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 serotonergic receptor subtype (ie, 5-HT_{2C}) 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.

Lancet 2011; 378: 621–31

Published Online
May 18, 2011
DOI:10.1016/S0140-6736(11)60095-0

Brain & Mind Research Institute, The University of Sydney, Camperdown, NSW, Australia (Prof I B Hickie MD, N L Rogers PhD)**; and School of Management and Marketing, Institute for Health and Social Science Research, Central Queensland University, Mackay, QLD, Australia** (N L Rogers)

Correspondence to:
Prof Ian B Hickie, Brain & Mind Research Institute, 94 Mallett Street, Building F, Level 4, Camperdown, NSW 2050, Australia
ian.hickie@sydney.edu.au

Introduction

Major depression is a leading cause of premature death and ongoing disability.[1,2] Although the therapeutic benefits of drugs for less severe forms of depression is debatable,[3,4] 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.[5,6]

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.[8–10]

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 systems[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.[10] 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,

Search strategy and selection criteria

This article is not a systematic review. We searched PubMed for articles on "melatonin", "melatonin analogues", "melatonin analogs", "agomelatine", "ramelteon", "tasimelteon", "PD-6735", "depression", "antidepressants", "circadian disruption", "circadian rhythms", "chronotherapeutics", "chronobiotics", and "sleep". Only papers or abstracts published in English were reviewed. Searches were done for the period 1948 to February, 2011. The "agomelatine" search was supplemented with information from the US National Institutes of Health ClinicalTrials.gov website, the International Standard Randomised Controlled Trial Number Register website, and the European Medicines Agency website. This search was also supplemented with information from contact with the manufacturer of agomelatine (Servier Laboratories) and suggested additional references from reviewers of this article.

early wakening, 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]

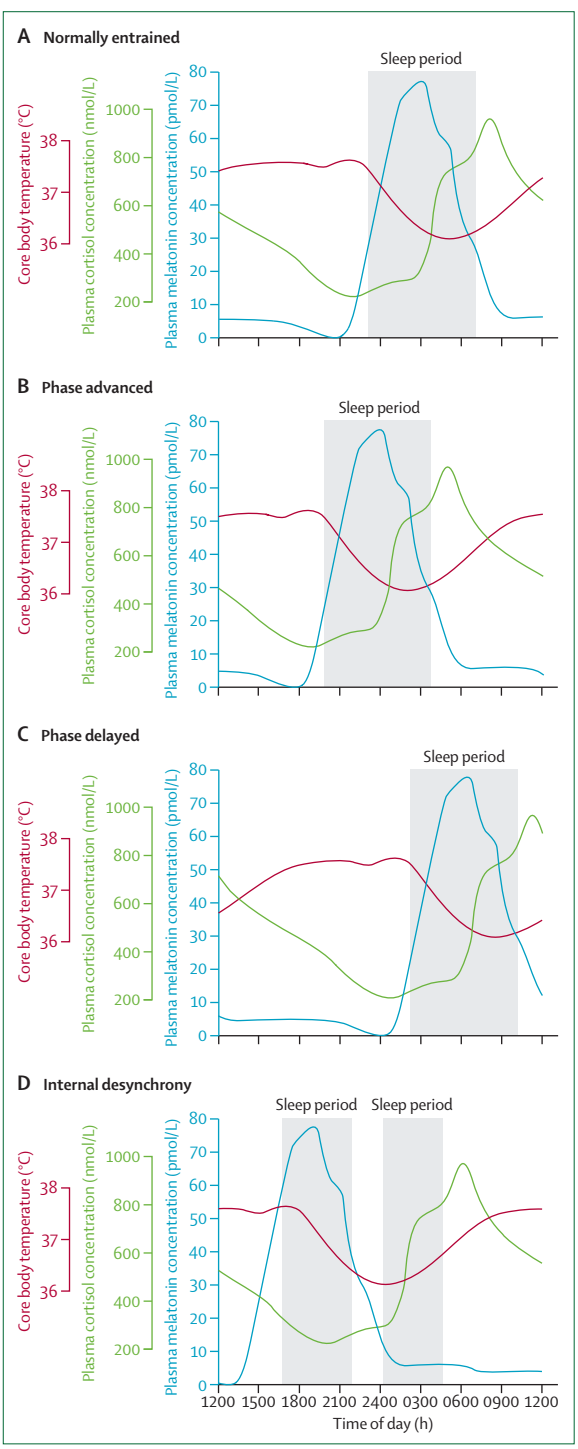

Figure 1: **Circadian rhythmicity for individuals who are normally entrained (A), phase advanced (B), phase delayed (C), or who have internal desynchrony (D)**
Sleep periods are indicated by grey-shaded area, with time of day on bottom axis. (A) Normally entrained: onset of melatonin secretion occurs 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.[12–14]

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 homoeostatic sleep system, REM sleep is modulated by the circadian system.[22] 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, musculoskeletal pain, and loss of normal diurnal variation in the subjective reporting of energy levels.[23] Primary circadian 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.[28,29]

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

essential feature of antidepressant compounds.[30] 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.[31]

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.[32] 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.[33]

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 neurohormonal (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[18] or blue[34] light, treatment with melatonin,[35] 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.[36] 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 chronobiotic effects.[37] 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,[38] and might increase the circadian period.[38,39] More recently, the chronobiotic effects of lithium have been reported to be probably attributable to its action on glycogen synthase kinase 3β,[40] which is a central regulator of the endogenous circadian clock.[41]

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.[42] 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.[43] This effect has adverse consequences on normal daytime wakefulness, neurocognitive functioning, and safety (eg, while driving a motor vehicle or operating machinery).[43]

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.[44,45] 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,[43] in addition to changes in

	Effect	Other notes
GSK3B	Bipolar disorder	Target of lithium; central regulator of circadian clock
CLOCK	Bipolar disorder	T3111C SNP: CC genotype is associated with greater insomnia in patients undergoing antidepressant treatment, and greater insomnia and decreased need for sleep in patients with bipolar disorder
ARNTL (also known as *BMAL1* or *MOP3*)	Bipolar disorder	Data from SNP and haplotype analysis studies
PER3	Bipolar disorder, seasonal affective disorder	Bipolar disorder data from haplotype analysis studies
TIMELESS (also known as *TIM1*)	Bipolar disorder	Data from SNP analysis studies
PER2, *NPAS2*, *ARNTL*	Seasonal affective disorder	Combinations of these genes result in additive effects and thus further increased risk of seasonal affective disorder

GSK3B=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,[24] Partonen and colleagues,[25] Wulff and colleagues,[26] and Mansour and colleagues[27] provide further details of the links between circadian genes and affective disorders.

