

The Pathogenesis and Treatment of Insomnia Combined with Depression

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Abstract: Under the fast pace and high pressure of modern society, many people suffer from sleep disorders such as insomnia, and then suffer from depression and anxiety. This article may lead to a better understanding of the mechanisms of insomnia combined with depression and its treatment. Vital and meaningful, these mechanisms include synaptic plasticity, neurotransmitter dysfunction, the hypothalamic-pituitary-adrenocortical (HPA) axis, and diminished brain-derived neurotrophic factor (BDNF) levels. Evidence for mechanism-guided integrated therapies is scarce. In clinical practice, pharmacological therapies, including antidepressants, Cognitive behavioural therapy (CBT), physiotherapeutics, acupuncture treatment, and mindfulness interventions, are generally utilised. A more profound comprehension of the pathophysiological mechanisms and the development of comprehensive and effective treatment strategies for insomnia co-occurring with depression can enhance neuropsychiatrists' ability to manage this comorbidity more effectively. This study bridges these gaps by delineating novel neurobiological crosslinks underlying comorbidity and establishing a targeted combined intervention protocol.

Keywords: insomnia, sleep, pathogenesis, cognitive behavioral therapy, depression

Introduction

Insomnia refers to when a patient has the opportunity to sleep (environment, time), but due to specific reasons (trouble falling asleep or staying asleep), the quality and duration of sleep cannot meet personal needs, affecting social function during the day. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), the global prevalence of insomnia is approximately 10%. In contrast, the prevalence of insomnia in Chinese adults is 9.2%-11.2%.¹ The more significant the insomnia symptoms, the higher the incidence of hypertension and depression.²⁻⁴ Patients with insomnia reported higher levels of depression than those without insomnia, and insomnia may be an essential factor in exacerbating depression.⁵ Insomnia and depression are linked to adverse health outcomes in the elderly population, which encompass cognitive deterioration, increased incidence of falls, and diminished quality of life. Both insufficient sleep duration (less than 7 hours) and excessive sleep duration (more than 8-9 hours), along with symptoms of insomnia, are identified as risk factors for the development of depression among older adults.⁶ Importantly, insomnia is not only a disease often accompanied by various mental disorders^{7,8} but also a significant risk factor for developing depression.^{9,10} In addition, a study showed that greater severity of insomnia reduces the likelihood of major depressive disorder (MDD) remission.¹¹ Sun and Tan et al¹² found that daytime dysfunction was more severe in cases of major depressive disorder in the insomnia group than in the primary insomnia group. The number of REM periods (NRP), time of REM sleep (RT), and percentage of RT (RT%) in the major depressive disorder with insomnia group significantly exceeded those in the primary insomnia group and the generalised anxiety disorder with insomnia group. Li et al¹³ showed that the improvement of insomnia symptoms in 10 weeks is synchronised with the improvement of depressive mood. Clinicians should pay attention to insomnia symptoms in the elderly as part of the prevention and treatment of depressive symptoms.

Mechanisms Linking Combined Depression and Insomnia

Synaptic Plasticity

In a study conducted by Zhang et al¹⁴ male C57BL/6 J mice were assigned to several experimental groups: a Control group, a lipopolysaccharide (LPS) group, a sleep deprivation (SD) group, and a combined LPS + SD group. The findings indicated that the expression levels of proinflammatory cytokines IL-1 β , IL-6, and TNF- α were elevated in the LPS group, with further increases observed in the LPS + SD group. Additionally, the levels of synaptic plasticity-related proteins, including BDNF, PSD-95, and SYN, were diminished in the LPS group and further decreased in the LPS + SD group. The results suggest that chronic sleep deprivation exacerbates LPS-induced anxiety, depression, and cognitive deficits by enhancing the production of proinflammatory cytokines and suppressing the expression of proteins associated with synaptic plasticity. Li et al¹⁵ conducted a study indicating that sleep deprivation exacerbates hippocampal synaptic plasticity impairment in rats subjected to Chronic Unpredictable Mild Stress (CUMS) by inhibiting the secretion of melatonin from the pineal gland, which in turn leads to more pronounced depression-like behaviours. Treatment with venlafaxine and melatonin in combination with SD can repair the damage of hippocampal neural dendritic spines, thereby enhancing learning, memory, and cognitive function in CUMS rats.

