Novel melatonin-based therapies: potential advances in the treatment of major depression

Ian B Hickie, Naomi L Rogers

Major depression is one of the leading causes of premature death and disability. Although available drugs are effective, they also have substantial limitations. Recent advances in our understanding of the fundamental links between chronobiology and major mood disorders, as well as the development of new drugs that target the circadian system, have led to a renewed focus on this area. In this review, we summarise the associations between disrupted chronobiology and major depression and outline new antidepressant treatment strategies that target the circadian system. In particular, we highlight agomelatine, a melatonin-receptor agonist and selective serotoninergic receptor subtype (ie, 5-HT₂C) antagonist that has chronobiotic, antidepressant, and anxiolytic effects. In the short-term, agomelatine has similar antidepressant efficacy to venlafaxine, fluoxetine, and sertraline and, in the longer term, fewer patients on agomelatine relapse (23·9%) than do those receiving placebo (50·0%). Patients with depression treated with agomelatine report improved sleep quality and reduced waking after sleep onset. As agomelatine does not raise serotonin levels, it has less potential for the common gastrointestinal, sexual, or metabolic side-effects that characterise many other antidepressant compounds.

Introduction

Major depression is a leading cause of premature death and ongoing disability.²³ Although the therapeutic benefits of drugs for less severe forms of depression is debatable,⁴⁵ the overall value that results from the wider provision of both drug and psychological treatments for patients with depression is clear. Benefits include reduced suicide rates, increased participation in the workforce, reduced secondary alcohol or other substance misuse, decreased risk of cardiovascular disease, and, through more regular and extensive use of appropriate health services, destigmatisation of depression and anxiety.⁴⁴

As long-term antidepressant therapy is often an essential component of treatment for individuals with severe depression, the drive to develop drugs with improved safety profiles has intensified. Although the newer antidepressant drugs have clinically important differences in efficacy and tolerability,⁷ most drug development remains focused on the moderation of the same monoamine targets (eg, serotonin, norepinephrine, or dopamine). Recently, there have been major advances in our understanding of the biology of the circadian system, the clinical significance of disrupted daily cycles, the adverse effects of many antidepressant drugs on circadian cycles and sleep architecture, and the mechanism by which lithium has profound effects on circadian biology. In view of the development of one melatonin analogue with reported antidepressant activity, agomelatine, these advances have led to a renewed focus on the potential clinical benefits that could be derived from modulation of the circadian system.⁴⁸

Circadian and sleep–wake systems

The circadian system is central to the maintenance of the daily sleep–wake cycle and sense of wellbeing. This system coordinates key physiological components, including the sleep–wake, thermoregulatory, endocrine, immune, cardiovascular and metabolic systems⁹⁻¹¹ (figure 1). Although circadian rhythms are disturbed in many neuropsychiatric states (eg, psychotic disorders, post-infectious illnesses, chronic fatigue states, and chronic pain), they are fundamentally disrupted in major depression, atypical depression, and seasonal affective disorder.⁹ Notable fluctuations are also intrinsically linked to the various phases of bipolar mood disorders.¹⁵

Circadian disturbances in depression

There are strong links between circadian disturbance and some of the most characteristic symptoms of clinical depression, including delayed sleep onset, non-restful sleep, early-morning wakening, daytime fatigue, and blunting or reversal of the normal morning peaks in subjective energy, mood, and alertness.¹⁰ The pattern of circadian disruption is highly variable, with some patients having phase advances (characterised by early sleep-onset,
early waking, and advancing of the secretory rhythms of melatonin, cortisol, and norepinephrine; figure 1B), whereas others have phase delays (ie, late sleep-onset with delayed morning-wakening; figure 1C).

There are also reductions in the amplitude of diurnal variations of other key features such as core-body temperature or plasma concentrations of cortisol.10,11,15–19

Under conditions of internal desynchronisation (figure 1D), the timing of several circadian rhythms (eg, core body-temperature, plasma concentrations of melatonin and cortisol, sleep–wake timing) are out of phase both with each other and the external environment.11

In our opinion, this breakdown in the internal links between key sleep, mood, cognitive, and other physiological cycles results in polyphasic sleep patterns, excessive sleepiness or fatigue while awake, depressed mood, and impaired neurocognition.