Table 1: **Genetic overlap between the circadian system and affective disorders**

a range of physiological functions, including melatonin secretion[12] and metabolic variables.[46]

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).[42] 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.[47–49] In a Cochrane meta-analysis,[48] 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),[34] thereby allowing lower intensities of light to be used to achieve equivalent phase shifts.

Melatonin

Melatonin has high affinity for two receptors (MT_1 and MT_2), which are located throughout the brain, including in the suprachiasmatic nucleus of the hypothalamus, substantia nigra, hippocampus, cerebellum, ventral tegmental area, and nucleus accumbens.[35,50] These brain areas are involved in regulating various homoeostatic 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.[51] Changes in the brain content and the ratio of MT_1 to MT_2 receptors have been reported in neurodegenerative disorders (eg, Alzheimer's disease),[52] with similar changes reported after chronic antidepressant use.[50,51] Although a third melatonin binding site (MT_3) has been identified,[53] 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.[35] 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.[54,55] 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.[35] Additionally, nocturnal elevation in melatonin's plasma concentrations is associated with increased sleep propensity, reduced body temperature, and decreased alertness.[35,50]

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).[35] 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.[35]

Is melatonin an antidepressant?

Exogenous melatonin has some antidepressant-like actions in animal models.[56] Daily treatment with melatonin reverses the adverse effects of chronic stress in mice.[57] By contrast, treatment with melatonin alone in human beings does not seem to be an effective antidepressant strategy.[58] 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.[59] Addition of chronobiotic drugs such as melatonin to currently used antidepressant therapies can, however, improve overall outcomes.[33,51]

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.[60] 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 MT_1 and MT_2. Additionally, one compound, agomelatine, also binds to the $5\text{-}HT_{2B}$ and $5\text{-}HT_{2C}$ 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[37] provide further detail about the animal studies done with these compounds.

	Trade names	Approval	Binding*	Sleep effects	Chronobiotic effects	Antidepressant effects
Hormone						
Melatonin[37]	..	..	MT_1, MT_2, MT_3	Promotes sleep initiation, especially during biological day (ie, when endogenous concentrations are low)	Phase advance and phase delay; entrains circadian system	Synergistic effects when given adjunctively with antidepressant and when given alone in animals
Melatonin (Neurim Pharmaceuticals)[61]	Circadin	EMA 2007	MT_1, MT_2, MT_3	Mimics the endogenous melatonin profile by releasing melatonin gradually over 8–10 h	Phase advance	No data available
Analogues						
Agomelatine (Servier)[62,63]	Valdoxan, Melitor, Thymanax	EMA 2009	MT_1, MT_2, 5-HT_{2B} (antagonist), 5-HT_{2C} (antagonist)	Significant benefits in patients with depression	Phase advance; entrains circadian system	Yes: major depressive disorder in adults
Ramelteon (Takeda Pharmaceutical Company)[64]	Rozerem	FDA 2005	MT_1, MT_2	Decreased sleep latency, increased total sleep time in patients with insomnia, reduction in slow-wave sleep	Phase advance	No data available
Tasimelteon (VEC-126; Vanda Pharmaceuticals)[65]	..	FDA phase 3 clinical trial completed 2010; orphan drug designation 2010	MT_1, MT_2	Promotes sleep initiation and sleep maintenance (tested during 5-h phase advance) and concurrent shift in endogenous circadian rhythms	Phase advance and phase delay	No data available
TIK-301 (PD-6735, LY-156, 735; Tikvah Pharmaceuticals)[66]	..	FDA phase 2 clinical trial since 2002; orphan drug designation 2004	MT_1, MT_2	Decreased sleep latency in patients with insomnia	Promotes phase advance	No data available

MT=melatonin receptor. EMA=European Medicines Agency. 5-HT=serotonin receptor. FDA=US Food and Drug Administration. Rajaratnam and colleagues[37] provide further details of effects of melatonin and melatonin analogues. *All receptors are agonistic unless otherwise specified.

Table 2: **Effects of melatonin and melatonin analogues**

Circadin

Melatonin in the Circadin formulation works in the same way as does endogenous melatonin at the MT_1 and MT_2 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_1 and MT_2 receptors and low affinity for MT_3 binding sites.[68] 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.[64,69–73] 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_1 and MT_2 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]

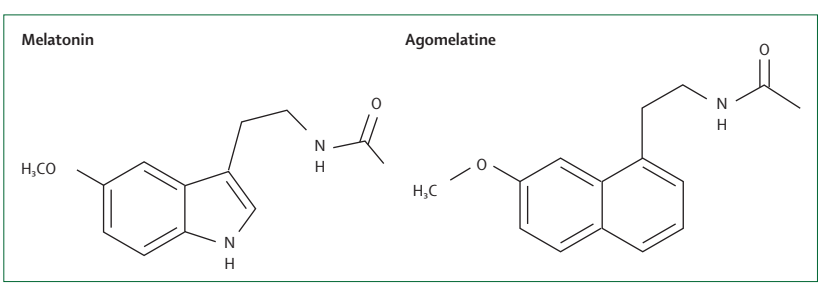

Figure 2: **Structure of melatonin (*N*-acetyl-5-methoxytryptamine) and agomelatine (*N*-[2-(7-methoxy-1-naphthyl)ethyl] acetamide)**

PD-6735

This compound is a selective agonist at MT_1 and MT_2 receptors with substantial chronobiotic 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]

