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To cite this article: Elisa Brietzke, Gustavo H. Vazquez, Melody J.Y. Kang & Claudio N. Soares (2019): PHARMACOLOGICAL TREATMENT FOR INSOMNIA IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER, Expert Opinion on Pharmacotherapy, DOI: [10.1080/14656566.2019.1614562](https://doi.org/10.1080/14656566.2019.1614562)

To link to this article: <https://doi.org/10.1080/14656566.2019.1614562>

Accepted author version posted online: 02 May 2019.

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Publisher: Taylor & Francis

Journal: *Expert Opinion on Pharmacotherapy*

DOI: 10.1080/14656566.2019.1614562

**PHARMACOLOGICAL TREATMENT FOR INSOMNIA IN PATIENTS WITH
MAJOR DEPRESSIVE DISORDER**

Elisa Brietzke^{1,2}, Gustavo H. Vazquez^{1,2}, Melody J.Y. Kang³, Claudio N. Soares^{1,2,3}

1. Department of Psychiatry, Queen's University School of Medicine, Kingston, ON, Canada.
2. Providence Care Hospital, Kingston, ON, Canada.
3. Center of Neuroscience Studies (CNS), Queen's University, Kingston, ON, Canada.

Corresponding author

Elisa Brietzke

752 King Street West, Postal Bag 603

Kingston, ON K7L7X3

Tel: 613 544 4900 ext 73002

Fax: 613 548 5580

E-mail: elisa.brietzke@queensu.ca

ABSTRACT

Introduction: Insomnia in Major Depressive Disorder (MDD) is highly prevalent and associated with increased suffering and functional impairment. Effective, evidence-based treatments for insomnia in MDD are an unmet need in clinical practice.

Areas covered: Herein, the authors provide a review of the clinical correlates, putative neurobiological mechanisms and treatment options for the management of insomnia in individuals with MDD.

Expert opinion: Sleep disturbances in MDD should be recognized as at least one of the following: 1) a domain of depressive psychopathology; 2) a consequence of rhythm disruptions; 3) a manifestation of comorbidities of sleep disturbances; 4) a manifestation of the influence of sex hormones in the brain in MDD; 5) a general medical comorbidity; and 6) a side effect of antidepressant medications. Assessment of insomnia in clinical practices is routinely performed with the use of non-structured interviews. Other methods, such as standardized questionnaires and sleep diaries, along with complementary methods such as actigraphy, and polysomnography are more scarcely applied. Smartphones and personal devices offer a promising strategy with the use of passive, long-lasting, and ecologically valid assessments despite the lack of studies specifically targeting insomnia in individuals with MDD. New therapeutic approaches are essential, including novel targets such as orexins/hypocretin and the endocannabinoid system.

Keywords: Major Depressive Disorder; Insomnia; Sleep; Mood Disorders; Hypnotic.

Article Highlights

- Evidence-based treatments for insomnia in individuals with MDD constitute an unmet need in clinical practices.
- Insomnia in MDD should be considered as a domain of depressive psychopathology, a medical comorbidity, or an adverse event caused by psychiatric medications.
- Innovative tools for the assessment of sleep and circadian rhythms include the use of smartphones and personal devices, which can offer reliable and ecologically valid data.
- Most strategies commonly used in clinical practices are derived from secondary analyses in randomized controlled trials.
- New molecular targets, such as orexins/hypocretins circuits and cannabinoids are a promising strategy to manage insomnia in MDD.

1. Introduction

Insomnia is a very common complaint both in the general population and in individuals with Major Depressive Disorder (MDD) (1,2). Around 10% of the general population suffers from insomnia associated with significant consequences, such as daytime sleepiness or fatigue, reduced or lack of energy, poor concentration, memory impairment, emotional lability (e.g. irritability, anxiety, mood swings), and interpersonal difficulties (3-5). The prevalence of insomnia in individuals with MDD is much higher, with some reports suggesting that up to 90% of the patients with MDD may experience insomnia at some point of their illness trajectory (6,7).