Most patients with depression have prolonged sleep latencies and a high frequency of arousals and awakenings during the night. Consequently, hypersomnia, daytime fatigue, or napping might be prominent.20 Additionally, polysomnographically defined changes in sleep architecture in patients with depression include decreased time spent in slow-wave sleep, reduced periods of rapid eye-movement (REM) sleep, reduced latency to the first REM episode, and increased amounts of stage 1 and stage 2 sleep.21 Although non-REM sleep (stage 1, stage 2, and slow-wave sleep) is mainly regulated by the homeostatic sleep system, REM sleep is modulated by the circadian system.21 The goal of antidepressant treatment is not only to restore sleep–wake patterns but also to resynchronise circadian-dependent biology and its link with the external environment.

Disruption of circadian function as a cause of neuropsychiatric disorders

There has been increased emphasis on the possibility that disturbed circadian function is a major risk factor to a range of neuropsychiatric disorders. From this perspective, disturbance of circadian rhythms (independent of specific diagnosis) results in a phenotype characterised by depressed mood, daytime fatigue, poor concentration, disturbed circadian function is a major risk factor to a range of neuropsychiatric disorders and primary mood disorders share some common genetic risk factors (table 1) and similar environmental determinants. Relevant environmental factors include prolonged sleep disruption, alcohol or other substance misuse, transmeridian travel or shiftwork, and other medical conditions (eg, acute infection). Behavioural or pharmacological interventions that focus on the restoration of normal circadian function result not only in substantial improvements in mood but also in substantial improvements in cognition and daytime fatigue.20,21

Circadian limitations of current treatments of major depression

For more than 50 years, drug treatments for major depression have targeted monoamine systems. Although many of the older tricyclic drugs had beneficial effects on sleep onset or sleep duration (mostly via histaminergic mechanisms), they also suppressed REM sleep. In fact, REM suppression was previously thought to be an

Figure 1: Circadian rhythmicity for individuals who are normally entrained (A), phase advanced (B), phase delayed (C), or who have internal desynchrony (D). Sleep periods are indicated by grey-shaded area, with time of day on bottom axis. (A) Normally entrained: onset of melatonin secretion occurs about 2 h before sleep onset and just before nocturnal decline in core temperature. Plasma concentrations of cortisol reach nadir in evening and peak in morning, soon after sleep offset. (B) Phase advanced: temporal link between circadian rhythms of core temperature, plasma concentrations of melatonin and cortisol, and timing of sleep are maintained; however, all are shifted to earlier clock time relative to normal entrainment. (C) Phase delayed: temporal link between circadian rhythms of core temperature, plasma concentrations of melatonin and cortisol, and timing of sleep are maintained; however, all are shifted to later clock time relative to normal entrainment. (D) Internal desynchrony: temporal link between circadian rhythms of core temperature, plasma concentrations of melatonin and cortisol, and timing of sleep are shifted relative to one another, and are out of phase with one another. Based on data from Rogers and colleagues.22–24
essential feature of antidepressant compounds. The most commonly prescribed selective serotonin-reuptake inhibitors often disrupt slow-wave sleep and REM cycles (at least in the short term) and do not necessarily restore normal circadian function.

These adverse effects of new antidepressants often result in the co-prescription of other sedative drugs. In severe cases of depression, adjunctive therapy with second-generation antipsychotic drugs that have prominent sedative or mood-stabilising properties (eg, olanzapine or quetiapine) is now commonplace. Hypnotic drugs that simply reduce sleep onset or night-time awakenings do not relieve depression. Similarly, drugs that are purely sedative have only limited effects on restoring normal chronobiology, and long-term treatment poses high risks of tolerance and addiction. Restoration of normal chronobiology is increasingly thought to be a marker of effectiveness for antidepressant treatments. Failure to restore normal rhythms is highly predictive of ongoing symptoms or early relapse.

