have this symptom and want to alleviate or cure it;
Severe: When sick or uncomfortable, this symptom has a serious impact on daily life.

Symptoms present at the time of onset	None	Mild	Moderate	Severe
Dizziness, headache		√		
Sleep disorders (difficulty falling asleep, multiple dreams, easy awakening, early awakening)				√
Fatigue easily	√			
Poor mood and decreased interest	√			
Cardiovascular symptoms (palpitation, chest tightness, chest pain, shortness of breath)				√
Easily nervous or anxious			√	
Prone to negative thoughts, excessive thinking			√	
Memory loss, attention loss	√			
Gastrointestinal symptoms (bloating, abdominal pain, loss of appetite, constipation, diarrhea, taste, nausea)		√		
Sore muscles (neck, shoulders, waist, back)	√			
Easy to cry			√	
Tingling, tingling and twitching in the hands, feet or parts of the body	√			
Blurred vision	√			
Irritable, sensitive to sound				√
Compulsions		√		
Limbs easily sweat and tremble or hot and cold	√			
Worry about getting sick frequently		√		
Difficulty breathing, great sigh of joy			√	
Pharynx discomfort, throat obstruction	√			
Easy to urinate frequently and urgently				√

Column Totals: 8 + 8 + 12 + 16

Figure 4. Somatic Self-rating Scale, Generalized Anxiety Disorder-7, and the Patient Health Questionnaire-9 results

the same time, baseline anxiety and depression are often associated with poor cardiovascular outcomes. Lindekilde *et al.* discovered that anxiety and depression have obvious connection with increased risk of mortality in patients implanted with ICD, but not with the occurrence of ICD shock.[5] They also recommended that anxiety and depression should be included in the risk stratification of mortality. Moreover, compared with anxiety, depression has higher risk coefficient.[5]

It is worth noting that younger patients are more prone to experience anxiety and depressive disorder. Fumagalli *et al.* found that cardiac implantable electronic devices, including ICDs, are more widely utilized in the elderly population, but young patients tend to face more difficulties (P = 0.035) and more severe psychological burdens (mainly in their professional [P < 0.001] and private life [P = 0.033]).[10] Pedersen *et al.* also found that older age was associated with lower risk of new anxiety disorder in patients with ICD implantation (hazard ratio [HR]: 0.54), as well as depression disorder (HR: 0.57).[11] Moreover, ERS is more common in young and middle-aged men, especially among athletes. Therefore, more attention should be diverted to dissecting the psychology of this group.

To improve the prognosis and quality of life of the ERS patients, it is necessary to identify the psychological problems of these patients with ICD implantation and consider corresponding treatment that includes pharmacotherapy and non-pharmacological cognitive behavioral therapy. In terms of medication, benzodiazepines and 5-HT1A receptor agonists are commonly used to treat anxiety disorders.[12] Selective serotonin reuptake inhibitors are first-line antidepressants,[13] but sertraline has been reported to cause cardiac events such as ventricular tachycardia, sinus arrest, and even SCD, which may be related to QT prolongation.[14]

Non-pharmacological therapy mainly consists of cognitive behavioral therapy, mindfulness emotion therapy, and exercise therapy. Cognitive behavioral therapy

can be used to treat anxiety and depression by changing the unreasonable cognition of patients. Most of the remote interventions are both feasible and convenient as they can be administered through WiFi-accessible smartphones. Previous studies have also shown that cognitive behavioral therapy is effective in treating ICD-implanted patients with symptoms of depression and anxiety.[15] As a complementary intervention employed to treat issues such as anxiety, mindfulness has been shown to be effective in controlling cardiovascular disease, promoting greater emotional stability, and helping to improve the mood of individuals with heart disease [16] Aditee *et al.* showed that meditation reduced atrial fibrillation episodes and sustained ventricular tachycardia after conducting a pilot study of the effects of meditation on 25 patients with ICD implantation for heart failure.[17] Besides, it is safe and feasible to use smartphones to deliver mindfulness intervention to patients with ICD implantation to improve their anxiety.

Other non-drug therapies, including aerobic exercise, have also been linked to significant reductions in anxiety and depression in patients with ICD implantation. Exercises have been proved for their intervening effects on many mental health problems. For instance, a study found that aerobic exercise can improve general psychological distress and anxiety, while resistance training can improve disease-specific symptoms, anxiety sensitivity, pain tolerance, and tolerance to uncertainty.[18] In the study, about 50% of the patients with ICD implantation chose to avoid committing daily household activities, sexual activities, and physical exercise of moderate-to-high intensity to prevent the occurrence of ICD shock. A study suggests that moderate-to-vigorous exercise training is safe to patients with ICD and effective in controlling their physical health and cardiopulmonary outcomes, with no increase in adverse events such as ICD shock or SCD.[19] For patients with ICD, we recommend practicing aerobic exercise as the main exercise but avoid climbing, swimming, and other forms of exercise that require excessive arm extension. The exercise intensity can be gradually increased from low to moderate intensity while ensuring that the real-time heart rate during exercise is 20 beats lower than the heart rate at which ICD shock is induced. The duration of exercise can also be gradually increased from 10 – 15 min to 30 – 60 min. It is necessary to adjust the intensity, time, and frequency of aerobic exercise according to individual differences.

4. Conclusion

In summation, frequent ICD shocks due to VF attacks can negatively affect the psychological state of patients. Conversely, post-traumatic stress disorder, anxiety, or depression that occur after shock can in turn increase the risk of ventricular arrhythmia and may become the trigger for ICD shocks, which is particularly evident in this case. To improve the prognosis of patients with ICD implantation, early cognitive behavioral therapy, appropriate physical exercise, and pharmacological intervention should be considered to alleviate their mental health problems.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: Zhiming Yu
Investigation: Yue Sun
Writing – original draft: Yue Sun
Writing – review & editing: Zhiming Yu

Ethics approval and consent to participate

The consent of the patient has been obtained, before his participation, to use his clinical data and psychological assessment results.

Consent for publication

The patient has consented to publishing his clinical data in this case report. The authors have implemented the necessary measures to ensure the anonymity of the patient by removing the easily distinguishable, patient-specific information.

Availability of data

All demographic characteristics, clinical data, and laboratory test results of the patient can be obtained from this case report. The patient's ICD programming data were obtained from the review of the ICD work diary of the outpatient return visit.

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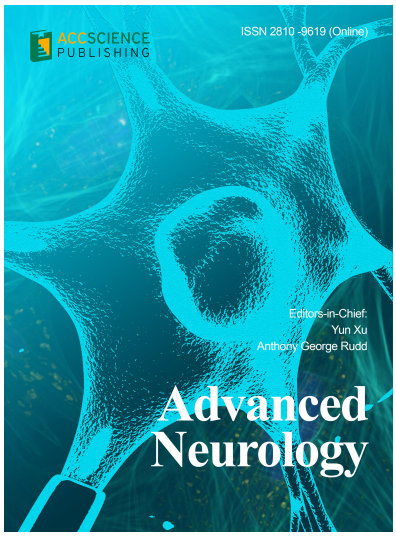

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