Sleep problems may vary with a variety of studies reporting difficulties in initiating sleep, a reduction in total duration of sleep, increased number and frequency of awakenings, a sensation that the sleep was not restorative enough, diurnal somnolence, or different combinations of these factors (8,9). MDD is traditionally associated with terminal insomnia, although difficulties in initiating sleep may be even more frequent (10). Hypersomnia can also be found during major depressive episodes, either in isolation or in combination with insomnia (11). Thus, the link between sleep and mood disorders is complex in its clinical characterization, in its biological underpinnings, and potentially in therapeutic approaches required for its management (12,13).

The extent to which the treatment of insomnia in MDD is poorly understood has led to clinical consequences such as the excessive or prolonged use of benzodiazepines (BDZ). Although useful short-term, the long-term consumption of BDZ should be restricted due to risks of abuse, dependence, falling, delirium, other cognitive dysfunctions, acute respiratory failure, car accidents, and withdrawal symptoms (14-16).

Enduring insomnia has an adverse impact of diurnal functioning and overall functional recovery, even when the severity of depressive symptoms is mitigated or even

largely reduced (17-18). Therefore, the lack of evidence-based treatments for insomnia in individuals with MDD should be considered an unmet need in clinical practice. In order to tackle this challenge, a critical appraisal of current practices should be considered, including off-label prescription of pharmacological agents, as well as the investigation of novel agents to treat insomnia in MDD.

Although the optimum treatment of insomnia in MDD is likely multi-faceted and behavioral strategies are one of its cornerstones, the main objectives of this review are to summarize the evidence of pharmacological treatments of insomnia in MDD and discuss novel, useful approaches in research and clinical practice. The description of normal physiology of sleep is out of the scope of this review – for that, we suggest the work of Chokverty (19).

2. Clinical Correlates of Insomnia in MDD

2.1 Insomnia as a domain of depressive psychopathology

The different conceptual approaches to the symptomatic heterogeneity in depressive psychopathology have reached a new milestone in time with the launching of The NIMH Research Domain Criteria (RDoC) project. According to the RDoC framework, biological substrates of different dimensions of depression could be assessed using multiple methods of analysis, going from behavior and emotional experiences, to neural circuits, to molecules and genes (20). Although the adoption of RDoC in research of sleep and depression is still in its incipient stages, some evidence suggests that the presence and severity of insomnia in MDD could be related to a subgroup of patients with a heightened predisposition to more severe illness trajectories (Figure 1).

For example, insomnia was identified as a predictor of recurrent depressive episodes in a STAR*D data analysis (21), with insomnia during the maintenance phase of an MDD

treatment being a significant predictor of both relapse and recurrence (21). These results are also seen in specific populations with depression, such as pregnant women with MDD (22); child and adolescents (23) and older adults (24).

Cognitive deficits in MDD also seem to be influenced by the presence and severity of sleep problems (25). It is well defined both in healthy individuals and the subjects with MDD that a proper time for sleep as well as normal sleep architecture is needed to promote memory consolidation (26). In a group of people with MDD, those with insomnia had significantly increased connectivity between the anterior medial prefrontal cortex to both the parahippocampal cortex and the hippocampal formation, compared to those without sleep disturbances. This finding supports the notion of a specific MDD phenotype with changes in the default mode network, a critical circuit for cognition (27).

Another supporting argument for insomnia to be a marker of severity of course in MDD is its association with suicidality. Insomnia has been consistently associated with suicidal ideation (28,29), and is an independent predictor of suicide attempts in longitudinal studies (30). Total duration of sleep is inversely correlated with suicide risk in patients with severe depression (31).

2.2 Insomnia as a manifestation of the disruption of rhythms in MDD

There is evidence that the presence of insomnia in patients with MDD could be the expression of impairments in circadian regulation of biological rhythms (Figure 1). Replicated results suggest that irregular sleep patterns could occur earlier than the emergence of a full blown depressive episode in individuals with MDD (32), opening an exciting avenue of investigation linking a set of genes involved in sleep-wake cycle regulation and behavioral manifestations of MDD. Interestingly, these new results were similar to older observations that showed interventions targeting circadian rhythm, such as sleep deprivation, having antidepressant properties (33). A recent meta-analysis including various forms of sleep

deprivation techniques have shown antidepressant response rates between 45-50% across samples with different clinical characteristics (e.g. sex, age, medication status, criteria used to define response) (34).

