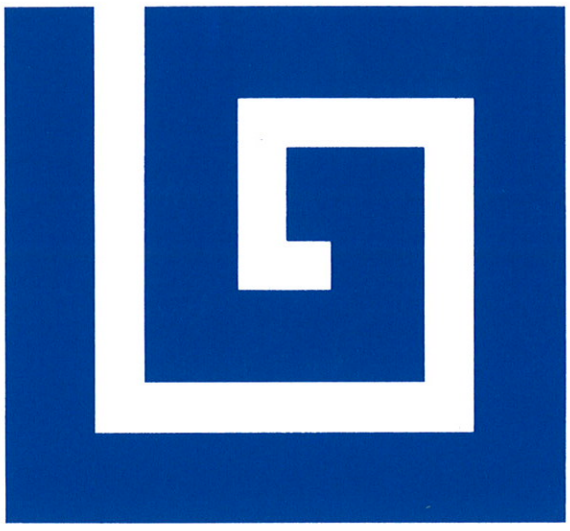

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Sleep, mood disorders and antidepressants: the melatonergic antidepressant agomelatine offers a new strategy for treatment

Venkatramanujam Srinivasan, Amnon Brzezinski, D. Warren Spence, Seithikurippu R. Pandi-Perumal, Rüdiger Hardeland, Gregory M. Brown, Daniel P. Cardinali

Abstract

Insomnia often precedes the appearance of mood changes. While the presence of disturbed sleep prior to the onset of depressed mood is useful prognostically, the ultimate co-occurrence of these symptoms can pose a considerable challenge for pharmaceutical therapy. Most currently used antidepressants (tricyclics, monoamine oxidase inhibitors, serotonin-norepinephrine reuptake inhibitors, serotonin receptor-2 antagonist/serotonin reuptake inhibitors, selective serotonin reuptake inhibitors) are effective antidepressants but they have the disadvantage that often aggravate sleep disturbances. An ideal antidepressant should address both problems: such an antidepressant should exert a rapid onset of action both on depressive symptomatology as well on sleep problems. The recently introduced novel antidepressant agomelatine has melatonergic agonist and 5-HT_{2C} antagonistic properties, and has been found effective in improving both depressive mood and sleep disturbances. Its mechanism of action differs from the currently used antidepressants. It thus represents a possible first line drug for treatment of mood disorders such as major depressive disorder, bipolar disorder and seasonal affective disorder. This review summarises what is known about the clinical efficacy and mechanism of action of agomelatine and compares these findings with those of currently available antidepressants.

Introduction

Mood disorders are almost regularly associated with sleep disturbances. The possibility that insomnia does not primarily reflect a consequence or an accompanying phenomenon of affective disorders, but may rather represent a major triggering factor for the development of depressive symptoms has been the subject of interest and debate among clinical and psychobiological researchers for many years. In fact, insomnia is not only considered as to be a main symptom of affective disorders, but has turned out to be a major risk factor for these diseases. Adults with insomnia have been reported to have a lifetime prevalence of major depression that is 10 to 20 times higher than those without insomnia (1). Sleep disturbances and changes in sleep form the diagnostic criterion for mood disorders in the *Diagnostic and Statistical Manual of Mental disorders - Text revision, Fourth Edition (DSM-IV-TR-2000)*. Sleep disturbances are present both preceding and during major depressive or manic episodes. Profound disturbances in sleep architecture have been reported in about 80% of depressive patients with major depressive disorders (MDD) or bipolar disorder (BPD) (2,3). The presence of sleep abnormalities in the first degree relatives of depressed patients who never experienced depressive episodes suggests that changes in sleep structure and quality can be viewed as markers of depressive illness (4,5). The importance of stable sleep wake rhythms and proper sleep hygiene have been advocated for prevention of relapses in the development of mania in BPD (6,7). Systematic reviews of these relationships have concluded that the early treatment of sleep disturbance should be considered an essential part of an effective program for the therapeutic management and prevention of relapse in mood disorders (8,9).