Agomelatine

Agomelatine is unique in that it is a selective agonist at MT_1 and MT_2 receptors and an antagonist at 5-HT_{2B} and 5-HT_{2C} receptors.[62] 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.[75] After

	n*	HAM-D score (baseline)	HAM-D score (at end)	Difference†	CGI-S/I score (baseline)	CGI-S/I score (at end)	Difference†
CL2-014[87]							
Agomelatine 1 mg per day	136	27·9 (3·0)	13·2 (8·2)	2·17 (NS)	4·8 (0·7)	2·9 (1·5)	0·41 (NS)
Agomelatine 5 mg per day	146	27·3 (2·6)	14·7 (8·5)	0·64 (NS)	4·9 (0·7)	3·1 (1·5)	0·19 (NS)
Agomelatine 25 mg per day	135	27·4 (2·7)	12·8 (8·2)	2·57 (p=0·034)	4·7 (0·7)	2·8 (1·4)	0·42 (NS)
Paroxetine 20 mg per day	144	27·3 (3·4)	13·1 (8·4)	2·25 (p=0·030)	4·9 (0·7)	2·8 (1·5)	0·51 (p≤0·05)
Placebo	136	27·4 (3·1)	15·3 (8·9)	..	5·0 (0·7)	3·3 (1·5)	..
CL3-022§[75]							
Agomelatine 25 mg per day	129	27·6 (2·9)	14·5 (8·2)	1·17 (p=0·193)‡	5·0 (0·5)	3·3 (1·4)	0·19 (NS)
Fluoxetine 20 mg per day	133	27·5 (2·8)	13·3 (7·6)	2·55 (p=0·005)‡	5·0 (0·6)	3·1 (1·4)	0·38 (p≤0·05)
Placebo	147	28·0 (3·6)	15·9 (8·6)	..	5·0 (0·6)	3·5 (1·5)	..
CL3-023§[75]							
Agomelatine 25 mg per day	141	25·7 (2·8)	13·0 (8·0)	0·63 (p=0·504)	4·6 (0·7)	2·9 (1·3)	0·17 (NS)
Paroxetine 20 mg per day	137	26·1 (2·9)	12·2 (8·1)	1·58 (p=0·095)	4·6 (0·7)	2·7 (1·3)	0·37 (p≤0·05)
Placebo	137	26·0 (2·7)	13·8 (8·0)	..	4·5 (0·6)	3·1 (1·3)	..
CL3-024§[75]							
Agomelatine 25 mg per day	148	26·4 (3·0)	12·0 (8·2)	0·90 (p=0·291)	4·7 (0·7)	2·9 (1·4)	0·17 (NS)
Agomelatine 50 mg per day	147	26·5 (3·4)	13·4 (8·2)	0·41 (p=0·629)	4·8 (0·7)	3·0 (1·4)	0·02 (NS)
Fluoxetine 20 mg per day	146	26·5 (3·4)	12·5 (7·4)	0·53 (p=0·538)	4·7 (0·7)	2·9 (1·3)	0·11(NS)
Placebo	158	26·9 (3·4)	13·4 (8·4)	..	4·7 (0·7)	3·0 (1·4)	..
CL3-026 (in an elderly population >60 years)§[75]							
Agomelatine 25 mg per day	109	≥24 (MADRS)	10·6 (9·4) (MADRS)	0·19 (p=0·89)	NR	NR	NR
Placebo	109	≥24 (MADRS)	9·6 (8·7) (MADRS)	..	NR	NR	..
CL3-042[88]							
Agomelatine 25–50 mg per day	116	27·4 (2·7)	13·9 (7·7)	3·18 (p=0·002)	4·9 (0·7)	3·1 (1·4)	0·5 (p=0·006)
Placebo	119	27·2 (2·7)	17·0 (7·9)	..	4·9 (0·7)	3·6 (1·4)	..
CL3-043[89]							
Agomelatine 25–50 mg per day	106	26·5 (2·8)	14·1 (7·7)	2·3 (p=0·026)‡	4·8 (0·7)	3·2 (1·3)	0·44 (p=0·017)‡
Placebo	105	26·7 (3·0)	16·5 (7·4)	..	4·8 (0·7)	3·6 (1·3)	..
CAG0178A2302 (NCT00411242)[90]							
Agomelatine 25 mg per day	158	26·8 (SE 0·3)	15·0 (SE 0·6)	2·2 (p=0·010)‡	Only presented graphically		NR (p=0·010)‡
Agomelatine 50 mg per day	161	26·8 (SE 0·3)	15·9 (SE 0·7)	1·2 (p=0·144)‡			NR (p=0·115)‡
Placebo	163	26·4 (SE 0·2)	17·1 (SE 0·6)	..			..
CAG0178A2301 (NCT00411099)[91]							
Agomelatine 25 mg per day	156	26·7 (SE 0·3)	15·9 (SE 0·6)	0·6 (p=0·505)‡	NR	NR	NR (p=0·144)
Agomelatine 50 mg per day	161	27·1 (SE 0·3)	14·1 (SE 0·6)	2·5 (p=0·004)‡	NR	NR	NR (p=0·003)
Placebo	167	27·1 (SE 0·3)	16·6 (SE 0·7)	..	NR	NR	..
CAG0178A2303 (NCT00463242)§[75]							
Agomelatine 25–50 mg per day	162	27·2 (SE 0·3)	17·1 (SE 0·6)	0·5 (p=0·539)‡	NR	NR	NR
Paroxetine 20–40 mg per day	163	27·0 (SE 0·3)	14·0 (SE 0·6)	3·4 (p<0·001)‡	NR	NR	NR
Placebo	158	26·9 (SE 0·3)	17·3 (SE 0·6)	..	NR	NR	..