In addition, the idea that MDD is a circadian rhythm illness is reinforced by mounting evidence showing that diurnal rhythmicity (sleep, temperature, mood and hormone secretion) is altered during depressive episodes (35). Mechanisms behind rhythm in MDD remain largely unknown; however, recently several studies have shown support for epigenetic and transcriptional changes in a subgroup of genes called CLOCK genes which are responsible for controlling biological rhythms (36). Disruption of normal expression of CLOCK genes was found in individuals with MDD, especially in the anterior cingulate cortex (ACC), a region critical for integration of somatic stimuli, regulation of hedonic tonus, reward behaviors, and emotional regulation (35). Interestingly, transcription of CLOCK genes may be acutely changed by sleep deprivation and by another rapid action antidepressant, intravenous ketamine (37).

Taken together, these findings suggest that the difficulties in initiating sleep could be part of a more global phenomenon of rhythm dysregulation in MDD, and possibly linked to transcriptional abnormalities in CLOCK genes. Therapies targeting this set of genes, such as ketamine, may have circadian regulation as a part of their mechanisms of action (37), and may have the potential to mitigate these problems.

2.3 Insomnia as a manifestation of comorbid sleep disturbances in MDD

The concomitant presence of insomnia and other sleep disturbances among MDD patients has been clearly documented (1,38) (Figure 1). The prevalence of sleep disturbance is higher among individuals with MDD compared to the general population (39). Obstructive sleep apnea (OSA), for example, is found in approximately 20% of individuals with MDD,

particularly among obese and older individuals (40). The presence of OSA is a well-known risk factor for the development of depression in long-term follow-up studies (41).

Insomnia was found in around 68% of the subjects with OSA (42) and this specific comorbidity has been related to a higher risk for suicidal ideation and suicide planning in MDD (43). As OSA is not routinely assessed in psychiatric standard care, more frequent screenings and increased awareness should be promoted, especially in patients with treatment-resistant presentations and residual symptoms (44). Although the screening for OSA is not often conducted in psychiatric settings, there are simple and feasible methods to improve the detection of OSA, such as The Snoring, Tiredness, Observed apnea, High BP, BMI, Age, Neck circumference, and Male gender (STOP-Bang) Questionnaire. It is a reliable, concise, and easy-to-use screening tool, with yes/no responses and a score that ranges from 0 to 8 (45). This instrument has high sensitivity and specificity. It's sensitive for scores ≥ 3 to detect moderate to severe OSA and severe OSA is 93% and 100%, respectively. Patients with a STOP-Bang score lower than 3 are classified as low risk, whereas those with a score of 5 to 8 can be classified as high risk, for moderate to severe OSA (45). It has been largely adopted in anesthesia and surgical assessment with excellent performance in this context (46).

Another very relevant sleep disturbance in populations with MDD is restless legs syndrome (RLS), a sensory-motor condition in which the person has the sensation that they must move their legs in order to obtain relief (47). These symptoms are typically experienced in the transitions between wake and sleep, and can adversely affect sleep onset or maintenance. Several reports support the association between RLS and MDD (48-50), and the prevalence of RLS was associated with the severity of depressive symptoms in this population, with reports varying between 46-52% depending of the depression subtype (more common in depression with melancholic characteristics) (50). Although the mechanisms

behind the association between MDD, RLS, and insomnia are still speculative, recent evidence suggest that the involvement of persistent dysregulation of inflammatory responses could play a role (51). As RLS could be a cause of insomnia in MDD, this condition should be addressed to reduce potentially harmful consequences in depression outcomes (52).

2.4 Insomnia as a manifestation of the influence of sex hormones in the brain in MDD

Both sleep disorders and MDD are more prevalent in women than in men. Some have speculated that the modulatory effects of sex hormones on sleep-wake behaviors and mood might contribute to heightened risk for both conditions in women. Specifically, their unique sleep expression throughout their reproductive life cycle, including premenstrual sleep disturbances, sleep problems during pregnancy, postpartum and menopausal years, may contribute (53) (Figure 1).