A circadian focus for antidepressant treatments

A circadian focus for treatments of depression places emphasis not only on the restoration of normal daily variations in the sleep–wake cycle, but also on the restoration and synchronisation of other key neuro-hormonal (eg, variations in plasma concentrations of melatonin and cortisol), physiological (eg, body temperature), and neurocognitive signs (eg, alertness). A prerequisite is re-entrainment of the circadian system to the cues in the external environment. Several strategies are available to achieve this goal, including appropriately timed exposure to bright or blue light, treatment with melatonin, and restructuring of sleep–wake timing. One study reported positive effects of combining pharmacological interventions with adjunctive circadian-based therapies (ie, sleep deprivation, exposure to bright light, and sleep-phase advance) to reduce depressive symptoms in patients with bipolar disorder. In patients who were randomly assigned to receive the adjunctive circadian-based interventions (n=32), a significantly greater antidepressant effect was evident 48 h after the start of treatment (effect size 0.56, p=0.03), which was sustained for up to 7 weeks (0.51, p=0.02), compared with patients who received drugs alone (n=17).

Recently, several melatonin analogues have been developed and, as expected, they showed chronobiologic effects. Some of the drugs that have traditionally been used in the management of mood disorders also affect key regulatory aspects of the circadian system. The mood stabiliser lithium produces phase delay, and might increase the circadian period. More recently, the chronobiotic effects of lithium have been reported to be probably attributable to its action on glycogen synthase kinase 3β, which is a central regulator of the endogenous circadian clock.

Behavioural manipulation of the circadian system

Several behavioural treatments focus on manipulation of the circadian and related sleep–wake systems. The main target has typically been the sleep phase, with less emphasis on increasing daytime activity (particularly in the morning period) or reduction in daytime napping. Total or partial sleep deprivation during the second half of the night has short-term antidepressant effects. The antidepressant effect of sleep deprivation is reversed after subsequent sleep episodes, and periods of repeated sleep deprivation result in a build-up of a sleep debt. This effect has adverse consequences on normal daytime wakefulness, neurocognitive functioning, and safety (eg, while driving a motor vehicle or operating machinery).

Exposure to chronic sleep restriction (7–14 days), with allowable time in bed limited to less than 6 h per night, results in cumulative deficits in neurocognitive performance. The negative effects of sleep restriction on neurocognitive outcomes are reversed after recovery sleep. Other studies have indicated similar effects with fewer days of sleep restriction, in addition to changes in

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<th>Other notes</th>
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<td>CLOCK</td>
<td>Bipolar disorder</td>
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<td>ARNTL (also known as BMAL1 or MOP3)</td>
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<td>PER3</td>
<td>Bipolar disorder, seasonal affective disorder</td>
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<tr>
<td>TIMELESS (also known as TIM1)</td>
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<tr>
<td>PER2, NPAS2, ARNTL</td>
<td>Seasonal affective disorder</td>
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GS1B=glycogen synthase kinase 3β; CLOCK=clock homologue; SNP=single-nucleotide polymorphism; ARNTL=aryl hydrocarbon receptor nuclear translocator-like. PER=period homologue; TIMELESS=timeless homologue. NPAS2=neuronal PAS domain-containing protein gene 2. McClung, Partonen and colleagues, Wulff and colleagues, and Mansour and colleagues provide further details of the links between circadian genes and affective disorders.
a range of physiological functions, including melatonin secretion and metabolic variables. Although bright-light therapy can reverse depressive symptoms, this technique has mainly been used in patients with seasonal affective disorder (also known as winter depression). The effectiveness of bright-light exposure is assumed to result from the acute daytime suppression of melatonin, resulting in long-term phase-shifts and restoration of an appropriate relation with the external environment. Even though most studies of bright-light therapy have been done in patients with seasonal affective disorder, several short-term studies, of small sample size, have indicated efficacy with bright-light therapy for non-seasonal depression. In a Cochrane meta-analysis, bright-light therapy alone, or as an adjunct to either antidepressant drugs or to sleep deprivation, had some modest effects. Recently, the circadian system was reported to be most sensitive to light in the blue wavelength range (460 nm), thereby allowing lower intensities of light to be used to achieve equivalent phase shifts.