Sleep abnormalities in mood disorders

Mood disorders are among the most common forms of psychiatric illness. The major variants of mood disorders are MDD, BPD (manic or depressive episodes) and seasonal affective disorder (SAD). Epidemiological and electroencephalographic studies implicate sleep disturbances as a frequent underlying factor in mood disorders (5,10). Insomnia in young age is a lifetime risk for developing mood disorders. In half of the new-onset or recurrent episodes and in three quarters of manic episodes, insomnia preceded the appearance of mood changes (11,12). Various investigations have shown that discrepancies exist between subjective reports and objective measures of sleep efficiency (SE) in patients with mood disorders and no clear consensus has been achieved concerning which type assessment most accurately reflects the true SE in

these patients. Under- or overestimation of sleep parameters such as sleep onset latency (SOL), sleep depth, number of awakenings and total sleep time (TST) have been reported (13,14). However, polysomnographic (PSG) studies on patients with MDD or BPD have found objective findings of sleep disturbances, and thus PSG measurements have been advocated for use as biologic markers for mood disorders of both these clinical groups (15). Depressive patients experience all the main symptoms of insomnia, i.e., difficulty in falling asleep, difficulty in staying asleep and early morning awakenings (16). Decrease in SE, slow wave sleep (SWS), TST with increased SOL and nocturnal awakenings have all been reported in patients with MDD (17). A reduction in SWS, shortening of REM onset latency (REMOL), increased REM sleep and sleep continuity disturbances were prominent symptoms noted in untreated depressive patients (18). REM sleep abnormalities are considered specific symptoms of MDD. The temporal distribution of REM sleep is typically altered during overnight sleep in depressives (2,19,20). Abnormalities in the timing of the REM/non-REM (NREM) cycle in patients with depression have been interpreted as a consequence of disorganized pathways that regulate the sleep/wake cycle (21). The antidepressants that are in clinical use suppress REM sleep and increase REMOL before ameliorating symptoms of depression.

Although unipolar and bipolar types of depression can be clearly distinguished no significant differences are observed between these two groups in terms of nocturnal sleep patterns (22-26). PSG studies in patients with BPD with depression or mania have shown that shortened REMOL and disturbed sleep continuity occur during manic episodes (27). Bunney and his co-workers (28) were the first to report that BPD patients exhibited marked reductions in sleep during the night before they switched from depression and similar findings were reported by others (29). These and other similar findings prompted many to suggest that BPD symptoms are due to internal desynchronisation of circadian rhythms (30).

Antidepressants and sleep

Since 1950 a wide range of antidepressants have been developed for the treatment of depressive disorders. These include the tricyclics, monoamine oxidase inhibitors (MAOI), serotonin (5-HT)-norepinephrine (NE) reuptake inhibitors (SNRIs), serotonin receptor-2 antagonist/serotonin reuptake inhibitors (SARIs), and selective serotonin reuptake inhibitors (SSRIs). These drugs constitute the third most widely prescribed class of therapeutic agents worldwide with SSRIs accounting for 80% of the total market share (31). Antidepressant effects on sleep are exerted through inhibition of 5-HT or

NE reuptake, effects on 5-HT_{1A} receptors or on several subtypes of 5-HT_2 receptors, actions on α_1 and α_2 adrenergic or histaminergic receptors (32). While some antidepressants improve SE by ameliorating depressive symptoms others exert rapid beneficial effects on initiation and maintenance of sleep (33-35). The introduction of SNRIs and SSRIs has changed the strategies for clinical treatment of depressive disorders (36,37).

Currently SSRIs constitute the major class of antidepressants that are prescribed, but their use increases insomnia (38). At least one third of patients taking SSRIs also receive concomitant sedative-hypnotic medications (35). These findings have led to advocacy that the effects of antidepressants on sleep should be a primary concern in prescribing decisions for depressed patients (37). A brief account of antidepressant's effects on sleep will be reviewed here before considering how the novel melatonergic antidepressant agomelatine can be used for treating depression and associated sleep disturbances.

Tricyclic and monoamine oxidase inhibitor antidepressants

Tricyclics and MAOI have been in use for more than 30 years for treatment of MDD. Though their efficacy has been repeatedly demonstrated , these drugs are also known to suppress REM sleep and to increase REMOL (39,40). An exception is triimipramine which does not produce REM suppression (40). NE and 5-HT neurons, which are directly affected by tricyclics, are involved in the regulation of both mood and sleep. PSG studies with MAOI have shown that they prolong SOL, impair sleep continuity, and increase wake after sleep onset (WASO) (41,42).