The interactions between sleep disorders, depression, and vasomotor symptoms among menopausal women have been a focus of mechanistic and therapeutic studies. Contrary to initial thoughts or the so-called ‘domino theory’, depression and insomnia in menopausal women cannot be solely explained by the presence of nocturnal vasomotor symptoms leading to a disrupted sleep (54,55).

In a recent study, women undergoing estradiol withdrawal experienced more depressive symptoms in association with sleep disturbance and the number of nighttime, but not daytime, hot flashes. These results suggest that some hypoestrogenic women could be particularly susceptible to the development of menopause-associated depressive symptoms in the context of sleep disruption and reports of bothersome nighttime vasomotor symptoms (56).

2.5 Insomnia as a manifestation of general medical comorbidity

Different general medical comorbidities have insomnia as one of their symptoms; a condition referred to as secondary insomnia (Figure 1). Examples of these conditions are

those suffering from chronic pain, such as migraine (57,58), orofacial pain (59), and musculoskeletal pain (60,61). Overall, the data from studies using different designs suggest a bidirectional and proportional association between sleep duration and pain intensity. The prevalence of insomnia in chronic pain is especially high among women, with high intensity of pain and in the presence of anxiety symptoms (62).

Other general medical conditions commonly associated with insomnia are coronary heart disease (63), type 2 diabetes mellitus (64) and cancer (65). The division between primary versus secondary insomnia has been criticized by some authors, as it suggest that only treating the comorbid condition will automatically produce improvement of insomnia. Nevertheless, most studies suggest that both sleep and the comorbid condition should be addressed simultaneously (61).

2.6 Insomnia as a side effect of antidepressive medications

Several antidepressants have insomnia among their side-effects, including the most commonly prescribed serotonin selective reuptake inhibitors. In addition, other antidepressants such as dual inhibitors (venlafaxine, desvenlafaxine and duloxetine) also could cause insomnia (Figure 1). Agents such as bupropion and vilazodone (66) that are commonly prescribed alone or in association can also compromise sleep in the beginning of the night. It is thought that activation of 5HT₂, dopaminergic, and noradrenergic agents would be responsible for this side-effect. A summary of the potential of different antidepressants in producing insomnia could be found in Table 1.

This side effect is clinically significant for several reasons. First, it may be associated with a prolonged period of time required to achieve response. Data from two samples, including one from Sequenced Treatment Alternatives to Relieve Depression (STAR*D) suggest that late responders to citalopram also reported higher levels of antidepressant-induced initial insomnia, compared to early responders, suggesting that antidepressant-

induced insomnia could play a role in delayed recovery in MDD (67). In addition, there is a possibility of patients adopting unhealthy ways to cope with insomnia, such as alcohol use (68).

A significant gap of the literature on this topic is the lack of systematic investigation on the direct comparison between agents regarding this side-effect. In addition, the correlation between improvement of insomnia and production of daytime sleepiness was not completely investigated (69). Another limitation is the variety of heterogeneous methods to assess presence and severity of treatment emergent insomnia in clinical trials (70).

Regarding the approach of antidepressant-induced insomnia, one of the most investigated strategies is to add on hypnotic agents such as zolpidem. One randomized controlled trial investigates adjunctive zolpidem for patients with MDD and persistent insomnia in the presence of effective and stable treatment with SSRIs. Compared to placebo, zolpidem at a dose of 10 mg was associated with improvement of sleep quality, sleep duration, and reduced number of awakenings (71).