Neurotransmitter Dysfunction

5-hydroxytryptamine (5-HT) regulates sleep, cognition, emotion, and other advanced functions. It has been found that the activation of 5-HT neurons can induce non-REM active arousal.¹⁶ Under the catalysis of enzymes, tryptophan can be converted into 5-HT, which is further synthesised to produce neurotransmitters such as melatonin and 5-hydroxyindole, because abnormal tryptophan metabolism can lead to insomnia.¹⁷ At the same time, the neurotransmitters gamma-aminobutyric acid (GABA) and adenosine (AD) promote sleep.^{18,19} Sleep disorders may lead to anhedonia and depressive symptoms by affecting the function of the reward system.²⁰ The fundamental mechanism underlying the reward loop is the mesolimbic dopamine system, characterised by dopaminergic neurons originating from the ventral tegmental area and projecting to the nucleus accumbens (NAc). Alterations in the connectivity of the NAc are believed to significantly influence the pathophysiology of depression and insomnia.^{21–23} Gong et al²⁴ indicate that genetic variations associated with dopamine may differentially affect the reward network in patients with chronic insomnia disorder (CID), depending on the presence or absence of depressive symptoms. Benson et al²⁵ primarily focused on the investigation of GABA and glutamate concentrations in the brains of individuals diagnosed with MDD and Primary Insomnia (PI) through the application of single-voxel proton magnetic resonance spectroscopy (¹H MRS). They emphasised that the reduced levels of glutamate found in patients with MDD may be a result of the disorder itself rather than a consequence of the accompanying sleep disturbances.

Neuroinflammation

Mei et al²⁶ discovered four genes linked to inflammation that may be related to insomnia and depression: CREB1, CYBB, FYN, and CCR5. CREB1 could serve as a potential biomarker and therapeutic target for depression and insomnia, as supported by findings from a rat model and a Mendelian Randomization (MR) study. The animal study demonstrated that the swift antidepressant effects of SD on mice subjected to Chronic Restraint Stress (CRS) are attributed to a decrease in the neuroinflammatory response within the anterior cingulate cortex (ACC) and an enhancement of neuroplasticity in both the prefrontal cortex (PFC) and ACC.²⁷ Li et al²⁸ propose that a reduction in BDNF due to the activation of NOD-like receptor protein 3 (NLRP3) inflammasomes in astrocytes constitutes a critical pathological event underlying depressive-like behaviours resulting from SD. Concurrently, leptin is observed to increase the expression of 5-HT_{2B} receptors in astrocytes, thereby enhancing the effectiveness of fluoxetine in alleviating depression-like behaviours linked to chronic SD. Costemale-Lacoste et al²⁹ the study showed that Glycogen Synthase Kinase-3 β (GSK3 β) rs334558 was associated with insomnia, although it does not correlate with the severity of major depressive episodes (MDE) in individuals diagnosed with depression. Consequently, targeting GSK3 β in patients experiencing MDE alongside severe insomnia may represent a promising approach to enhance symptom management more effectively.

Dysfunction in the HPA

The effects of the HPA axis and sleep are reciprocal Zhang et al¹⁰ conducted a systematic review and meta-analysis of longitudinal studies, revealing that elevated baseline morning cortisol levels are significant predictors of subsequent depression. The Pittsburgh Sleep Quality Index (PSQI) was employed to evaluate sleep quality in clinical investigations. Santiago et al²⁷ reported that patients diagnosed with significant depression exhibited significantly higher PSQI scores compared to healthy control subjects. Their findings indicated a correlation whereby increased morning cortisol levels were associated with poorer sleep quality and an elevated risk of major depression. Conversely, a clinical trial conducted by van Neijenhof et al²⁸ found no significant interaction between a diagnosis of depression or the severity of depressive symptoms and any cortisol parameters concerning insomnia symptoms or sleep duration.²⁹ Asarnow et al³⁰ consider future research needs to involve more basic experiments and clinical studies to clarify the specific mechanisms between sleep disorders, depression, and HPA axis functioning. Additionally, it is essential to examine the impact of various sleep disorders, including insomnia and sleep deprivation, on cortisol levels. This investigation will enhance our understanding of the hypothalamic-pituitary-adrenal (HPA) axis as a potential mechanism contributing to the comorbidity of insomnia and depression. Zhou et al³¹ reported a reduction in regional cerebral blood flow (rCBF) following a period of sleep deprivation lasting 36 hours (comprising two days and one night). Initial findings indicate a heightened susceptibility to hypoperfusion as a consequence of insufficient sleep. The mechanisms contributing to this phenomenon may involve endothelial dysfunction, excessive microglial activation, alterations in cytokine levels, hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis, increased oxidative stress, and disturbances in monoamine neurotransmitter systems, among others.

