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Agomelatine: Its Role in the Management of Major Depressive Disorder

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Abstract: Circadian rhythm abnormalities, as shown by sleep/wake cycle disturbances, constitute one of the most prevalent signs of depressive illness; advances or delays in the circadian phase are documented in patients with major depressive disorder (MDD), bipolar disorder, and seasonal affective disorder (SAD). The disturbances in the amplitude and phase of rhythm in melatonin secretion that occur in patients with depression resemble those seen in chronobiological disorders, thus suggesting a link between disturbed melatonin secretion and depressed mood. Based on this, agomelatine, the first MT_1/MT_2 melatonergic agonist displaying also 5-HT_{2C} serotonergic antagonism, has been introduced as an antidepressant. Agomelatine has been shown to be effective in several animal models of depression and anxiety and it has beneficial effects in patients with MDD, bipolar disorder, or SAD. Among agomelatine's characteristics are a rapid onset of action and a pronounced effectiveness for correcting circadian rhythm abnormalities and improving the sleep/wake cycle. Agomelatine also improves the 3 functional dimensions of depression—emotional, cognitive, and social—thus aiding in the full recovery of patients to a normal life.

Keywords: agomelatine, melatonin receptors, serotonin receptors, antidepressants, anxiolytics

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The Link between Circadian Rhythm Disturbances and Human Depression

Depression and circadian rhythms

Depression is a family of complex multifactorial illnesses that are characterized by disruptions of several physiological, neuroendocrine, and behavioral processes. According to a WHO report, the depressive disorders account for the fourth leading cause of global burden of disease and by the year 2020 they are expected to be the second highest cause of morbidity.¹

Circadian rhythm abnormalities, as shown by sleep/wake cycle disturbances, constitute one of the most prevalent signs of depression; advances or delays in the circadian phase are documented in patients with major depressive disorder (MDD), bipolar disorder, or seasonal affective disorder (SAD).^{2,3} Disturbance of the sleep/wake cycle is one of the DSM-IV diagnostic criteria for depression,⁴ and people with major depression commonly experience changes in sleep/wake cycle regulation that are seen as abnormal total sleep duration, poor sleep efficiency, overwhelming rapid eye movement (REM) sleep, and early morning awakening.^{5,6}

In addition to an altered sleep-wake cycle, daytime mood variation and periodic recurrences are clinical findings that relate depression with the circadian system.⁷ A significant proportion of patients show regular changes in the intensity of depressive mood during the day, with parallel changes in anxiety symptoms, attention capacity, and psychomotor symptoms that frequently accompany depression. Depressive patients with melancholic characteristics typically have an early morning awakening and morning worsening in their mood state. Both symptoms are part of the clinical diagnostic criteria of the melancholic depressive subtype. While the findings imply that altered circadian rhythms have a primary causal influence in depression, definitive evidence on this point is not yet available.⁸

An internal desynchronization of circadian oscillators with a strong oscillator being linked to phase advances was postulated.⁹ In patients with unipolar and bipolar depression, evidence has been provided for a phase advance of the temperature-REM sleep cycle in relation to the rest/activity cycle.¹⁰ Phase advances in the rhythm of melatonin secretion have now been documented in numerous studies of patients

with MDD.^{11–15} However, in some studies MDD patients show a phase delay in melatonin secretion.^{16–18} Delays in the onset of urinary 6-sulfatoxymelatonin (a6MTs) excretion were reported in a study of 382 postmenopausal women with MDD.¹⁹ In that study a close association between depressive symptoms and delayed offset of a6MTs excretion was found, suggesting that the timing of melatonin secretion is important for the regulation of mood.

A number of studies have shown that the phase of melatonin secretion also varies systematically with mood changes in bipolar affective disorders. Phase advances of at least 1 hour were observed in the nocturnal melatonin peak during the manic phase as compared to the euthymic or depressed phase.²⁰ Phase delays in circulating melatonin have also been documented in bipolar type 1 patients.²¹

In contrast to bipolar patients, patients suffering from SAD exhibit delayed circadian rhythms,²² with delayed offset of melatonin secretion of about 2 hours being reported.^{23,24} Clinical studies involving chronobiological manipulations such as exposure to bright light in the morning and/or melatonin administration in the evening have been found useful for reducing phase abnormalities and depressive symptomatology in SAD patients.²⁵

Organization of the circadian system

In mammals, the circadian timing system is composed of many individual, tissue-specific cellular clocks.²⁶ At a molecular level, these circadian clocks are based on clock genes, some of which encode proteins able to feedback and inhibit their own transcription. To generate coherent physiological and behavioral responses, the phases of this multitude of cellular clocks are orchestrated by a master circadian pacemaker residing in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus.²⁷ The central clock is a key regulator of many bodily functions that follow a circadian rhythm such as sleep and wakefulness, thermoregulation, and glucose homeostasis and fat metabolism.