Melatonin
Melatonin has high affinity for two receptors (MT1 and MT2), which are located throughout the brain, including in the suprachiasmatic nucleus of the hypothalamus, substantia nigra, hippocampus, cerebellum, ventral tegmental area, and nucleus accumbens. These brain areas are involved in regulating various homeostatic systems, including sleep–wake activity and thermoregulation. The exact roles of these two G-protein-coupled receptors is not clear, and the ratios of expression of the two receptors might be important for some of the actions of melatonin. Changes in the brain content and the ratio of MT1 to MT2 receptors have been reported in neurodegenerative disorders (eg, Alzheimer’s disease), with similar changes reported after chronic antidepressant use. Although a third melatonin binding site (MT3) has been identified, melatonin binds to this site with much lower affinity and its role is less clear.

Melatonin is produced and secreted in the pineal gland. In healthy individuals without disrupted chronobiology or depression, melatonin’s secretion is high at night with only negligible circulating concentrations during daylight hours. Melatonin has an important role in the circadian timing system by binding to receptors in the suprachiasmatic nucleus and to other cells and systems throughout the body. Melatonin’s binding to the suprachiasmatic nucleus has two effects: inhibition of neuronal firing in the suprachiasmatic nucleus and entrainments or phase shifts in circadian rhythms. Additionally, nocturnal elevation in melatonin’s plasma concentrations is associated with increased sleep propensity, reduced body temperature, and decreased alertness.

Exogenous melatonin treatment
Melatonin is now widely available in the USA where it is deemed to be a dietary supplement. Different formulations of melatonin are sold internationally, with both immediate-release and sustained-release options available. Appropriately timed administration of melatonin has chronobiotic properties and can assist with phase shifting the circadian system (either alone or, more typically, in combination with light exposure). In addition to its chronobiotic effects, melatonin also increases sleep propensity, reduces sleep latency, decreases alertness and neurocognitive functioning, and lowers core body temperature. Although these outcomes are desirable at night, they might be thought of as adverse effects if melatonin is given during the day.

Is melatonin an antidepressant?
Exogenous melatonin has some antidepressant-like actions in animal models. Daily treatment with melatonin reverses the adverse effects of chronic stress in mice. By contrast, treatment with melatonin alone in human beings does not seem to be an effective antidepressant strategy. Although melatonin might improve sleep–wake timing and increase sleep duration in patients with major depressive disorder, there seem to be few more specific antidepressant effects. Addition of chronobiotic drugs such as melatonin to currently used antidepressant therapies can, however, improve overall outcomes.

Although some antidepressants improve several sleep variables, including sleep efficiency and increasing the amount of REM sleep, others (eg, tricyclic antidepressants and selective serotonin-reuptake inhibitors) have negative effects on sleep architecture, reducing the duration of REM sleep and increasing REM latency. Because REM sleep is under circadian control, this latter finding might indicate changes in the circadian system rather than in the sleep system. As disruptions to other variables affected by the circadian system, including melatonin, core temperature, and cortisol, are also common in patients with depression, antidepressant treatments should target these broader domains. The compounds that bind melatonergic receptors might be expected to have such effects.

Melatonin analogues
By contrast with most formulations of melatonin available commercially, the development of specific melatonin analogues means that we now have access to compounds that are being systematically evaluated pharmacologically and behaviourally. Although all melatonin analogues have been investigated for their sleep-promoting effects, they differ in their chemical structure and binding affinities for MT1, MT2. Additionally, one compound, agomelatine, also binds to the 5-HT2c and 5-HT1c receptors and has been studied more extensively as a primary antidepressant drug. Table 2 lists a summary of actions of melatonin analogues. Rajaratnam and colleagues provide further detail about the animal studies done with these compounds.
New Drug Class

Circadin
Melatonin in the Circadin formulation works in the same way as does endogenous melatonin at the MT, and MT receptors, and reduces the time to fall asleep and improves the quality of sleep and morning alertness in people aged over 55 years with insomnia.61,67