Decreased Level of BDNF

Chronic SD and insomnia increase the risk of depression by down-regulating BDNF expression, leading to dysfunction in the hippocampus and prefrontal cortex. The BDNF Val66Met polymorphism may influence individual susceptibility to depression, anxiety, and insomnia by altering BDNF availability and expression. Acute REM SD may improve sleep quality and emotional status by restoring BDNF expression.³² Chronic stress may cause dysregulation of the HPA axis, leading to sleep disorders and depression, with a decrease in BDNF levels. Acute stress, including partial SD, may serve as an expedited intervention to restore BDNF levels in certain individuals experiencing insomnia or depression.³³ Zaki et al's³⁴ study included 199 insomniacs and 51 healthy control participants. Sleep parameters were assessed by polysomnography (PSG), and cognitive function and depressive symptoms were evaluated using the Montreal Cognitive Assessment (MoCA) and the Hamilton Depression Rating Scale (HDRS). The findings indicate that the Val66Met polymorphism of the BDNF gene may have an impact on the cognitive function of patients suffering from insomnia, as well as potentially influencing the depressive symptoms experienced by these individuals (Figure 1).

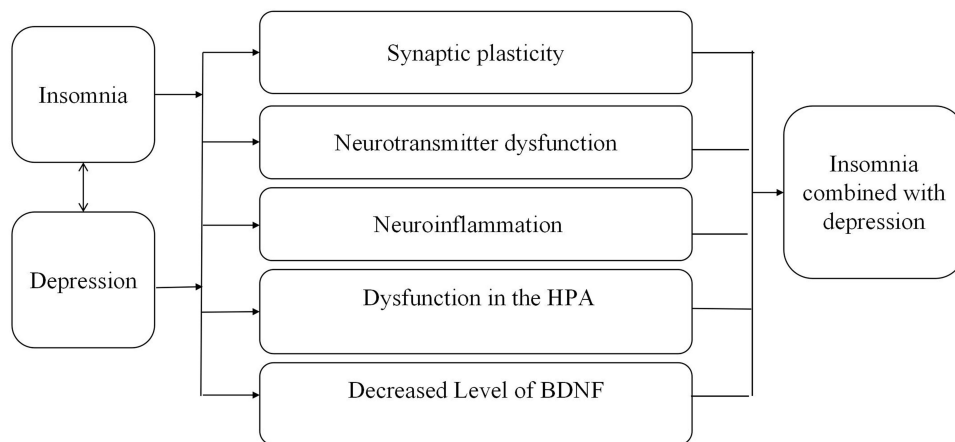


Figure 1 A summary of the the pathogenesis of insomnia combined with depression.

Treatments

Antidepressants

Commonly used drugs include SSRIs, SNRIs, Noradrenergic and specific serotonergic antidepressants (NaSSA), serotonin receptor antagonists and reuptake inhibitors (SARIs), NE and dopamine reuptake inhibitors (NDRIs), tricyclic antidepressants (TCAs), etc. Some antidepressants have a sedative effect, which is especially suitable for the treatment of depression with insomnia. Paroxetine, sertraline, fluoxetine, and citalopram in SSRIs and venlafaxine and duloxetine in SNRIs may reduce sleep efficiency, shorten REM sleep duration, prolong REM sleep latency, increase arousal, and impair sleep continuity in the early stage of use. Therefore, it is recommended that patients with depression take them in the morning and avoid taking them at night to prevent affecting their sleep.