Serotonin-norepinephrine reuptake inhibitors

SNRI drugs improve mood in depressive patients by inhibiting the pre-synaptic and astrocytic uptake of both 5-HT and NE (43). Studies with venlafaxine at doses ranging from 75 to 225 mg/day have shown that it causes sleep disturbances such as increase in WASO, REMOL and decrease in TST (42,44,45). REM sleep suppression has also been noted with venlafaxine treatment (46). Similarly, an increase in the frequency of periodic leg movements in sleep (PLMS) has been observed following venlafaxine treatment. PLMS are repetitive highly stereotyped leg movements that occur during sleep and/or waking state and are due to EEG arousals or awakenings that are associated with difficulties in initiating and maintaining sleep. The PLMS movements are the result of enhanced serotonergic availability and decreased dopamine effects caused by venlafaxine administration (46).

Serotonin-2 receptor antagonist/serotonin reuptake inhibitors (SARIs)

Trazodone and nefazodone belong to the SARI category. These drugs inhibit 5-HT_2 receptors and are also involved in the regulation of sleep (47). Trazodone also inhibits α_1-adrenergic and histamine H_1 receptors (48). Because of its effects on H_1 receptors, trazodone causes sedating effects and daytime somnolence (42). Further, trazodone has been found effective in increasing TST, reducing SOL and REM sleep time (42). Nefazodone treatment of depressive patients has been found to preserve sleep continuity and decrease the number of awakenings (49). However, its effects on SE are less consistent, and increases or no effects have been observed as well (21).

Selective serotonin reuptake inhibitors (SSRIs)

This category of drugs represents a major class of antidepressants that have been used clinically since the importance of serotonin in mood regulation was recognized. SSRIs constitute about 80% of all prescriptions for antidepressants in the market (31). These drugs block the presynaptic uptake of 5-HT and activate its receptors, thereby enhancing the interaction of 5-HT with multiple pre- and post-synaptic receptors. However, the usage of SSRIs in depressed patients may result in adverse effects.

Fluoxetine administration at 20 mg doses for four weeks caused significant reductions in SE, a finding that correlated with plasma fluoxetine levels (21). A similar decrease in SE was reported in another study (50). Suppression of REM was also observed with fluoxetine (21). Paroxetine, another drug of the SSRI category was found in one study to reduce SE and to increase the number of awakenings after 4 weeks of treatment in depressive patients. It did not however influence TST or SOL (51). In normal, healthy subjects, paroxetine in 20 mg doses was also found to reduce SE and additionally to increase WASO. Further, REM sleep was reduced and prolongation of REMOL was observed (52). An association between the use of SSRIs and suppression of REM and prolongation of REMOL was confirmed in a study conducted on 274 patients (46). Use of SSRIs also causes a number of negative effects subsequent to over-stimulation of the serotonergic system. These have included symptoms such as agitation, headaches, gastrointestinal distress and sexual dysfunction (5).

Which properties should be combined in an ideal antidepressant?

From the foregoing discussion it is clear that while some antidepressants promote sleep initiation and maintenance (5-HT receptor antagonists) many antidepressants, particularly SSRIs, fluoxetine, and the SNRI venlafaxine exert adverse effects on sleep. As such, the sleep promoting effects of these drugs are either limited or non-existent (17). Due to the tendency of many of these drugs to exacerbate insomnia the concomitant administration of either benzodiazepine or highly specific gamma-amino butyric acid $(GABA)_A/\alpha_1$ adrenergic receptor ligands such as zolpidem have been advocated as combined treatment strategies (35).