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), ISRCTN38378163 (CL2-005), ISRCTN55250367 (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.[76] Further factors affecting bioavailability include sex, use of oral contraceptives, and smoking.[75] 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_{2C} receptors.[62]

Although agomelatine has expected chronobiotic effects, it also has clinically significant antidepressant[77,78] and anxiolytic[79] properties. These psychotropic effects have been proposed to be caused by the synergy between the melatonin-based (MT_1, MT_2 receptor-dependent) and monoamine-based (5-HT_{2C} 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.[80]

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

	n*	HAM-D score (baseline)	HAM-D score (at end)	Difference†	CGI-S/I score (baseline)	CGI-S/I score (end)	Difference†
Active comparator trials							
CL3-046 (ISRCTN49376288)[92]							
Agomelatine 25–50 mg per day	150	26·1 (2·8)	10·3 (7·0)	1·68 (p=0·031)	4·7 (0·7)	2·5 (1·1)	0·28 (p=0·043)
Sertraline 50–100 mg per day	157	26·5 (3·0)	12·1 (8·3)	..	4·7 (0·7)	2·8 (1·3)	..
CL3-035[93]							
Agomelatine 25–50 mg per day	165	25·9 (3·2)	9·9 (6·6)	1·1 (p=0·154)	3·2 (0·8)	1·6 (0·7)	0·32 (p=0·016)
Venlafaxine 75–150 mg per day	167	26·0 (3·3)	11·0 (7·4)	..	3·6 (0·9)	1·6 (0·8)	..
CL3-036[94]							
Agomelatine 50 mg per day	137	27·9 (4·1) (MADRS)	10·1 (7·8) (MADRS)	0·3 (p=0·751)	4·4 (NR)	NR	NR
Venlafaxine (extended release) 150 mg per day	139	27·9 (4·6) (MADRS)	9·8 (7·9) (MADRS)	..	4·5 (NR)	NR	..
CL3-045 (ISRCTN19313268)[95]							
Agomelatine 25–50 mg per day	247	28·5 (2·7)	11·1 (7·3)	1·49 (p=0·024)‡	5·0 (0·6)	2·6 (1·3)	0·22 (p=0·059)‡
Fluoxetine 20–40 mg per day	257	28·7 (2·5)	12·7 (8·5)	..	5·0 (0·6)	2·8 (1·4)	..
CL3-056[96]							
Agomelatine 25–50 mg per day	71	26·1 (2·3)	NR	1·46 (p=0·002)	4·7 (0·6)	NR	NR
Escitalopram 10–20 mg per day	67	26·0 (2·9)	NR	..	4·7 (0·7)	NR	..
CL3-030[97]							
Agomelatine 25 mg per day	88	22·6 (2·4) (MADRS)	6·1 (3·5) (MADRS)	0·9 (p=0·064)	4·1 (0·8)	1·6 (0·8)	0·0 (p=1·000)
Paroxetine 20 mg per day	104	22·9 (2·2) (MADRS)	5·2 (3·2) (MADRS)	..	4·2 (0·8)	1·6 (0·7)	..
Prevention of relapse or recurrence trials							
CL3-041 (ISRCTN53193024)							
24 weeks[98]							
Agomelatine 25–50 mg per day	165	6·1 (2·6)	7·5 (7·0)	3·13 (p≤0·001)	1·8 (0·8)	2·1 (1·2)	0·5 (p=0·009)
Placebo	174	6·0 (2·7)	10·6 (8·4)	..	1·8 (0·7)	2·6 (1·5)	..
44 weeks[99]							
Agomelatine 25–50 mg per day	165	6·1 (2·6)	7·8 (7·4)	3·69 (p<0·001)	1·8 (0·8)	2·1 (1·3)	0·6 (p=0·002)
Placebo	174	6·0 (2·7)	11·5 (8·6)	..	1·8 (0·7)	2·7 (1·5)	..
CL3-021§[75]							
Agomelatine 25 mg per day	185	6·0 (2·7)	9·3 (7·4)	0·32 (NS)	1·8 (0·8)	2·3 (1·5)	0·0 (NS)
Placebo	179	6·2 (2·7)	9·6 (7·5)		1·8 (0·8)	2·3 (1·5)	
CAG0178A2304 (NCT00467402; prevention of recurrence)§[100]							
Agomelatine 25 mg per day	64	4·6 (3·6)	NR	OR = 0·90 (p=0·667)	NR	NR	X^2(p=0·572)
Agomelatine 50 mg per day	76	6·1 (3·4)	NR		NR	NR	
Placebo	141	6·0 (3·3)	NR	..			..

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, ISRCTN96725312 (CL3-062), ISRCTN68222771 (CL3-048; elderly population), ISRCTN38378163 (CL2-005), ISRCTN55250367 (CL3-063), and ISRCTN44737909 (CL3-056).

Table 4: **Summary of active comparator and prevention of relapse trials of agomelatine in human beings**

timing of the temperature and melatonin rhythms and advanced the timing of the daily decrease in heart rate.[63] The termination of the sleep period and REM sleep-propensity were also phase-advanced, with no other effects reported on sleep variables.[81] Consistent phase-shifting effects were also reported in a later study of healthy elderly men, with advances in the timing of the temperature and cortisol rhythms induced by agomelatine, again with no effect on any sleep variables.[82]

Antidepressant-like effects of agomelatine have been reported in animal studies.[83] In human beings, an extensive set of randomised controlled trials have been completed.[84–86] Typical therapeutic doses in these trials were 25–50 mg of agomelatine. Comparator antidepressants included fluoxetine, paroxetine, sertraline, and venlafaxine (table 3 and table 4). Of the three published placebo-controlled trials used to support drug registration,[87–89] the absolute difference in response rates (ie, 50% reduction in the 17-item Hamilton Rating Scale for Depression score) between agomelatine and placebo were 14·8% (95% CI 1·5–27·4),[89] 15·2% (3·3–26·4),[87] and 19·0% (6·5–31·5).[88]

However, the wider set of studies of agomelatine now available highlights the more general problem encountered in the evaluation of new antidepressants—that separation from placebo is an inconsistent finding.[3,4] As with other new drugs, agomelatine seems to be more effective in patients with more severe depression.[84,95] Whether agomelatine is more effective in patients with specific abnormalities in circadian function or more severe sleep disturbance is yet to be established.