With the appearance of antidepressant efficacy, insomnia symptoms can be gradually improved. Antidepressants characterised by sedative properties, such as doxepin, mirtazapine, and trazodone, are known to facilitate rapid improvements in sleep quality. However, their long-term use may be associated with complications arising from excessive sedation.³⁵ Mirtazapine, a representative drug of NaSSA, can significantly reduce sleep fragmentation, enhance sleep effectiveness and personal perception of sleep quality, shorten sleep latency, and improve early awakening in depressed patients. Agomelatine is an antidepressant with unique pharmacological effects, which works as a melatonin agonist and 5-HT receptor antagonist, and has hypnotic, antidepressant, and anxiolytic effects. It is safe and independent, antidepressant, and anxiolytic effects, and is safe and independent. Still, mirtazapine may cause weight gain.³⁵ The study conducted by Mi et al³⁶ included a cohort of 102 patients diagnosed with MDD. These participants were randomly allocated to receive either agomelatine ($n = 50$) or mirtazapine ($n = 52$), along with a control group of 50 healthy individuals. Sleep parameters were assessed using PSG at baseline, 4 and 8 weeks and functional connectivity analysis was performed. The results showed that both agomelatine and mirtazapine could significantly improve sleep disorders and depressive symptoms in MDD patients, but agomelatine was better at improving sleep structure and functional connectivity. This retrospective descriptive cohort study offers contemporary evidence indicating that the utilisation of trazodone is prevalent among individuals suffering from insomnia, frequently in conjunction with particular combined conditions, including depression.³⁷ Everitt et al's³⁸ study showed that short-term administration of low-dose doxepin and trazodone may result in a modest enhancement in sleep quality when compared to a placebo. A survey consisting of 16 questions was sent to 433 Canadian child and adolescent psychiatrists, with 67 responses meeting the criteria for a depression diagnosis. Of these, 40% of patients had sleep problems. The results showed that melatonin was most commonly used to address sleep issues in adolescents with depression and was considered to have the least side effects. The most frequently reported side effects were nightmares (16.4%), headaches (9.0%), and fatigue (9.0%). Trazodone and quetiapine were considered the main medications for treating sleep disorders associated with depression in children and adolescents, with side effects often causing excessive sleepiness (37.3% and 58.2%, respectively) and daytime fatigue (35.8% and 49.3%). Doctors generally avoid using benzodiazepines and non-benzodiazepine sleep medications due to concerns about their adverse effects.³⁹ The main adverse reactions of trazodone are drowsiness, dizziness, fatigue, which emphasize the importance of fall prevention in older patients. Tricyclic antidepressants can be used for the treatment of sleep disorders, mainly characterised by sleep maintenance disorders and early awakening. Goerke et al's⁴⁰ clinical trials have found that amitriptyline, a tricyclic antidepressant, can increase sleep time and improve sleep efficiency in patients with depression and insomnia. In addition, amitriptyline may cause adverse reactions such as decreased slow-wave sleep, increased heart rate, and periodic leg movements during sleep. However, tricyclic antidepressants have anticholinergic and other adverse reactions and are easy to induce epilepsy and orthostatic hypotension, so they are usually not the first choice.⁴¹

Vortioxetine (VOR) is classified as a multimodal antidepressant, functioning as an antagonist at the 5-HT₃, 5-HT₇, and 5-HT_{1D} receptors, while also serving as a partial agonist at the 5-HT_{1B} receptor and an agonist at the 5-HT_{1A} receptor.⁴² Liguori et al⁴³ conducted a retrospective analysis involving a cohort of 15 patients diagnosed with major depressive disorder and complaints of insomnia who were started on VOR to relieve depressive symptoms. The PSQI, Epworth Sleepiness Scale (ESS), and Beck Depression Inventory (BDI) were administered at both the baseline and follow-up assessments. The results showed that VOR not only improved depressive symptoms but also significantly improved insomnia symptoms, especially in

subjective sleep quality and continuity. It is suggested that future studies should further explore the mechanism of VOR and its impact on sleep architecture through prospective studies with large sample sizes and more diverse assessment tools such as polysomnography. A separate study was conducted to evaluate the impact of vortioxetine treatment on sleep architecture in adolescents diagnosed with depression, with a particular focus on alterations in REM sleep as documented through video-polysomnography (v-PSG). Thirty hospitalized adolescents (mean age 15 years, 21 females) who were treated with VOR (at doses of 10/15/20 mg/day) and had v-PSG testing before and after treatment participated in the study. The findings indicated that VOR notably alleviated insomnia and depression symptoms in depressed adolescents and had a considerable effect on inhibiting REM sleep. REM inhibition may be a positive marker in the treatment of depression, which may be achieved through its multiple mechanisms of action on 5-HT receptors. The primary limitations of this study are the small sample size and the predominance of female participants. Future research should aim to incorporate a larger sample size and take into account gender differences.⁴⁴

One study included 31 patients with a clinical diagnosis of major depressive disorder with insomnia, 23 of whom completed the whole course. Fluvoxamine has demonstrated a correlation with improvements in depressive symptoms and sleep quality. The final remission rate was significantly lower in patients who still had insomnia on the 14th day of treatment, so early intervention (such as hypnotics or behavioural therapy) should be given to depressed patients who still had insomnia after 2 weeks of treatment, which may improve the remission rate of depression. Fluvoxamine increases serum melatonin levels through various mechanisms, possibly by enhancing serotonin synthesis or reducing hepatic metabolism. However, the limitations of this study are that there is no placebo control, the placebo effect cannot be excluded, and the efficacy difference between fluvoxamine and other antidepressants has not been evaluated.⁴⁵