In view of their effects in depressed patients it is clear that caution should be exercised while prescribing antidepressants. An ideal antidepressant should not only mitigate symptoms of depression but also improve sleep quality and efficiency and promote a feeling of freshness in the next morning following a night's sleep (53). Moreover, the superior efficacy of an antidepressant rests primarily on an earlier onset of action and improved clinical effect (54). These capabilities not only reduce the suffering associated with depression but also help to contain the high cost of treatment. Based on these criteria, the SSRIs and SNRIs have only limited efficacy in treating severe depression and also have a long latency of action (55,56). The efficacy of SSRIs in severe depression expressed as a 50% score reduction in Hamilton rating scale for Depression (HAM-D) has been shown to vary from 53% to 64% for SSRIs and from 43% to 70% for tricyclic antidepressants (54). Moreover, the onset of antidepressant action of SSRI also ranges from 3 to 4 weeks (57). Most of the currently available antidepressants produce sexual dysfunction, a side effect that often interferes with recovery from depression from a depressive episode (58,59). This Side effect greatly influences the acceptability of the drug by patients and hence any antidepressant without discontinuation symptoms will be beneficial to the patient.

Melatonin in mood disorders

Melatonin is the major hormone secreted from the pineal gland of all mammals including man. The rhythm of its secretion, characterized by high levels during the nighttime hours and low levels during the day, is endogenous and is driven by the hypothalamic circadian master clock, the suprachiasmatic nucleus (SCN). Melatonin is involved in a number of physiological functions such as the regulation of circadian rhythms, reproduction, gastrointestinal function, immune mechanisms, sleep-wakefulness rhythm, antioxidant defence mechanisms and control of human mood and behaviour (60,61).

Melatonin participates in the regulation of these mechanisms by acting through G-protein coupled membrane receptors (GPCRs) such as MT_1 and MT_2 receptors (62) and, presumably, nuclear receptors (63). The secretion of melatonin at night has many physiological implications. Melatonin, which has both sleep promoting and circadian rhythm regulating activities, peaks in humans during the period of greatest increases in sleep propensity (64,65). The fact that its nocturnal increase occurs approximately 2h in advance of the individual's habitual sleep time has prompted many investigators to suggest that melatonin is involved in the physiological regulation of sleep.

Melatonin activity has been proposed as both a state marker and trait marker for mood disorders (66). Wetterberg and his co-workers formulated the "*low melatonin syndrome*" hypothesis of depression, a concept that relates low melatonin secretion to an increased susceptibility to depressive disorders (67). Diminished secretion of melatonin is said to be partially responsible for the deterioration of sleep maintenance seen in depressives. Indeed, some studies have shown that melatonin secretion is decreased in depressives (68-70). However, increases in melatonin secretion have also been documented in depressives (71,72). Since a drop or rise in melatonin levels in depression is paralleled by a comparable alteration in 5-HT levels, further research is needed to identify the subgroups of depression involved and the associated biochemical abnormalities (67). In any case, the disturbance in melatonin secretion in depression supports the probable involvement of melatonin in the regulation of mood (66). In addition to changes in the amplitude of nocturnal or diurnal melatonin secretion, a number of studies also have found disturbances in the melatonin rhythm of patients with MDD, BPD and SAD. Both phase advances and phase delays in melatonin secretion have been observed in patients with MDD (66). Similarly, a phase delay of the melatonin rhythm has been reported in patients with SAD (73). A phase-delay in the circadian pacemaker relative to timing of the sleep/wake cycle has been assumed to be responsible for the pathogenesis of SAD (74). It is hypothesized that the symptoms of hypersomnia and late awakening seen in SAD patients are due to the delayed phase and long duration of melatonin secretion that occurs in this group (75).

Melatonin has been evaluated and has been found to have weak antidepressant effects (76). Its action spectrum indicates efficacy in cases in which disturbances of the circadian system are causative for the disorder, such as poor entrainment of oscillators with external time cues, due to exceptionally short or long spontaneous circadian periods [familial advanced sleep phase syndrome (FASPS) and delayed sleep phase syndrome (DSPS)] and or to impairments of the light-input pathway (deficiency of melanopsin-containing retinal ganglion cells or blindness), or to insufficient internal coupling of oscillators (as assumed for BPD).

With regard to MDD, the situation is more complex because of multiple possible causes. Nevertheless, melatonin has sometimes been found to be effective for improving sleep in MDD patients. In a study conducted with 10 individuals having MDD, administration of slow release melatonin 5mg/day and fluoxetine over a period of 4 weeks improved the sleep quality (77). In another study of patients suffering from DSPS and depression, melatonin administration not only improved the TST but also reduced the psychometric scores of depression (78). These studies lend support to the concept of the relationship between sleep disturbances and depression.