Ramelteon
Ramelteon has high affinity for MT and MT receptors and low affinity for MT binding sites.4 In studies of transient insomnia and chronic insomnia, done in both general adult and older adult populations, ramelteon had a modest effect on sleep latency and total sleep time.68 In these studies, patients were allocated a set time in bed for sleep; consequently, the increase in total sleep time induced by ramelteon was attributable to the reduction in the time taken to fall asleep. Ramelteon has been approved by the US Food and Drug Administration (FDA) for the treatment of insomnia, particularly in individuals in whom insomnia is associated with delayed sleep onset.

Tasimelteon
This compound has high affinity for MT, and MT receptors and produces phase shifts, in animal models, that are of similar magnitude to those induced by melatonin.74 In human beings, there is evidence of improvements in the latency to sleep and improved sleep maintenance, when sleep was attempted at an earlier phase than normal (ie, during the early afternoon).65 Additionally, there is notable phase shifting after treatment with tasimelteon, with dose-dependent phase advances in the timing of the dim-light melatonin onset after a 5-h phase advance of the light–dark cycle.65

PD-6735
This compound is a selective agonist at MT and MT receptors with substantial chronobiologic and soporific properties. In patients with chronic primary insomnia, reductions in sleep latency were reported after a range of doses.66 After a 9-h phase advance of the light–dark cycle, PD-6735 increased the rate of re-entrainment in a range of circadian rhythms, including those of core body temperature, and plasma concentrations of cortisol, potassium, sodium, and chloride.66

Table 2: Effects of melatonin and melatonin analogues

<table>
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<tr>
<th>Analogues</th>
<th>Trade names</th>
<th>Approval</th>
<th>Binding*</th>
<th>Sleep effects</th>
<th>Chronobiotic effects</th>
<th>Antidepressant effects</th>
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<td>Agomelatine (Servier)</td>
<td>Valdoxan, Melitor, Thymanax</td>
<td>EMA 2009</td>
<td>MT, MT, 5-HT (antagonist), 5-HT (antagonist)</td>
<td>Significant benefits in patients with depression</td>
<td>Phase advance; entrains circadian system</td>
<td>Yes; major depressive disorder in adults</td>
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<td>Ramelteon (Takeda Pharmaceutical Company)</td>
<td>Rozerem</td>
<td>FDA 2005</td>
<td>MT, MT</td>
<td>Decreased sleep latency, increased total sleep time in patients with insomnia, reduction in slow-wave sleep</td>
<td>Phase advance</td>
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<td>Tasimelteon (VEC-126, Vanda Pharmaceuticals)</td>
<td>FDA phase 3 clinical trial completed 2010; orphan drug designation 2010</td>
<td>MT, MT</td>
<td>Promotes sleep initiation and sleep maintenance (tested during 5-h phase advance) and concurrent shift in endogenous circadian rhythms</td>
<td>Phase advance and phase delay</td>
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<td>TIK-301 (PD-6735, LV-156, 735; Tikvah Pharmaceuticals)</td>
<td>FDA phase 2 clinical trial since 2002; orphan drug designation 2004</td>
<td>MT, MT</td>
<td>Decreased sleep latency in patients with insomnia</td>
<td>Promotes phase advance</td>
<td>No data available</td>
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MT=melatonin receptor. EMA=European Medicines Agency. 5-HT=serotonin receptor. FDA=US Food and Drug Administration. Rajaratnam and colleagues37 provide further details of effects of melatonin and melatonin analogues. *All receptors are agonistic unless otherwise specified.