Ketamine

The systematic reviews and meta-analyses encompassed the Montgomery-Åsberg Depression Rating Scale (MADRS), the Quick Inventory of Depressive Symptomatology Self-Report (16-item) scale (QIDS-SR16), the PSQI, and the Insomnia Severity Index (ISI). Sleep was quantitatively assessed through nocturnal electroencephalography (EEG), revealing a reduction in nocturnal wakefulness alongside an increase in both slow-wave sleep and REM sleep. These findings indicate that ketamine is effective in alleviating the severity of insomnia associated with depression.⁴⁶

Nonpharmacological Treatment

Cbt

Numerous studies have demonstrated that CBT is an effective therapeutic approach for insomnia combined with depression.^{3,47–50} Boland et al⁵¹ used the PubMed and PsycINFO databases to search for relevant clinical studies using the keywords “insomnia + depression + treatment + prevention”. A total of 186 studies were initially identified, of which 168 studies remained after duplicates were eliminated. After screening, six studies met the inclusion criteria, four studies showed that face-to-face Cognitive Behavioural Therapy for Insomnia (CBT-I) reduced the risk of depression in the elderly by 53% within three years, and digital CBT-I (dCBT-I) reduced the risk of moderate and severe depression in the general adult population by 49% within one year. The elderly, pregnant women and general adults all benefited significantly, suggesting that the effect was not limited by age/physiological status. In specific populations, a study involving postpartum women revealed that 18% of participants who had an Edinburgh Postnatal Depression Scale (EPDS) score of less than 10 at baseline subsequently developed postpartum depression within the usual care group. In contrast, no participants in the CBT-I group experienced this outcome. Cunningham et al⁵² conducted a systematic review that indicates face-to-face CBT-I as a treatment for depression accompanied by insomnia possesses substantial supporting evidence, demonstrating efficacy comparable to that of antidepressant medications. However, the potential additive effect of combining CBT-I with antidepressants remains uncertain, and there may be a “ceiling” effect to consider. Additionally, there is a paucity of literature addressing the optimal number and frequency of CBT-I sessions, as well as the effectiveness of CBT-I in conjunction with other temporal therapies. The current research predominantly relies on short-term follow-up data, and further studies are required to validate the long-term efficacy. Irwin et al⁵³ conducted a single-center, parallel-group, double-blind, randomized clinical trial that

involved the participation of 431 older adults from a community-based sample, the study comprised 291 adults aged 60 years and older who were diagnosed with insomnia and did not have a major depressive disorder or any significant health events in the preceding year. The participants were randomly allocated to receive either CBT-I ($n = 156$) or Sleep Education Therapy (SET) ($n = 135$) over a duration of two months. The findings indicated that CBT-I markedly decreased the occurrence of initial or recurrent major depression among elderly individuals suffering from insomnia, demonstrating superior efficacy compared to SET. CBT-I may be an effective way to prevent depression in elderly individuals with insomnia. Nevertheless, the study is subject to certain limitations, including a restricted sample size and the absence of a placebo control. Future studies should consider larger sample sizes and explore the possibility of combining CBT-I with other interventions. For insomnia patients with depression, post-traumatic stress disorder, alcohol dependence, and other mental disorders, CBT not only improves insomnia symptoms but also improves combined mental health, especially in depression. Early studies have shown that CBT can significantly improve sleep quality and reduce depressive symptoms.⁵⁴ Recent findings from randomized controlled trials indicate that therapist-guided digital CBT-I, particularly when combined with CRS, represents a promising and viable method for individuals with high-risk insomnia to effectively mitigate the exacerbation of depressive symptoms.⁵⁵ Insufficient sleep, defined as less than five hours per night, may diminish the efficacy of CBT-I in conjunction with pharmacological treatment for patients who present with combined MDD and insomnia.⁵⁶ Cheng et al⁵⁷ conducted a randomized controlled trial to evaluate the effects of digital cognitive behavioral therapy for insomnia (dCBT-I) on depressive symptoms in individuals suffering from insomnia. The experimental group received dCBT-I through an online platform, while the control group was provided with online sleep education. Participants assigned to the online sleep education group received a series of six weekly emails that covered various topics, including the fundamentals of natural sleep regulation, how health issues can affect sleep, the influence of sleep-disrupting substances like caffeine, nicotine, and alcohol, as well as advice on how to create a bedroom environment that promotes better sleep. The findings revealed that dCBT-I effectively reduced depressive symptoms among those with insomnia. Additionally, older participants were less likely to discontinue the dCBT-I program, suggesting that older adults could effectively engage with the internet-based treatment. Furthermore, the study found that online sleep education did not lead to a significant decrease in depressive symptoms. Spina et al⁵⁸ showed that CBT-I not only improves the objective sleep quality of individuals experiencing combined insomnia and depression, but also enhances their capacity to accurately evaluate their own sleep patterns. This improvement is crucial for the effective long-term management of both conditions. By minimizing the gap between subjective and objective sleep assessments, CBT-I may facilitate the development of healthier sleep habits among patients and bolster their confidence in the treatment process. In conclusion, CBT-I could become the preferred treatment for insomnia accompanied by depression in the future.