In the active comparator trials, agomelatine (25–50 mg) had similar efficacy to venlafaxine (75–150 mg; extended-release 150 mg)[93,94] and was more efficacious than fluoxetine (20–40 mg),[95] and sertraline (50–100 mg).[92] Significant improvements on a range of sleep variables, including improved sleep quality (mean difference 5·63, 95% CI 0·85–10·41, p=0·021), reduced wake after sleep onset (4·86, 0·23–9·49, p=0·040), and fewer insomnia reports (0·37, 0·01–0·72, p=0·044) were found with agomelatine than with venlafaxine.[93]

In a long-term prevention of depression relapse trial,[98,99] the final relapse rate with agomelatine at 24 weeks was 20·6% compared with 41·4% for placebo (a difference of 20·8% [95% CI 11·0–30·0]) and agomelatine at 10 months was 23·9% versus 50·0% for placebo (approximate difference of relapse estimates 26·4% [95% CI 12·7–39·0]). Data from two other relapse prevention trials did not indicate that agomelatine was more efficacious than placebo (table 4). Finally, by contrast with paroxetine, agomelatine does not seem to be associated with discontinuation symptoms.[97]

	Proportion reporting side-effects (agomelatine)*	Proportion reporting side-effects (comparator)*	Side-effects associated with agomelatine†	Side-effects significantly more prevalent with agomelatine than with comparator
Placebo-controlled trials				
Agomelatine 25 mg per day[87]	51·1% (70 of 137)	54·7% (76 of 139)	Headache (6·6%)	None
Agomelatine 25–50 mg per day[88]	42·4% (50 of 118)	42·5% (51 of 120)	Headache (5·1%), fatigue (5·1%)	None
Agomelatine 25–50 mg per day[89]	57·5% (61 of 106)	62·9% (66 of 105)	Dizziness (9·3%), nasopharyngitis (6·5%), influenza (6·5%)	None
Agomelatine 25–50 mg per day[90]	70·3% (232 of 330)	65·5% (108 of 165)	Headache (13·3%), somnolence (9·1%), dizziness (7·3%), diarrhoea (7·3%), nausea (6·1%), fatigue (5·8%), sedation (5·2%), nasopharyngitis (5·2%)	None
Agomelatine 25–50 mg per day[91]	75·1% (244 of 325)	74·6% (126 of 169)	Headache (16·3%), nausea (12·0%), diarrhoea (10·5%), dizziness (8·6%), dry mouth (7·1%), somnolence (7·1%), sedation (6·8%), fatigue (5·2%), insomnia (5·2%)	Nausea (p=0·05)
Active comparator trials				
Agomelatine 25–50 mg per day *vs* Sertraline 50–100 mg per day[92]	48·0% (73 of 152)	49·1% (78 of 159)	Headache (8·6%), dry mouth (5·3%)	None
Agomelatine 25–50 mg per day *vs* Venlafaxine 75–150 mg per day[93]	51·2% (85 of 166)	57·1% (96 of 168)	Headache (9·6%), nausea (6·0%)	None
Agomelatine 50 mg per day *vs* Venlafaxine (extended release) 150 mg per day[94]	20·4% (28 of 137)‡	38·1% (53 of 139)‡	Nausea (11·7%), headache (10·2%), upper respiratory tract infections (7·3%)	None
Agomelatine 25–50 mg per day *vs* Fluoxetine 20–40 mg per day[95]	57·2% (143 of 250)	56·3% (148 of 263)	Headache (16·0%), nausea (8·0%), somnolence (6·0%)	None
Prevention of relapse				
Agomelatine 25–50 mg per day *vs* Placebo (24 weeks)[98]	51·5% (85 of 165)	52·3% (91 of 174)	Headache (7·9%), nasopharyngitis (6·7%), back pain (5·5%)	None
Agomelatine 25–50 mg per day *vs* Placebo (44 weeks)[99]	59·4% (98 of 165)	56·9% (99 of 174)	Headache (9·7%), nasopharyngitis (9·1%), back pain (6·7%)	None

*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 Hamon[101] 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).[101–104] 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).[105]

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).[101]

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-HT_{2C} 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 Lily, 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, supported by Servier, the manufacturers of agomelatine. NLR has received grant support from Vanda Pharmaceuticals, Servier, Pfizer, 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.

Acknowledgments

We thank Bradley Whitwell, Tracey Davenport, and Georgina Luscombe for their assistance with editing and graphics.

References

1 Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet* 1997; **349:** 1498–504.
2 Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006; **367:** 1747–57.
3 Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS Med* 2008; **5:** e45.
4 Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Eng J Med* 2008; **358:** 252–60.
5 Hickie I. Is depression overdiagnosed? No. *BMJ* 2007; **335:** 329.
6 Hall WD, Mant A, Mitchell PB, Rendle VA, Hickie IB, McManus P. Association between antidepressant prescribing and suicide in Australia, 1991–2000: trend analysis. *BMJ* 2003; **326:** 1008.
7 Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* 2009; **373:** 746–58.
8 Wirz-Justice A. Diurnal variation of depressive symptoms. *Dialogues Clin Neurosci* 2008; **10:** 337–43.
9 Monteleone P, Maj M. The circadian basis of mood disorders: recent developments and treatment implications. *Eur Neuropsychopharm* 2008; **18:** 701–11.
10 Germain A, Kupfer DJ. Circadian rhythm disturbances in depression. *Hum Psychopharmacol* 2008; **23:** 571–85.
11 Czeisler CA, Buxton OM, Khalsa SBS. The human circadian timing system and sleep-wake regulation. In: Kryger MH, Roth T, Dement WC, eds. Principles and practice of sleep medicine, 4th edn. Philadelphia: WB Saunders, 2005: 375–94.
12 Rogers NL, Dinges DF. Interaction of chronic sleep restriction and circadian system in humans. *J Sleep Res* 2008; **17:** 406–11.
13 Rogers NL, Price NJ, Mullington JM, Szuba MP, Van Dongen HPA, Dinges DF. Plasma cortisol changes following chronic sleep restriction. *Sleep* 2000; **23:** A70–71.
14 Rogers NL, Price NJ, Szuba MP, Van Dongen HPA, Dinges DF. Effect of sustained caffeine on core body temperature during 88 hours of sustained wakefulness. *Sleep* 2001; **24:** A172–73.
15 Mansour HA, Monk TH, Nimgaonkar VL. Circadian genes and bipolar disorder. *Ann Med* 2005; **37:** 196–205.
16 Moore RY. Organization and function of a central nervous system circadian oscillator: the suprachiasmatic hypothalamic nucleus. *Fed Proc* 1983; **42:** 2783–89.
17 Miller JD, Morin LP, Schwartz WJ, Moore RY. New insights into the mammalian circadian clock. *Sleep* 1996; **19:** 641–67.
18 Duffy JF, Wright KP Jr. Entrainment of the human circadian system by light. *J Biol Rhythms* 2005; **20:** 326–38.
19 Souetre E, Salvati E, Belugou JL, et al. Circadian rhythms in depression and recovery: evidence for blunted amplitude as the main chronobiological abnormality. *Psychiatry Res* 1989; **28:** 263–78.
20 Kaplan KA, Harvey AG. Hypersomnia across mood disorders: a review and synthesis. *Sleep Med Rev* 2009; **13:** 275–85.
21 Roberts RE, Shema SJ, Kaplan GA, Strawbridge WJ. Sleep complaints and depression in an aging cohort: a prospective perspective. *Am J Psychiatry* 2000; **157:** 81–88.
22 Dijk DJ, Czeisler CA. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. *J Neurosci* 1995; **15:** 3526–38.
23 Hickie I, Davenport T, Wakefield D, et al, and Dubbo Infection Outcomes Study Group. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. *BMJ* 2006; **333:** 575.
24 McClung CA. Circadian genes, rhythms and the biology of mood disorders. *Pharmacol Ther* 2007; **114:** 222–32.
25 Partonen T, Treutlein J, Alpman A, et al. Three circadian clock genes Per2, Arntl, and Npas2 contribute to winter depression. *Ann Med* 2007; **39:** 229–38.