Agomelatine, a melatonergic antidepressant

Agomelatine, a melatonergic agonist developed by Servier Laboratories (France), is a naphthalenic compound chemically designated as [*N*-[2-(7-methoxynaphth-1-yl)ethyl] acetamide]. It is metabolized in the liver by three cytochrome P_{450} (CYP) isoenzymes (CYP1A1, CYP1A2, and CYP2C9) (79). Agomelatine has a high affinity for MT_1 and MT_2 receptor sites (80). The affinities to human MT_1 and MT_2 receptors (K_i=61.5 pM and 268 pM, respectively) are in the range of those for melatonin, but it additionally acts as a 5-HT_{2C} receptor antagonist (IC_{50}=270 nM), with very low affinities to most other 5-HT receptor subforms (81-83). Because of a moderate binding for 5-HT_{2B} receptors it is sometimes also considered as an antagonist of this latter subtype (84), but the practical relevance of this property is still uncertain. It has no significant affinity towards muscarinic, histaminergic, adrenergic, GABAergic or dopaminergic receptors and their subtypes (82).

In several animal models of depression such as the learned helplessness model (85), forced swim test (83) and social stress model (86) agomelatine has been shown to display significant antidepressant activity. Agomelatine was recently licensed in Europe by the European Medicines Agency for major depressive episodes in adults. It should be noted that the combination of properties as a melatonergic agonist and 5-$HT_{2B/2C}$ antagonist has recently been identified in another compound, β-methyl-6-chloromelatonin (TIK-301, formerly known under the code LY 156735) (84,87). TIK-301 was reported to be a more potent 5-HT_{2C} antagonist than agomelatine (88). TIK-301 differs from agomelatine also by a relatively higher MT_2 affinity, as is typical for 6-chlorinated indole melatonin receptor agonists (89). To date, as long as the compound is not approved as an antidepressant, and in the absence of further clinical studies directed towards treatment of depressive disorders, no advantage over agomelatine can be assumed.

An appropriate dosage of agomelatine has to consider the differences in the affinity to melatonin receptors and 5-HT_{2C}, which is by orders of magnitude lower than that for MT_1 and MT_2. If only a chronobiotic, i.e., phase-shifting action is desired, melatonin is already effective at relatively low doses, eventually down to 0.3 mg (90) and, with regard to the similar affinities of agomelatine, the same should be assumed for this drug. However, if direct antidepressant effects via 5-HT_{2C} inhibition are required, much higher doses of agomelatine (25 or 50 mg/day) have to be applied. At suitable levels, the action as a 5-HT_{2C} antagonist has been demonstrated *in vivo*. In freely moving rats, it exhibits typical secondary effects of 5-HT_{2C} inhibition, such as enhancements of fronto-cortical NE and dopamine concentrations, an action not inhibited by melatonergic antagonists (82).

Clinical efficacy of agomelatine in mood disorders

The first multicenter, multinational, placebo-controlled study of agomelatine's effects in depression was undertaken on 711 depressed patients drawn from 102 centres located in Europe, mainly in Belgium, France and UK (57). Agomelatine in doses of 25 mg/day was administered to MDD patients for a period of 8 weeks and its effect compared to the SSRI paroxetine (20 mg/day). By using remission analysis (remission defined as HAM-D score of <7) both agomelatine (30.4%) and paroxetine (25.7%) caused significantly more remissions than placebo. Responder analysis (50% or more reduction in HAM-D) showed that agomelatine was significantly better (61.5%) than placebo (46.3%), while the paroxetine response was closer to placebo (56.3%). In the severely depressed group of patients (586 patients with HAM-D score >25 at inclusion), agomelatine was significantly better than placebo in reducing depressive symptoms ($P<0.05$). In this study agomelatine was also found to be better tolerated than paroxetine (57).

The efficacy and safety of agomelatine were also tested in another multicenter study conducted in 21 centres involving 212 outpatients drawn across Finland, Canada, and South Africa (91). In this 6 week double-blind randomized, placebo-controlled study, agomelatine was given in 25-50 mg doses. At the end of 6 week period it was noted that agomelatine caused significant improvement in the clinical state of the patients as compared to placebo ($P=0.045$). In the severely depressed population of this study (with baseline HAM-D score of 25 or higher) agomelatine in doses 25 or 50 mg/day, caused significant reduction in HAM-D score and improved the clinical status of

patients when compared to placebo (P=0.024).The significantly higher rate of responders to agomelatine (49.1%) versus placebo (34.3%) and the shorter time to first response further supported the clinical efficacy of agomelatine (91).