Physiotherapy

Zhou et al⁵⁹ executed a randomized, double-blind study involving patients diagnosed with Major Depressive Disorder (MDD) who also presented with symptoms of insomnia. The participants were randomly assigned to receive either transcranial direct current stimulation (tDCS) or a sham tDCS, alongside their standard treatment protocol. A total of 47 patients were designated to the tDCS group, while 43 patients were allocated to the sham tDCS group. The findings indicated that tDCS not only alleviated symptoms of depression and anxiety but also positively influenced sleep quality among patients with MDD. Therefore, for individuals experiencing both depression and insomnia, tDCS may serve as a beneficial adjunct to pharmacological interventions. Pu et al⁶⁰ conducted a study in which one hundred participants were randomly assigned to either a high-frequency rTMS group or a pseudo-rTMS group, with fifty individuals in each group. All patients received concurrent treatment with agomelatine. Serum levels of NE, 5-HT, BDNF, and melatonin were measured. rTMS may improve depression symptoms by regulating neurotransmitters and neurotrophic factors, promoting non-REM (NREM) sleep, enhancing slow wave activity, and improving sleep quality. The combination of agomelatine and rTMS presents a promising therapeutic approach for individuals experiencing mild to moderate depression accompanied by insomnia.

Acupuncture Treatment

Zhao et al⁶¹ systematic review showed that total of 776 potentially relevant articles were identified. Following the elimination of duplicate entries and the implementation of a comprehensive text review, a total of 21 studies, encompassing 1571 participants, fulfilled the established criteria, with 19 of them undergoing meta-analysis. The research found that acupuncture is a beneficial therapy for patients with active depression accompanied by insomnia. It can be used alone or in combination with medication to improve sleep quality and alleviate depressive symptoms. For residual insomnia symptoms in patients with past or partially relieved depression, acupuncture's effectiveness is limited. Additional research is required to establish the most effective dosage and to explore other potentially beneficial treatment modalities, including the integration of acupuncture with conventional therapies such as antidepressants, hypnotics, and cognitive behavioral therapy for insomnia (CBT-I). Zhao et al⁶² involved a cohort of 70 perimenopausal women, aged between 18 and 70 years, who were experiencing insomnia and met the DSM-IV criteria for depression. The participants were randomly allocated to one of three groups: real acupuncture (RA), sham acupuncture (SA), or standard care. Each participant underwent acupuncture treatment three times per week over a duration of eight weeks, culminating in a total of 24 sessions. The findings indicate that acupuncture is both safe and effective for perimenopausal women with depression and insomnia symptoms and can significantly improve their sleep quality and depression symptoms. In terms of safety, acupuncture operations are safe, and related adverse events (AEs) are few and mild. The most common adverse reaction was blood stasis (7.72%), which usually subsided within a few days. Compared with drugs (such as hypnotics or antidepressants), the incidence and severity of adverse events caused by acupuncture are lower.⁶³ Yin et al^{64,65} conducted a 32-week clinical trial that was both patient- and evaluator-blinded, randomised, and sham-controlled, comprising an 8-week intervention followed by a 24-week observational follow-up. Participants, aged between 18 and 70 years, were diagnosed with insomnia and met the criteria for depression as outlined in the DSM-IV. A total of 200 patients were enrolled in the study, with 67 assigned to the electroacupuncture group, 66 to the sham acupuncture group, and 67 to the standard care control group. The findings indicated that electroacupuncture treatment resulted in significant improvements in both sleep quality and depressive symptoms among patients with depression, demonstrating favourable safety and tolerability profiles.