26 Wulff K, Gatti S, Wettstein JG, Foster RG. Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. *Nat Rev Neurosci* 2010; **11:** 589–99.

27 Mansour HA, Talkowski ME, Wood J, et al. Association study of 21 circadian genes with bipolar I disorder, schizoaffective disorder, and schizophrenia. *Bipolar Dis* 2009; **11:** 701–10.

28 Hickie I, Davenport T. A behavioural approach based on reconstructing the sleep-wake cycle. *Cogn Behav Pract* 1999; **6:** 442–50.

29 Frank E. Interpersonal and social rhythm therapy: a means of improving depression and preventing relapse in bipolar disorder. *J Clin Psychol* 2007; **63:** 463–73.

30 Vogel GW, Buffenstein A, Minter K, Hennessey A. Drug effects on REM sleep and on endogenous depression. *Neurosci Biobehav Rev* 1990; **14:** 49–63.

31 Dumont GJH, de Visser SJ, Cohen AF, van Gerven JM, on behalf of the Biomarker Working Group of the German Association for Applied Human Pharmacology. Biomarkers for the effects of selective serotonin reuptake inhibitors (SSRIs) in healthy subjects. *Br J Clin Pharmacol* 2005; **59:** 495–510.

32 Touitou Y, Bogdan A. Promoting adjustment of the sleep-wake cycle by chronobiotics. *Physiol Behav* 2007; **90:** 294–300.

33 Wirz-Justice A. From the basic neuroscience of circadian clock function to light therapy for depression: on the emergence of chronotherapeutics. *J Affect Dis* 2009; **116:** 159–60.

34 Lockley SW, Brainard GC, Czeisler CA. High sensitivity of the human circadian melatonin rhythm to resetting by short wavelength light. *J Clin Endocrinol Metab* 2003; **88:** 4502–05.

35 Wright KP Jr, Rogers NL. Endogenous versus exogenous effects of melatonin. In: Pandi-Perumal SR, Cardinali DP, eds. Melatonin: from molecules to therapy. New York: Nova Science Publishers, 2007: 547–69.

36 Wu JC, Kelsoe JR, Schachat C, et al. Rapid and sustained antidepressant response with sleep deprivation and chronotherapy in bipolar disorder. *Biol Psychiatry* 2009; **66:** 298–301.

37 Rajaratnam SM, Cohen DA, Rogers NL, et al. Melatonin and melatonin analogues. *Sleep Med Clin* 2009; **4:** 179–93.

38 Klemfuss H. Rhythms and the pharmacology of lithium. *Pharmacol Ther* 1992; **56:** 53–78.

39 Johnsson A, Pflug B, Engelmann W, Klemke W. Effect of lithium carbonate on circadian periodicity in humans. *Pharmakopsychiatr Neuropsychopharmakol* 1979; **12:** 423–25.

40 Quiroz JA, Gould TD, Manji HK. Molecular effects of lithium. *Mol Interv* 2004; **4:** 259–72.

41 Iitaka C, Miyazaki K, Akaike T, Ishida N. A role for glycogen synthase kinase-3beta in the mammalian circadian clock. *J Biol Chem* 2005; **280:** 29397–402.

42 Wirz-Justice A, Benedetti F, Berger M, et al. Chronotherapeutics (light and wake therapy) in affective disorders. *Psychol Med* 2005; **35:** 939–44.

43 Dinges DF, Rogers NL, Baynard MD. Chronic sleep deprivation. In: Kryger MH, Roth T, Dement WC, eds. Principles and practice of sleep medicine, 4th edn. Philadelphia: WB Saunders, 2005: 67–76.

44 Belenky G, Wesensten NJ, Thorne DR, et al. Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep-dose response study. *J Sleep Res* 2003; **12:** 1–12.

45 Van Dongen HPA, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* 2003; **26:** 117–26.

46 Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999; **354:** 1435–39.

47 Golden RN, Gaynes BN, Ekstrom RD, et al. The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. *Am J Psychiatry* 2005; **162:** 656–62.

48 Tuunainen A, Kripke DF, Endo T. Light therapy for non-seasonal depression. *Cochrane Database Syst Rev* 2004; **2:** CD004050.

49 Even C, Schröder CM, Friedman S, Rouillon F. Efficacy of light therapy in nonseasonal depression: a systematic review. *J Affect Dis* 2008; **108:** 11–23.

50 Pandi-Perumal SR, Trakht I, Srinivasan V, et al. Physiological effects of melatonin: role of melatonin receptors and signal transduction pathways. *Prog Neurobiol* 2008; **85:** 335–53.

51 Hirsch-Rodriguez E, Imbesi M, Manev R, Uz T, Manev H. The pattern of melatonin receptor expression in the brain may influence antidepressant treatment. *Med Hypoth* 2007; **69:** 120–24.

52 Brunner P, Sözer-Topcular N, Jockers R, et al. Pineal and cortical melatonin receptors MT1 and MT2 are decreased in Alzheimer's disease. *Eur J Histochem* 2006; **50:** 311–16.