3. Assessment of Insomnia in MDD

A detailed assessment of sleep in MDD can be obtained by the use of complementary methods, such as polysomnography (PSG) and actigraphy. The polysomnography provides the assessment of sleep architecture through the analysis of variables extracted from different physiological parameters from the brain (EEG), muscles (EMG), and eye movements. Typically, individuals with MDD exhibit increased sleep latency, number, and duration of awakenings from sleep expressed as increased wake after sleep onset (WASO) time, decreased sleep efficiency, and early morning awakenings (72). The association of early morning awakenings and abnormal distributions of REM sleep is also typical of major depressive episodes, especially those with melancholic characteristics (73). Actigraphy

records wake–sleep cycles over several days, weeks or months which this enables the recording of both periods with *Zeitgebers* (i.e., constraints that influence the person's rhythms, such as work, physical activity of meal times) and periods without (74). Actigraphy is a useful and validated tool to assess psychomotor activity and sleep-wake rhythms in MDD (75,76). Combined with PSG, actigraphy provides objective assessments of sleep and rhythms, helping to determine biological validity in behavior-based parameters including MDD subtypes, severity of symptoms across different domains of depressive psychopathology, and prediction of relapse (76-78)

Although time-consuming and relatively expensive, objective assessments with the use of PSG and actigraphy in MDD have recently shown to be helpful in predicting critical outcomes in MDD. In a recent study by Bernet et al. (79), the presence of suicidal ideation in subjects with treatment resistant MDD was associated with less NREM Stage 4 sleep, and higher nocturnal wakefulness, regardless of severity of symptoms. These results reinforced the role of sleep in the suicidality risk, particularly in treatment-resistant depression, when such risks may be substantial.

One alternative to objectively assess sleep and circadian rhythms in individuals with MDD is through the passive gathering of data via wearable devices (80). Given the ubiquity and popularity of mobile apps, this strategy may be used to effectively obtain reliable and ecologically valid information on sleep patterns among individuals with MDD. Such practices, if proven reliable and reproducible, could be instrumental for mental health providers to better determine indicators of relapse or recurrence, and eventually offer self-regulatory strategies (81). However, wearable devices for monitoring sleep through movement and light sensors have yet to be successfully validated against gold standard methods such as PSG and actigraphy, creating opportunities for further development and cooperation between mood/sleep researchers and technology developers (82).

These objective criteria are also helpful in the assessment of sleep disruption in patients reporting poor sleep quality. It should be noted that the self-reported sleep onset, duration and quality do not always correspond to objective measures. For example, it could be important to identify patient-perceived insomnia (e.g. difficulty going to sleep at night or remain sleeping) which may co-occur with a long duration of sleep. It is possible that a patient with this profile report high scores in both insomnia and hypersomnia. Indeed, the association of insomnia and hypersomnia is not uncommon in MDD (6).

4. Management of Insomnia in MDD

Some antidepressants with sleep promoting properties have been used in clinical care of patients with MDD aiming to treat, with the same drug, both sleep and other domains of depressive psychopathology. The prescription of these agents is supported by clinical experience, as there are results showing superiority of these agents over others. For example, one study with patients with chronic or recurrent MDD randomized to receive (1) escitalopram + placebo, (2) bupropion-sustained-release + escitalopram, or (3) venlafaxine-extended-release + mirtazapine for 28 weeks, did not find a benefit of adding mirtazapine to the medication regimen to improve sleep compared to the other arms (83).

Some of the most commonly adopted agents are described below:

4.1. Agomelatine

Agomelatine is a dual action agent with pharmacological affinity for MT1 and MT2 melatonin receptors and 5-HT_{2C} antagonist properties. Randomized controlled trials suggest simultaneous efficacy of agomelatine for treating depressive symptoms and sleep impairments (84). In direct comparisons, standard SSRIs such as escitalopram have shown to be superior than agomelatine to promote early onset responses and higher remission rates; notwithstanding, agomelatine could be considered in specific cases in which insomnia is a

predominant symptom (85). This medication could also be used for patients who experience insomnia as a side-effect of SSRIs (86) or in cases when the use of sedative/hypnotic medications are not recommended (84).

4.2. Mirtazapine

Mirtazapine is a tetracyclic piperazinoazepine, with a peculiar structure that distinguishes it from any other antidepressant currently on the market. Mirtazapine is considered a good choice for patients with MDD and insomnia, as sedation is one of its main side-effects (87). Most of its use in primary insomnia is off-label, although there is some evidence supporting low doses of mirtazapine (7.5 mg) as a hypnotic, with good tolerability and positive effects on sleep quantity, efficiency (88,89), and functioning (90).