Mindfulness Interventions

A systematic review and meta-analysis indicate that non-pharmacological interventions may significantly alleviate symptoms of depression and fatigue in older insomniacs, and mindfulness interventions and exercise, in particular, may be particularly valuable.⁶⁶ Li et al⁶⁷ showed that a total of 10 Randomised Clinical Trials (RCTs) involving 1,058 subjects were systematically evaluated. The mindfulness intervention significantly reduced the scores of HAMD, HAMA, SDS, and SAS, suggesting that it can successfully alleviate the symptoms of depression and anxiety in individuals suffering from insomnia. Subgroup analysis revealed consistent effects of mindfulness therapy across different age groups and intervention times. The randomised efficacy trial included 25 participants in the mindfulness-based cognitive therapy (MBCT) group and 30 members of the waitlist control group (74.5% female; mean age 40.7 ± 12.9 years). This study shows that MBCT can significantly improve some insomnia symptoms in patients with recurrent depression, suggesting that MBCT could serve as a beneficial supplementary approach in the management of insomnia among these patients. However, to improve these patients' overall sleep status, other specialised sleep interventions may need to be combined.⁶⁸ Huberty et al⁶⁹ conducted a randomised controlled trial involving 239 adults who exhibited substantial insomnia symptoms, as indicated by scores of 10 or higher on the Insomnia Severity Index, and who had minimal to no prior experience with meditation. The findings suggest that meditation apps can enhance mental health by reducing depression and anxiety in adults facing sleep issues. Additionally, there were notable improvements in daytime sleepiness and arousal levels before bedtime. Chan et al⁷⁰ searched for randomised controlled trials from January 2010 to June 2020. They found 397 articles, and 10 studies involving 541 participants were included in the meta-analysis based on the inclusion criteria. The studies that qualified focused on internet mindfulness meditation intervention (IMMI), mindfulness meditation (MM), MBCT, mindfulness-based stress reduction (MBSR), and mindfulness-based touch therapy (MBTT). All mindfulness-based intervention programs (MBTT, MBCT, IMMI, and MBSR), with the exception of MM, proved to be effective options for addressing sleep issues in individuals with depression or anxiety disorders. Long-term follow-up should be considered in the future to verify its sustained effect. While Mindfulness-Based Interventions (MBIs) demonstrate encouraging outcomes, it is essential to take individual differences into

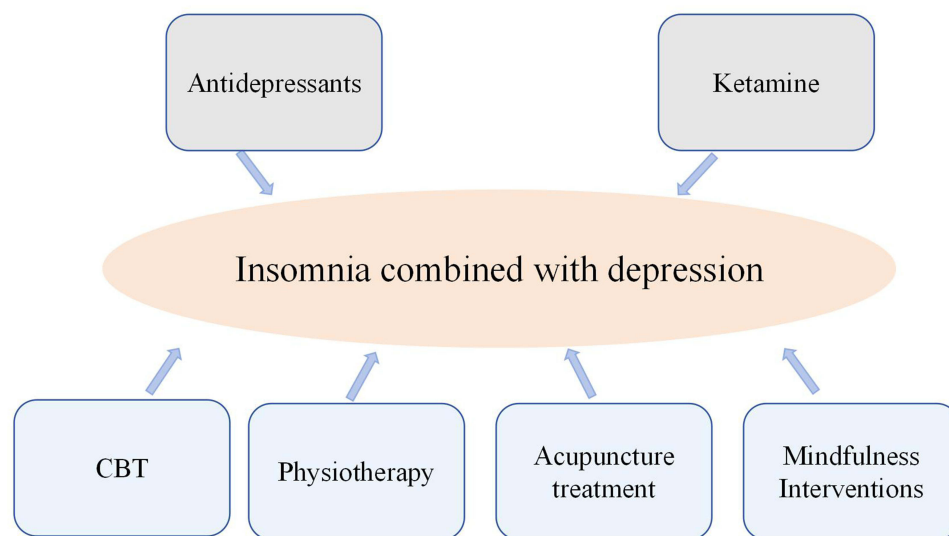


Figure 2 A summary of the the treatment of insomnia combined with depression.

account during their practical implementation and to integrate them with other therapeutic approaches to achieve optimal effectiveness.⁷¹

In the future, it is anticipated that additional large-scale multicenter randomised controlled trials will be conducted to investigate the synergistic effects of various medicinal treatments, traditional Chinese medicine, physiotherapy, mindfulness interventions, CBT-I, etc., in treating insomnia combined with depression (Figure 2).