A number of studies have tested variants of genes that control the circadian system for their association with mood disorder and circadian-related polymorphisms have also been reported in depressive illness. Single-nucleotide polymorphisms (SNP) of the circadian genes *Clock*, *NR1D1*, *Bmal1*, *Per3*, *Rora*,²⁸

Rorβ and *Cry2* have been associated with bipolar disorder.^{28–32} Notably, *Npas2* deficient mice³³ and *Clock* mutant mice³⁴ display behavior patterns resembling the manic state associated with bipolar disorder. In the case of SAD, the SNP examined for each of three circadian genes *Per2*, *Bmal1*, and *Npas2*, indicated an increased risk for developing depression.^{35,36} It must be noted, however, that most findings await replication in larger samples and populations.

The pineal methoxyindole melatonin is a synchronizer of the SCN clockwork. In mammals, melatonin is synthesized in the pineal gland in a rhythmic manner, with high levels during nighttime and low levels during daytime.³⁷ Melatonin phase-shifts circadian rhythms in the SCN by acting on the MT₁ and MT₂ melatonin receptors expressed by SCN neurons, thus creating a reciprocal interaction between the SCN and the pineal gland.³⁸ Melatonin's phase-altering effect is caused by its direct influence on the electrical and metabolic activity of the SCN. The circadian rhythm in the secretion of melatonin has been shown to be responsible for the sleep/wake rhythm in both normal and blind subjects (ie, in the absence of the synchronizing effect of light).³⁹

Since melatonin is involved in the regulation of both circadian rhythms and sleep, any antidepressant drug with effects on melatonin receptors could be an advantage in treatment. Melatonin treatment has been found to be effective in treating circadian rhythm disorders as well as insomnia.^{40,41} As far as its antidepressant activity, melatonin (10 mg/day) was inactive in affecting bipolar affective disorder⁴² and improved sleep with no effect on symptoms of depression in MDD.^{43,44} In SAD, melatonin (5 mg/day) was ineffective,⁴⁵ while in patients with delayed sleep phase syndrome and comorbid depression, melatonin administration improved the circadian profile scores of sleepiness, fatigue, and alertness, thus having antidepressant properties.⁴⁶

To improve the efficacy of melatonin's sleep promoting effects, several analogs of melatonin have been developed for treating circadian rhythm sleep disorders or insomnia. Among these, agomelatine (Valdoxan®, Servier, France) has been licensed by the European Medicines Agency (EMA) for the treatment of MDD in adults. Agomelatine has a unique pharmacological profile as it is both a MT₁/MT₂ melatonin receptor agonist and an antagonist of 5-HT_{2C} receptors.

As the first melatonergic antidepressant, agomelatine displays a non-monoaminergic mechanism.⁴⁷ As agomelatine addresses sleep disturbances as well as depressive symptoms and has early onset of action, even in severely depressed patients, it stands alone among the antidepressants for effective management of MDD.⁴⁸

Agomelatine: The First Melatonergic Antidepressant

Chemistry, pharmacokinetics and metabolism

Agomelatine has a molecular formula of C₁₅H₁₇NO₂ and a molecular weight of 243.30. It is a naphthalenic compound chemically designated as *N*-[2-(7-methoxynaphth-1-yl)ethyl] acetamide (Fig. 1). Agomelatine has a high agonist affinity at MT₁ and MT₂ receptors.⁴⁹ Agomelatine is also an antagonist of 5-HT_{2C} and 5-HT_{2B} serotonin receptors.⁵⁰ Agomelatine displays an overall selectivity (>100-fold) for MT₁ and MT₂ receptors as compared to other receptor sites. The affinity of agomelatine for melatonin receptors is comparable to that of melatonin (K_d = 8.52 × 10⁻¹¹ mol/L and 2.63 × 10⁻¹⁰ mol/L respectively). Agomelatine has no significant affinity for muscarinic, histaminergic, adrenergic or dopaminergic receptor subtypes,⁵¹ but it exhibits a high affinity as an antagonist of the human 5-HT_{2C} receptor (IC₅₀ = 0.270 μmol/L). Agomelatine

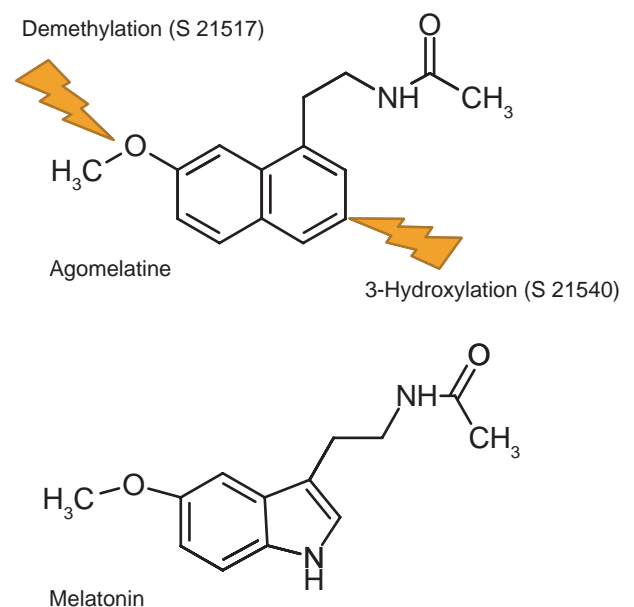


Figure 1. Chemical structure of agomelatine and melatonin. The major metabolites of agomelatine (S 21517) and S 21540 are shown.