Figure 2: Structure of melatonin (N-acetyl-5-methoxytryptamine) and agomelatine (N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide)
Agomelatine

Agomelatine is unique in that it is a selective agonist at MT<sub>1</sub> and MT<sub>2</sub> receptors and an antagonist at 5-HT<sub>2B</sub> and 5-HT<sub>2C</sub> receptors. Figure 2 shows the chemical structures of agomelatine and melatonin. Agomelatine has a rapid absorption rate: the time at which maximum blood concentration was achieved was between 45 min and 90 min after a single oral dose of 25–50 mg. After

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<td>Agomelatine 25-50 mg per day</td>
<td>158</td>
<td>26.8 (SE 0.3)</td>
<td>15.0 (SE 0.6)</td>
<td>2.2 (p=0.010)</td>
<td>Only presented</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Placebo</td>
<td>161</td>
<td>26.8 (SE 0.3)</td>
<td>15.9 (SE 0.7)</td>
<td>1.2 (p=0.144)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>CAGO1/BA2302 (NCT00411242)</strong></td>
<td></td>
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<tr>
<td>Agomelatine 25 mg per day</td>
<td>158</td>
<td>26.8 (SE 0.3)</td>
<td>15.0 (SE 0.6)</td>
<td>2.2 (p=0.010)</td>
<td>Only presented</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Placebo</td>
<td>161</td>
<td>26.8 (SE 0.3)</td>
<td>15.9 (SE 0.7)</td>
<td>1.2 (p=0.144)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>CAGO1/BA2301 (NCT00411099)</strong></td>
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<tr>
<td>Agomelatine 25 mg per day</td>
<td>156</td>
<td>26.7 (SE 0.3)</td>
<td>15.9 (SE 0.6)</td>
<td>0.6 (p=0.505)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Placebo</td>
<td>161</td>
<td>27.1 (SE 0.3)</td>
<td>14.1 (SE 0.6)</td>
<td>2.5 (p=0.004)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td><strong>CAGO1/BA2303 (NCT00463242)</strong></td>
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<tr>
<td>Agomelatine 25-50 mg per day</td>
<td>162</td>
<td>27.2 (SE 0.3)</td>
<td>17.1 (SE 0.6)</td>
<td>0.5 (p=0.539)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Placebo</td>
<td>158</td>
<td>26.9 (SE 0.3)</td>
<td>17.3 (SE 0.6)</td>
<td>-</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Values are mean (SD) unless otherwise stated. HAM-D=Hamilton Rating Scale for Depression. CGI-S/Clinical Global Impression—severity of illness scale. CGI-I=Clinical Global Impression—improvement scale. NS=not significant. MADRS=Montgomery-Åsberg Depression Rating Scale. NR=not reported. SE=standard error. *Sample size used for analysis. †Difference in final score for agomelatine-treated patients versus final score for comparator patients. ‡These values are estimated differences. §Studies are thought to have failed if the active drug did not separate from placebo. Additional agomelatine trials for the treatment of major depressive disorder that have recently been completed but are yet to be published include NCT00463242, NCT00467402 (prevention of relapse), NCT00411099, ISRCTN96725312 (CL3-062), ISRCTN68222771 (CL3-048; elderly population), ISRCTN8378163 (CL2-005), ISRCTN55252567 (CL3-063), and ISRCTN44737909 (CL3-056).

Table 3: Summary of placebo-controlled and active comparator trials of agomelatine in human beings
oral ingestion, agomelatine undergoes high hepatic first-pass metabolism, which contributes to the wide degree of interindividual variability in bioavailability. Further factors affecting bioavailability include sex, use of oral contraceptives, and smoking. Circulating agomelatine is mainly bound to plasma proteins (>90%) and is almost completely metabolised (with up to 80% of the dose excreted in the urine as metabolites). The mean terminal half-life is 140 min. There is an increase in dopamine and norepinephrine concentrations in the prefrontal cortex that results from antagonism of the 5-HT<sub>2C</sub> receptors.