Summary

Understanding the pathogenesis of insomnia and its combined depression is crucial for the precise diagnosis and treatment of individuals suffering from depression in conjunction with insomnia. This review has examined the mechanisms underlying the interplay between insomnia and depression. Various pathological changes contribute to the onset of depression during the progression of insomnia, including modifications in synaptic plasticity, neurotransmitter dysfunction, HPA axis, and diminished levels of BDNF, all contributing to insomnia combined with depression. However, its pathophysiological mechanism has not been fully explored and elucidated. In the future, numerous experiments may be conducted to investigate its biomarkers, thereby offering valuable insights for clinical diagnosis and treatment. Currently, insomnia with depression is mainly treated with antidepressants, vortioxetine, ketamine, fluvoxamine, CBT, physiotherapeutic, acupuncture treatment, and mindfulness interventions. In the future, extensive multicenter randomized controlled trials can be carried out to investigate the use of various treatment methods and determine their safety and efficacy.

Abbreviations

¹H MRS, single-voxel proton magnetic resonance spectroscopy; 5-HT, 5-hydroxytryptamine; ACC, Anterior cingulate cortex; AD, Adenosine; AEs, Adverse events; BDI, Beck Depression Inventory; BDNF, Brain-derived neurotrophic factor; CAR, Cortisol awakening response; CBF, Cerebral blood flow; CBFSR, Cerebral blood flow self-regulation; CBT, Cognitive behavioral therapy; CBT-I, Cognitive behavioral treatment for insomnia; CI, Chronic insomnia; CID, Chronic insomnia disorder; CORT, Corticosterone; CRS, Chronic restraint stress; CUMS, Chronic unpredictable mild stress; DA, Dopamine; dCBT-I, Digital cognitive behavioral therapy for insomnia; DLPFC, Dorsolateral prefrontal cortex; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; EA, Electroacupuncture; EEG, Electroencephalography; EPDS, Edinburgh Postnatal Depression Scale; ESS, Epworth Sleepiness Scale; FC, Functional connectivity; GABA, Gamma-aminobutyric acid; HAMA, Hamilton Rating Scale for Anxiety; HAMD, Hamilton Depression Scale; HDRS, Hamilton Depression Rating Scale; His, Histamine; HPA, Hypothalamic-pituitary-adrenocortical; IMMI, Internet mindfulness meditation intervention; ISI, Insomnia

Severity Index; MADRS, Montgomery-Åsberg Depression Rating Scale; MBCT, Mindfulness-based cognitive therapy; MBIs, Mindfulness-Based Interventions; MBSR, Mindfulness-based stress reduction; MBTT, Mindfulness-based touch therapy; MDD, Major depressive disorder; MDE, Major depressive episode; MM, Mindfulness meditation; MoCA, Montreal Cognitive Assessment; MR, Mendelian randomization; NAc, Nucleus accumbens; NaSSA, Noradrenergic and specific serotonergic antidepressants; NDRIs, NE and dopamine reuptake inhibitors; NE, Norepinephrine; NLRP3, NOD-like receptor protein 3; NREM, Non-REM; NRP, Number of REM periods; Oxs, Orexins; PFC, Prefrontal cortex; PMD, Perimenopausal depression; PMI, Perimenopausal insomnia; PRISMA, Preferred reporting items for systematic reviews and meta-analysis; PSG, Polysomnography; PSQI, Pittsburgh Sleep Quality Index; QIDS-SR16, Quick Inventory of Depressive Symptomatology Self-Report (16-item); RA, Real acupuncture; rCBF, Regional cerebral blood flow; RCTs, Randomized Clinical Trial; REM, Rapid eye movement; RT, Time of REM sleep; rTMS, Repetitive transcranial magnetic stimulation; SA, Sham acupuncture; SARIs, Serotonin receptor antagonists and reuptake inhibitors; SAS, Self-rating Anxiety Scale; SD, Sleep deprivation; SDS, Self-Rating Depression Scale; SE, Sleep efficiency; SET, Sleep Education Therapy; TCAs, Tricyclic antidepressants; tDCS, Transcranial direct current stimulation; TST, Total sleep time; VOR, Vortioxetine; v-PSG, Video-Polysomnography.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

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

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