In an open label study on bipolar I patients with HAM-D score of more than 18, agomelatine in the dose of 25 mg/day was administered for six weeks as treatment adjunctive to either lithium or valpromide (92). Agomelatine use was also extended up to 46 weeks. It was noted that patients who were severely depressed (HAM-D score of 25 or higher) showed a clinical response as early as 1 week following initiation of agomelatine treatment. Nineteen of the patients entered optional extension period for a mean of 211 days (6-325 days) and 11 of them completed 1 year extension period of study. There was no dropout from the study due to adverse events during the first 6 week of treatment. Clinical remission was effective suggesting that agomelatine at a 25 mg dose is effective for treatment of bipolar depressed patients (92).

In patients with SAD, the efficacy of agomelatine was evaluated for a period of 14 weeks (93). Efficacy was assessed by the Structured Interview Guide for the Hamilton Depression Rating Scale (SAD version; SIGH-SAD), the Clinical Global Impression of Severity (CGI-S) and Improvement (CGI-I) and the Circscreen, a self-rating scale for the assessment of sleep and circadian rhythm disorders. Use of agomelatine led to a progressive and statistically significant decrease of SIGH-SAD, CGI-S and CGI-I scores from 2 week onwards ($P < 0.001$). Treatment with agomelatine over 14 weeks yielded a response rate of 75.7%, and a remission rate of 70.3% in the intention-to-treat sample. Agomelatine was found to be well tolerated, with no adverse event being reported through the entire period of treatment (93).

Agomelatine’s effect on sleep in depressives

Agomelatine was effective not only in causing remission of illness in patients with either MDD, BPD or SAD but also was found effective in improving the quality and efficiency of sleep in these patients. Using the Leeds Sleep Evaluation Questionnaire in a study of 165 patients it was found that agomelatine (25 mg/day) caused earlier and greater improvements on the criteria of "getting into sleep" and quality of sleep. These improvements in sleep parameters were evident from 1 week of treatment onwards and did not occur in patients treated with venlafaxine (94). In a PSG study of 6 weeks of agomelatine treatment reveals that the duration of SWS increased without affecting REM sleep duration. The improvement in sleep quality measures was evident from the 1st week onwards (95,96). The effect of agomelatine on the cyclic alternating pattern of

sleep (CAPS) was evaluated in NREM sleep by using PSG (97). After 7 and 42 days of treatment, a significant decrease in CAPS time and CAPS cycles was seen thereby showing that agomelatine normalizes NREM sleep in depressive patients. The changes in NREM sleep variables preceded the improvement in subjective mood suggesting that part of agomelatine's effect is mediated through its ability to improve sleep architecture.

Agomelatine is, thus, a dual action drug that improves sleep quality in depressed patients and also produces rapid antidepressant action. EEG studies of the effects of agomelatine on sleep in MDD patients showed that SE increased and that intra-awakening decreased progressively from day 7 onwards, the differences from baseline being close to significance at day 14 (P=0.068 and P=0.076). These differences attained statistical significance at the last evaluation (42 days after treatment) (P=0.05) for the increase in SE, and P=0.04 for the decrease in intra sleep awakening. SWS duration and percentage of sleep period time in SWS (stages 3 and 4) increased significantly after agomelatine treatment (95,96)

Mechanism of agomelatine's antidepressant action

Conventional antidepressants elevate daytime mood by activating central nervous system (CNS) mechanisms. If these energizing effects are sustained into the night they will impair the quality of sleep (98). Agomelatine's combined mechanism of action helps to preserve sleep quality at night, while elevating mood during the daytime and, hence, depressives are able to experience an improved quality of life (47). Agomelatine's melatonergic effects of sleep promotion may counteract the antihypnotic effects caused by the drug's 5-HT_{2c} antagonism. 5-HT_{2c} receptors are concentrated in frontal cortex, amygdala, hippocampus and cortico-limbic structures that are involved in the regulation of mood and cognition. They are also present in the SCN (99). Antidepressants, while exerting their therapeutic effects, decrease the number of 5-HT_{2c} receptors (100). Decreases in the density of 5-HT_{2c} receptors have been demonstrated in the prefrontal cortex of suicide victims with history of depression, thus suggesting that prefrontal 5-HT_{2c} receptors are involved in the pathophysiology of depressive disorders (101,102).