Although agomelatine has expected chronobiologic effects, it also has clinically significant antidepressant<sup>67,68</sup> and anxiolytic<sup>69</sup> properties. These psychotropic effects have been proposed to be caused by the synergy between the melatonin-based (MT<sub>1</sub>, MT<sub>2</sub> receptor-dependent) and monoamine-based (5-HT<sub>2C</sub> receptor-dependent) effects. This compound might also achieve its antidepressant effect via some other non-circadian mechanism, such as increased production of brain-derived neurotrophic factor.<sup>70</sup>

Treatment with agomelatine in young, healthy men 5 h before bedtime produced a phase advance in the circadian

<table>
<thead>
<tr>
<th>n&lt;sup&gt;†&lt;/sup&gt;</th>
<th>HAM-D score (baseline)</th>
<th>HAM-D score (at end)</th>
<th>Difference †</th>
<th>CGI-S/I score (baseline)</th>
<th>CGI-S/I score (end)</th>
<th>Difference †</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL3-046 (ISRCTN49376288)&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Agomelatine 25-50 mg per day</td>
<td>150</td>
<td>26·1 (2·8)</td>
<td>26·5 (3·0)</td>
<td>1·68 (p=0·031)</td>
<td>4·7 (0·7)</td>
</tr>
<tr>
<td>CL3-035&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Agomelatine 25-50 mg per day</td>
<td>165</td>
<td>25·9 (3·2)</td>
<td>9·9 (6·6)</td>
<td>1·1 (p=0·154)</td>
<td>3·2 (0·8)</td>
</tr>
<tr>
<td>CL3-036&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Agomelatine 50 mg per day</td>
<td>137</td>
<td>27·9 (4·1)</td>
<td>9·9 (6·6)</td>
<td>1·1 (p=0·154)</td>
<td>3·2 (0·8)</td>
</tr>
<tr>
<td>CL3-045 (ISRCTN19312689)&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Agomelatine 25-50 mg per day</td>
<td>247</td>
<td>28·5 (2·7)</td>
<td>11·1 (7·3)</td>
<td>1·46 (p=0·002)</td>
<td>4·7 (0·6)</td>
</tr>
<tr>
<td>CL3-056&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Agomelatine 25-50 mg per day</td>
<td>71</td>
<td>26·1 (2·3)</td>
<td>9·9 (6·6)</td>
<td>1·1 (p=0·154)</td>
<td>4·7 (0·6)</td>
</tr>
<tr>
<td>CL3-030&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Agomelatine 25 mg per day</td>
<td>88</td>
<td>22·6 (2·4)</td>
<td>6·1 (3·5)</td>
<td>4·1 (p=0·064)</td>
<td>1·6 (0·8)</td>
</tr>
</tbody>
</table>

Values are mean (SD). HAM-D=Hamilton Rating Scale for Depression. CGI-S=Clinical Global Impression—severity of illness scale. CGI-I=Clinical Global Impression—improvement scale. MADRS=Montgomery-Åsberg Depression Rating Scale. NR=not reported. NS=not significant. OR=odds ratio. *Sample size used for analysis. †Difference in final score for agomelatine-treated patients versus final score for comparator patients. These values are estimated differences. §Studies are thought to have failed if the active drug did not separate from placebo. Additional agomelatine trials for the treatment of major depressive disorder that have recently been completed but are yet to be published include NCT00463242, NCT00467402 (prevention of relapse), NCT00411099, ISRCTN6725312 (CL3-062), ISRCTN68222771 (CL3-048, elderly population), ISRCTN85525037 (CL3-063), and ISRCTN44737995 (CL3-056).

Table 4: Summary of active comparator and prevention of relapse trials of agomelatine in human beings
Hamon101 provide further details about side-effects of agomelatine.

Table 5: Side-effects associated with agomelatine reported in placebo-controlled and active comparator trials

<table>
<thead>
<tr>
<th>Side-effects associated with agomelatine†</th>
<th>Proportion reporting side-effects (agomelatine)*</th>
<th>Proportion reporting side-effects (comparator)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache (6.6%)</td>
<td>51.1% (70 of 137)</td>
<td>54.7% (76 of 139)</td>
</tr>
<tr>
<td>Fatigue (5.8%)</td>
<td>42.4% (50 of 118)</td>
<td>42.5% (52 of 120)</td>
</tr>
<tr>
<td>None</td>
<td>57.5% (65 of 106)</td>
<td>62.9% (66 of 105)</td>
</tr>
<tr>
<td>None</td>
<td>70.3% (232 of 330)</td>
<td>65.5% (108 of 165)</td>
</tr>
<tr>
<td>None</td>
<td>75.1% (244 of 325)</td>
<td>74.6% (126 of 169)</td>
</tr>
<tr>
<td>Headache (6.6%), fatigue (5.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness (6.5%), nasopharyngitis (6.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness (7.3%), diarrhoea (7.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea (8.6%), dry mouth (7.1%), sedation (5.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache (6.6%), nasopharyngitis (6.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
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<td></td>
</tr>
<tr>
<td>Headache (6.6%), nasopharyngitis (6.5%)</td>
<td></td>
<td></td>
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<tr>
<td>None</td>
<td></td>
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<tr>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea (0.05)</td>
<td></td>
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</tr>
</tbody>
</table>