53 Spadoni G, Bedini A. Advances on the development of subtype selective melatonin ligands. In: Pandi-Perumal SR, Cardinali DP, eds. Melatonin: from molecules to therapy. New York: Nova Science Publishers, 2007: 33–45.

54 Weaver DR. Melatonin and circadian rhythmicity in vertebrates. Physiological roles and pharmacological effects. In: Turek FW, Zee PC, eds. Regulation of sleep and circadian rhythms. New York: Dekker, 1999: 197–262.

55 von Gall C, Stehle JH, Weaver DR. Mammalian melatonin receptors: molecular biology and signal transduction. *Cell Tissue Res* 2002; **309:** 151–62.

56 Rogers NL, Dinges DF, Kennaway DJ, Dawson D. Potential action of melatonin in insomnia. *Sleep* 2003; **26:** 1058–59.

57 Kopp C, Vogel E, Rettori MC, Delagrange P, Misslin R. The effects of melatonin on the behavioural disturbances induced by chronic mild stress in C3H/He mice. *Behav Pharmacol* 1999; **10:** 73–83.

58 Carman JS, Post RM, Buswell R, Goodwin FK. Negative effects of melatonin on depression. *Am J Psychiatry* 1976; **133:** 1181–86.

59 Dalton EJ, Rotondi D, Levitan RD, Kennedy SH, Brown GM. Use of slow-release melatonin in treatment-resistant depression. *J Psychiatry Neurosci* 2000; **25:** 48–52.

60 Srinivasan V, Pandi-Perumal SR, Trakht I, et al. Pathophysiology of depression: role of sleep and the melatonergic system. *Psychiatry Res* 2009; **165:** 201–14.

61 Lemoine P, Nir T, Laudon M, Zisapel N. Prolonged-release melatonin improves sleep quality and morning alertness in insomnia patients aged 55 years and older and has no withdrawal effects. *J Sleep Res* 2007; **16:** 372–80.

62 Millan MJ, Gobert A, Lejeune F, et al. The novel melatonin agonist agomelatine (S20098) is an antagonist at 5-hydroxytryptamine2C receptors, blockade of which enhances the activity of frontocortical dopaminergic and adrenergic pathways. *J Pharmacol Exp Ther* 2003; **306:** 954–64.

63 Krauchi K, Cajochen C, Mori D, Graw P, Wirz-Justice A. Early evening melatonin and S-20098 advance circadian phase and nocturnal regulation of core body temperature. *Am J Physiol* 1997; **272:** R1178–88.

64 Roth T, Seiden D, Sainati S, Wang-Weigand S, Zhang J, Zee P. Effects of ramelteon on patient-reported sleep latency in older adults with chronic insomnia. *Sleep Med* 2006; **7:** 312–18.

65 Rajaratnam SM, Polymeropoulos MH, Fisher DM, et al. Melatonin agonist tasimelteon (VEC-162) for transient insomnia after sleep-time shift: two randomised controlled multicentre trials. *Lancet* 2009; **373:** 482–91.

66 Nickelsen T, Samel A, Vejvoda M, Wenzel J, Smith B, Gerzer R. Chronobiotic effects of the melatonin agonist LY 156735 following a simulated 9h time shift: results of a placebo-controlled trial. *Chronobiol Int* 2002; **19:** 915–36.

67 Wade AG, Ford I, Crawford G, et al. Efficacy of prolonged release melatonin in insomnia patients aged 55–80 years: quality of sleep and next-day alertness outcomes. *Curr Med Res Opin* 2007; **23:** 2597–605.

68 Kato K, Hirai K, Nishiyama K, et al. Neurochemical properties of ramelteon (TAK-375), a selective MT1/MT2 receptor agonist. *Neuropharmacology* 2005; **48:** 301–10.

69 Roth T, Stubbs C, Walsh JK. Ramelteon (TAK-375), a selective MT1/MT2-receptor agonist, reduces latency to persistent sleep in a model of transient insomnia related to a novel sleep environment. *Sleep* 2005; **28:** 303–07.

70 Zammit G, Schwartz H, Roth T, Wang-Weigand S, Sainati S, Zhang J. The effects of ramelteon in a first-night model of transient insomnia. *Sleep Med* 2009; **10:** 55–59.

71 Erman M, Seiden D, Zammit G, Sainati S, Zhang J. An efficacy, safety, and dose-response study of Ramelteon in patients with chronic primary insomnia. *Sleep Med* 2006; **7:** 17–24.

72 Zammit G, Erman M, Wang-Weigand S, Sainati S, Zhang J, Roth T. Evaluation of the efficacy and safety of ramelteon in subjects with chronic insomnia. *J Clin Sleep Med* 2007; **3:** 495–504.

73 Roth T, Seiden D, Wang-Weigand S, Zhang J. A 2-night, 3-period, crossover study of ramelteon's efficacy and safety in older adults with chronic insomnia. *Curr Med Res Opin* 2007; **23:** 1005–14.

74 Vachharajani NN, Yeleswaram K, Boulton DW. Preclinical pharmacokinetics and metabolism of BMS-214778, a novel melatonin receptor agonist. *J Pharm Sci* 2003; **92:** 760–72.

75 European Medicines Agency. Evaluation of medicines for human use—CHMP assessment report for Valdoxan. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000915/WC500046226.pdf (accessed March 14, 2011).

76 Therapeutic Goods Administration, Department of Health and Ageing. Australian public assessment report for agomelatine. http://www.tga.gov.au/pmeds/auspar/auspar-valdoxan.pdf (accessed Feb 22, 2011).

77 Dubovsky SL, Warren C. Agomelatine, a melatonin agonist with antidepressant properties. *Expert Opin Investig Drugs* 2009; **18:** 1533–40.

78 de Bodinat C, Guardiola-Lemaitre B, Mocaer E, Renard P, Munoz C, Millan MJ. Agomelatine, the first melatonergic antidepressant: discovery, characterization and development. *Nat Rev Drug Discov* 2010; **9:** 628–42.

79 De Berardis D, Di Iorio G, Acciavatti T, et al. The emerging role of melatonin agonists in the treatment of major depression: focus on agomelatine. *CNS Neurol Dis Drug Targets* 2011; **10:** 119–32.