4.3. Trazodone

Trazodone was approved by FDA as an antidepressant, despite the scarcity of clinical trials as a hypnotic. Trazodone is used by around 1% of the USA population to manage insomnia (91) - usually in doses between 25 and 100 mg.

5. Expert Opinion

Treatment of insomnia in MDD is challenging, reflecting its heterogeneity in pathophysiology and clinical presentations. Considering that insomnia is related to relapse and recurrence of depressive episodes as well as severe outcomes such as suicidality, more effective treatments for insomnia in MDD are warranted. For that, some alternatives should be considered.

4.1. Key Findings in the Field

A compelling body of evidence supports the notion that insomnia in MDD should not be considered merely as a depressive symptom; instead, insomnia could be understood or characterized as a marker of risk for severity of course, relapse/recurrence, treatment

resistance, and functional impairment. The proper assessment and treatment of insomnia in MDD has the potential not only to provide relief to patients, but also to modify the course of the illness. In spite of this, tolerable and effective agents to treat insomnia are not widely available for patients with depression. Investigation of new therapeutic targets are required.

Promising new tools for clinical assessment and diagnosis of insomnia are emerging and require further attention. Among those, the use of new technologies for the evaluation of sleep patterns and other biological rhythms may lead to better accuracy in the diagnosis of sleep problems and reduction in the costs incurred for the acquisition of more objective sleep parameters. Repurposing existing drugs that were originally developed for other indications could be a valid approach in the next few years, while new biological targets are pursued.

4.2. Limitations of the Literature

Although several trials consider insomnia as a secondary outcome in the treatment of MDD, very few studies were designed specifically to address insomnia in this population (92). One rare example is a recent RCT that examined the effects of adjunctive treatment with brexpiprazole - the new second generation antipsychotic - on patients with MDD who presented with unsatisfactory responses to conventional antidepressants. In this trial, add-on brexpiprazole was successful in improving insomnia, diurnal somnolence, and overall functioning (93). A summary of the limitations of the literature is described in Table 2.

4.3. Future Perspectives

Existent evidence suggests that depressive psychopathology extends far beyond monoaminergic abnormalities; *hence*, new neurotransmitters systems remain as an underexplored pathway in the treatment of insomnia in MDD. The orexins/hypocretins system is one of these putative pathways. Orexins are neuropeptides which act in the brain

through binding with two different receptors, OX1R and OX2R, which activate a cell cascade mediated by a G-protein (94). Data suggest the involvement of orexins/hypocretins in multiple physiological functions including feeding, addiction, reward and motivation, anxiety and depression, cardiovascular regulation, pain, migraine, and neuroendocrine regulation including reproduction. Their actions have been shown to be particularly relevant to promote the transition from awake to sleep (95,96). Pharmacological orexin antagonism is linked to the promotion of sleep, and the so-called dual orexin antagonists (blockers of OX1R and OX2R) are beneficial in the treatment of insomnia, promoting both REM and non-REM sleep. In addition, emerging evidence suggest that orexin antagonism could have antidepressant properties, despite some mixed results from animal studies and in humans (97-99).

Another promising target is the endocannabinoid system, as both endocannabinoid levels and their receptors exhibit circadian oscillations (100). As of now, there is no clear benefit of cannabidiol for insomnia in MDD, although there have been reports of improvement of diurnal somnolence and sleep quality (101). The few studies in humans are corroborated by a more robust animal research suggesting a potential effect of cannabidiol and synthetic cannabinoids – such as nabilone in improvement of sleep (102).