Placebo-controlled trials

- Agomelatine 25 mg per day
- Agomelatine 25-50 mg per day
- Agomelatine 25-50 mg per day
- Agomelatine 25-50 mg per day
- Agomelatine 25-50 mg per day

Active comparator trials

- Agomelatine 25-50 mg per day
- Agomelatine 25-50 mg per day
- Agomelatine 25-50 mg per day
- Agomelatine 25-50 mg per day

Prevention of relapse

- Agomelatine 25-50 mg per day
- Agomelatine 25-50 mg per day

*All side-effects recorded via clinician-elicited patient self-report and physical examination. †Side-effects reported in more than 5% of patients on agomelatine. ‡Treatment-related side-effects. Kasper and Hamon101 provide further details about side-effects of agomelatine.

Table 5: Side-effects associated with agomelatine reported in placebo-controlled and active comparator trials
As agomelatine is not associated with increased levels of serotonin, it does not produce the same side-effect profile that is commonly seen with other novel antidepressants (notably, gastrointestinal changes, headaches, sexual difficulties, psychomotor agitation, or weight gain) and does not have the risk of other major adverse events (such as serotonin syndrome or serotonin discontinuation symptoms). Although nausea, dizziness, and headache are the symptoms most commonly reported by patients treated with agomelatine, these side-effects were reported at similar rates by those receiving placebo (table 5).  

The side-effect profile of agomelatine is equivalent to that of placebo for many common effects associated with antidepressant drugs, including weight gain, sexual functioning, and discontinuation effects (table 5).

Conclusions
Melatonin analogues provide a new and efficacious mechanism for producing notable phase shifts in human beings. Although these drugs have been mainly studied for sleep disorders, they also have the potential to be used as primary or adjunctive drugs across a wider range of neuropsychiatric disorders characterised by persistent circadian disturbance. Importantly, only agomelatine (which also binds 5-HT2c receptors) has been reported to have clinically significant antidepressant effects. Because of its favourable adverse effect and safety profile, and the potential to help to restore circadian function between depressive episodes, this drug might occupy a unique place in the management of some patients with severe depression and other major mood disorders.

Contributors
Both authors participated in the conception and writing of this article and have seen and approved the final version.

Conflicts of interest
IBH was previously chief executive officer and clinical adviser of beyondblue, an Australian National Depression Initiative. He has led projects for health professionals and the community supported by governmental, community agency, and drug industry partners (Wyeth, Eli Lilly, Servier, Pfizer, AstraZeneca) for the identification and management of depression and anxiety. He has served on advisory boards convened by the drug industry in relation to specific antidepressants, including nefazodone, duloxetine, and desvenlafaxine, and has participated in a multicentre clinical trial of agomelatine effects on sleep architecture in depression. IBH is also supported by a National Health and Medical Research Council Australian Medical Research Fellowship. He is a participant in a family-practice-based audit of sleep disturbance and major depression, funded by Vanda Pharmaceuticals, manufacturers of tasimelteon, and Cephalon, and has received honoraria for lectures from Pfizer, CSL Biotherapies, and Servier. She has previously received research funding from Vanda Pharmaceuticals, manufacturers of tasimelteon. She has also received an unrestricted educational grant from Servier. Research studies done by IBH and NLR are mainly funded by NHMRC project and program grants.

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86 International Standard Randomised Controlled Trial Number