By its action on MT_1 and MT_2 melatonergic receptors present in SCN, agomelatine normalizes the disturbed circadian rhythms including sleep-wakefulness, that occur in patients with MDD. Disruptions in circadian rhythms have been shown to correlate with clinical severity of depression, a finding that is attributed mainly to disturbances in the sleep/wake rhythm (103). The efficacy of agomelatine vs. sertraline to modify

the amplitude of the circadian rest-activity cycle and depressive and anxiety symptoms in patients with MDD was evaluated by using wrist actigraphy and sleep logs (104). A significant difference in favour of agomelatine on the relative amplitude of the circadian rest-activity cycle was observed at the end of the first week. Significant improvements in sleep latency and SE from week 1 to week 6 were similarly observed with agomelatine as compared to sertraline. Over the 6-week treatment period, depressive symptoms improved significantly more with agomelatine than with sertraline, as did anxiety symptoms (104). Inasmuch as it improves day-time alertness and mood, normalizes the sleep/wake rhythm and improves sleep quality and efficiency, it is concluded that agomelatine has advantages over any of the antidepressants that are in clinical use today.

Further, many antidepressants that are currently in use cause impairment of sexual function (105). By contrast, patients treated with agomelatine have been found to experience significantly less sexual dysfunction than those treated with placebo, thus supporting the conclusion that agomelatine is far superior in this regard than currently used antidepressants (106,107). Additionally, agomelatine does not produce a discontinuation syndrome such as has been reported with the use of other antidepressants. Agomelatine's overall side effect profile, which include the absence of discontinuation effects, or adverse effects on cardiac or sexual function, thus support its use as a treatment of choice for depressive disorders (108,109).

Conclusion

Sleep disturbances and changes in sleep constitute the major diagnostic criterion for mood disorders. Insomnia at young age also is a major risk factor which predicts the development for developing of mood disorders. Although most antidepressants in general improve SE, the SSRIs, currently the most commonly prescribed agents in this category, antidepressants such as SSRIs cause actually worsen worsening of insomnia symptoms in depressive patients. The generally recommended treatment strategy in this case and hence they need is the co-prescription of hypnotic-sedatives, for tackling the problem of sleep disturbances which themselves have a number of side effects. Further, the findings that disturbed sleep increases the susceptibility for, and can exacerbate the severity of mood disorder symptoms, emphasizes the importance of considering these problems when developing a treatment strategy. Hence, it is thus suggested that when prescribing an antidepressant, its effect in improving sleep quality and efficiency should be given primary importance.

The pineal hormone melatonin has a regulatory role in both sleep and sleep/wake rhythm. The development of a melatonin agonist agomelatine which also displays 5-HT_{2c} antagonism has proved to be useful in clinical trials undertaken in patients with MDD, BPD, and SAD. Unlike the other antidepressants agomelatine has proved to be effective in causing remission in severely depressed patients categories while also displaying a rapid onset of action. Agomelatine has been shown to improve both the quality and efficiency of sleep and, further, it does not cause REM sleep suppression as seen with other antidepressants. The side effect of this drug also is very close to that of placebo. The noteworthy feature of agomelatine is that it acts differently from other antidepressants by promoting nocturnal sleep and daytime alertness through a novel mechanism of action. Hence it is concluded that agomelatine is a good an excellent drug antidepressant to be used for use with patients with mood disorders.

Competing interest statement and disclosure statement

S.R. Pandi-Perumal is a stockholder and the President and Chief Executive Office of Somnogen Inc., a New York Corporation. He declared no competing interests that might be perceived to influence the content of this article. All remaining authors declare that they have no proprietary, financial, professional, nor any other personal interest of any nature or kind in any product or services and/or company that could be construed or considered a potential conflict of interest that might have influenced the views expressed in this manuscript.

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