Finally, inflammation has also been considered as a significant target for insomnia in MDD. Specifically, insomnia has been associated with chronic low grade inflammatory activation, evident by the detection of a peripheral increase of inflammatory mediators such as C-reactive Protein (CRP), Tumor Necrosis factor-alpha (TNF-alpha) and Interleukin-6 (IL-6) (103). These biomarkers were also largely demonstrated and reproduced in studies comparing individuals with MDD and healthy controls (104, 105). Although the effect of anti-inflammatory medications has not been systematically investigated in the treatment of MDD-associated insomnia, it is possible that the subgroup of patients with MDD and

insomnia represents a specific “inflammatory” phenotype, which could be useful in stratification of subjects for future clinical trials targeting inflammation in MDD (106).

Funding:

This manuscript was not funded.

Declaration of Interest

E Brietzke has received speaker's and advisory board membership honoraria from Daiichi Sankyo. She has also received research grant support from the São Paulo Research Foundation (FAPESP), the National Council for Scientific and Technological Development (CNPq) and the Coordination for the Improvement of Higher Education Personnel (CAPES). She is also the recipient of the L'Oréal For Women in Science Award. CN Soares has received research grants from the Ontario Brain Institute (OBI) and the Ontario Research Fund for Excellence (ORF-RE). He has also served as a consultant for Lundbeck, Sunovion, Bayer, Pfizer Inc and Otsuka. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer Disclosures:

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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Table 1. Classes of drugs and their effects on sleep

Drug Class	Sleep Continuity	Slow-wave Sleep (SWS)	REM latency	REM sleep	Mechanism of action regarding sleep
SSRI (e.g. fluoxetine, escitalopram, paroxetine, sertraline)	-/0	0/+	+	-	Selective inhibition of serotonin reuptake
SNRI and NRI (e.g., venlafaxine, duloxetine, reboxetine)	-	0/+	+	-	Inhibition of serotonin and norepinephrine reuptake
MAOI (e.g., tranylcypromine, moclobemide)	-/0	?	+	-	Inhibition of monoamine oxidase enzyme
Sedative TCA (e.g., amitriptyline, doxepin, trimipramine)	+	+	+	-	Inhibition of serotonin and norepinephrine reuptake, antihistaminergic effect
Activating TCA (e.g., imipramine, desipramine)	-	-	+	-	Inhibition of serotonin and norepinephrine reuptake
Agomelatine	+	+	0	0	Agonism at melatonin M1 and M2 receptors, antagonism at serotonergic 5-HT _{2C} receptors
Bupropion	0/-	0/+	0/-	0/+	Inhibition of dopamine and norepinephrine reuptake
Sedative antidepressants (e.g., mirtazapine, trazodone)	+	+	0	0	antagonism at serotonergic 5-HT _{2A} receptors, antihistaminergic effect
Vortioxetine	0/-	?	+	-	Inhibition of serotonin reuptake, modulation of serotonergic receptors activity

SSRI selective serotonin reuptake inhibitors, SNRI serotonin norepinephrine reuptake inhibitors, NRI norepinephrine reuptake inhibitors, TCA tricyclic antidepressants, MAOI monoamine oxidase inhibitors, “+” increase, “-“ decrease, “0” no effect, “?” unknown

Table 2. Limitations of the literature in the approach of insomnia in MDD.

Group of potential biases	Limitations	Example	Strategies to address
Selection	Few data on subpopulations	Most studies include general population, and few approached children and adolescents, pregnant women or elderly.	Stratification of samples.
	Samples not representative of the populations with insomnia and MDD in clinical practice	Studies not specifically designed to assess insomnia in MDD	Design studies specifically targeting insomnia in MDD (not only post-hoc analysis)
Outcomes assessment	Indirect assessment of insomnia	Extract data about sleep from depression scales (e.g. Ham-D, MADR)	Inclusion of specific and reliable questionnaires
	Subjective assessment of insomnia severity	Most studies do not use objective (and potentially expensive) methods to assess insomnia and sleep architecture	Use of wearable devices
Confounders	Psychiatric comorbidities	Incomplete consideration of biases such as anxiety, substance abuse and environmental stress	Sample size large enough to control for potential confounders. Careful definition of inclusion/exclusion criteria.
	General medical comorbidities	Incomplete consideration of factors such as Body Mass Index, sleep disturbances and other medical conditions and general medications	

Figure 1. Schematic representation of the clinical correlates of insomnia in MDD.