80 Païzanis E, Renoir T, Lelievre V, et al. Behavioural and neuroplastic effects of the new-generation antidepressant agomelatine compared to fluoxetine in glucocorticoid receptor-impaired mice. *Int J Neuropsychopharmacol* 2010; **13:** 759–74.

81 Cajochen C, Krauchi K, Mori D, Graw P, Wirz-Justice A. Melatonin and S-20098 increase REM sleep and wake-up propensity without modifying NREM sleep homeostasis. *Am J Physiol* 1997; **272:** R1189–96.

82 Leproult R, Van Onderbergen A, L'hermite-Balériaux M, Van Cauter E, Copinschi G. Phase-shifts of 24-h rhythms of hormonal release and body temperature following early evening administration of the melatonin agonist agomelatine in healthy older men. *Clin Endocrinol* 2005; **63:** 298–304.

83 Zupancic M, Guilleminault C. Agomelatine: a preliminary review of a new antidepressant. *CNS Drugs* 2006; **20:** 981–92.

84 Kennedy SH, Rizvi SJ. Agomelatine in the treatment of major depressive disorder: potential for clinical effectiveness. *CNS Drugs* 2010; **24:** 479–99.

85 ClinicalTrials.gov. Agomelatine search. http://clinicaltrials.gov/ct2/results?term=agomelatine (accessed March 14, 2011).

86 International Standard Randomised Controlled Trial Number Register. Agomelatine search. http://www.controlled-trials.com/isrctn/search.html?srch=agomelatine&sort=3&dir=desc&max=10&Submit=SUBMIT (accessed March 14, 2011).

87 Lôo H, Hale A, D'haenen H. Determination of the dose of agomelatine, a melatoninergic agonist and selective 5-HT(2C) antagonist, in the treatment of major depressive disorder: a placebo-controlled dose range study. *Int Clin Psychopharmacol* 2002; **17:** 239–47.

88 Olie JP, Kasper S. Efficacy of agomelatine, a MT1/MT2 receptor agonist with 5-HT2C antagonistic properties, in major depressive disorder. *Int J Neuropsychopharmacol* 2007; **10:** 661–73.

89 Kennedy SH, Emsley R. Placebo-controlled trial of agomelatine in the treatment of major depressive disorder. *Eur Neuropsychopharm* 2006; **16:** 93–100.

90 Stahl SM, Fava M, Trivedi MH, Caputo A, Shah A, Post A. Agomelatine in the treatment of major depressive disorder: an 8-week, multicenter, randomized, placebo-controlled trial. *J Clin Psychiatry* 2010; **71:** 616–26.

91 Zajecka J, Schatzberg A, Stahl S, Shah A, Caputo A, Post A. Efficacy and safety of agomelatine in the treatment of major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 2010; **30:** 135–44.

92 Kasper S, Hajak G, Wulff K, et al. Efficacy of the novel antidepressant agomelatine on the circadian rest-activity cycle and depressive and anxiety symptoms in patients with major depressive disorder: a randomized, double-blind comparison with sertraline. *J Clin Psychiatry* 2010; **71:** 109–20.

93 Lemoine P, Guilleminault C, Alvarez E. Improvement in subjective sleep in major depressive disorder with a novel antidepressant, agomelatine: randomized, double-blind comparison with venlafaxine. *J Clin Psychiatry* 2007; **68:** 1723–32.

94 Kennedy SH, Rizvi S, Fulton K, Rasmussen J. A double-blind comparison of sexual functioning, antidepressant efficacy, and tolerability between agomelatine and venlafaxine XR. *J Clin Psychopharmacol* 2008; **28:** 329–33.

95 Hale A, Corral R-M, Mencacci C, Ruiz JS, Severo CA, Gentil V. Superior antidepressant efficacy results of agomelatine versus fluoxetine in severe MDD patients: a randomized, double-blind study. *Int Clin Psychopharmacol* 2010; **25:** 305–14.

96 Quera-Salva M-A, Hajak G, Keufer-Le Gall S, Nutt D. Efficacy and safety of agomelatine in patients with major depressive disorder compared to escitalopram: a randomized, double-blind study. *Int J Neuropsych* 2010; **13:** P03–43.

97 Montgomery SA, Kennedy SH, Burrows GD, Lejoyeux M, Hindmarch I. Absence of discontinuation symptoms with agomelatine and occurrence of discontinuation symptoms with paroxetine: a randomized, double-blind, placebo-controlled discontinuation study. *Int Clin Psychopharmacol* 2004; **19:** 271–80.

98 Goodwin GM, Emsley R, Rembry S, Rouillon F, for the Agomelatine Study Group. Agomelatine prevents relapse in patients with major depressive disorder without evidence of a discontinuation syndrome: a 24-week randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2009; **70:** 1128–37.

99 Goodwin GM, Rouillon F, Emsley R. Long-term treatment with agomelatine: prevention of relapse in patients with major depressive disorder over 10 months. *Eur Neuropsychopharmacol* 2009; **18:** S338–39.

100 Novartis clinical trial results database. Agomelatine search. http://www.novctrd.com/ctrdwebapp/clinicaltrialrepository/displayfile.do?trialresult=3420 (accessed March 14, 2011).

101 Kasper S, Hamon M. Beyond the monoaminergic hypothesis: agomelatine, a new antidepressant with an innovative mechanism of action. *World J Biol Psychiatry* 2009; **10:** 117–26.

102 Montejo AL, Prieto N, Terleira A, et al. Better sexual acceptability of agomelatine (25 and 50 mg) compared with paroxetine (20 mg) in healthy male volunteers. An 8-week, placebo-controlled study using the PRSEXDQ-SALSEX scale. *J Psychopharmacol* 2010; **24:** 111–20.

103 Racagni G, Popoli M. The pharmacological properties of antidepressants. *Int Clin Psychopharmacol* 2010; **25:** 117–31.

104 Llorca P-M. The antidepressant agomelatine improves the quality of life of depressed patients: implications for remission. *J Psychopharmacol* 2010; **24:** S21–26.

105 Valdoxan product information. http://www.medicines.org.au/files/sepvaldx.pdf (accessed Feb 22, 2011).