binds only moderately to 5-HT_{2B} and shows negligible affinity for 5-HT_{2A} and 5-HT_{1A} receptors.

Pharmacokinetic modeling of the metabolism of agomelatine indicated that its uptake from the gastrointestinal tract follows a first order process and that it is immediately transported into the liver compartment.⁵² In the liver, three P 450 cytochromes are involved in agomelatine metabolism, namely CYP1A1, CYP1A2 and CYP2C9. The major metabolites have been identified as *N*-[2-(7-hydroxynaphth-1-yl) ethyl] acetamide (S 21517) and *N*-[2-(3-hydroxy-7-methoxynaphth-1-yl)ethyl] acetamide (S 21540) (Fig. 1). The hydroxylated, serotonin-like, S 21517 also showed affinity to 5-HT_{2C} receptors, whereas binding of S 21540 was considerably weaker.

Mechanism of action

Agomelatine is a high affinity ligand of MT₁ and MT₂ melatonergic receptors. Hence any discussion of its mechanism of action must consider first MT₁ and MT₂ receptor distribution in the brain.

In the mammalian brain, MT₁ and MT₂ receptors have been found in the SCN, prefrontal cortex, cerebellar cortex, hippocampus, basal ganglia, substantia nigra, ventral tegmental area, nucleus accumbens and in retinal horizontal, amacrine and ganglion cells⁵³ and choroid plexus.⁵⁴ The MT₁ receptor is highly expressed in the human SCN⁵⁵ and mainly in vasopressinergic neurons,^{56,57} a finding that can be critical since the release of vasopressin is one of the important components of the SCN circadian output.

MT₂ was not detected in an earlier investigation of the human SCN.⁵⁵ This receptor subtype is expressed in the SCN of numerous mammals and is particularly important for circadian phase shifting.^{58–61} Since circadian clock reset does occur in humans after the administration of melatonin or agomelatine,^{62–65} these changes must be induced by MT₁ signaling. Relatedly, the binding of melatonin to transcription factors of the retinoic acid receptor superfamily, including ROR α isoforms α , β and δ (formerly called RZR α) and the product of another gene, ROR β or RZR β , are increasingly considered as physiologically important. Some of these transcription factors interact with the circadian core oscillators, thereby influencing phasing, resetting, and period lengths of circadian rhythms. In the mammalian brain, expression of ROR α subforms and ROR β is detectable in the SCN and other parts of

the hypothalamus, the thalamus, pineal gland, retina, spinal cord, and pars tuberalis.⁶⁶ Remarkably, ROR β signal is highest in areas of highest MT₁ receptor density, suggesting the possibility that some sort of cooperation may exist between the membrane and nuclear receptors, especially in areas containing circadian oscillators. ROR β knockout mice exhibited significant circadian changes, including for example a larger phase advance and slower resynchronization than wild type mice.^{67,68} To what extent agomelatine share the properties of melatonin in binding to the transcription factors of the retinoic acid receptor superfamily remains to be defined.

The SCN is composed of neuronal oscillatory subsets, which differ in their recovery time after photic and non-photoc signals. Differential phased ventrolateral and dorsomedial zones have been observed in rats subjected to a forced desynchronization protocol, and the oscillators are operating with alternate or parallel rhythms in gene expression of the cellular circadian oscillator. The coordinating effect of melatonin was demonstrated in pinealectomized rats, in which methoxyindole injection almost normalized the phase relationship of *Per1* and *Per2* genes in SCN.⁶⁹ In a recent study we reported that treatment with melatonin phase-delayed the expression of *Per1*, *Per2* and *Cry1* in rat anterior pituitary by approximately 6 to 10 hours, the changes fitting well with the phase-delayed gene expression of anterior pituitary redox enzymes as well as with the phase-delay found in plasma corticosterone rhythm.⁷⁰ Interestingly, agomelatine has a significant effect on the SCN expression of *Per1* and *Per2* as assessed in a model of post-traumatic disorder in rats in which the administration of agomelatine normalized the SCN expression of *Per1* and *Per2*, as compared to controls.⁷¹ Collectively the findings suggest that the chronobiological effects of melatonin agonists are probably much more complex than commonly thought and that the multioscillator organization of the circadian system must be taken in consideration.

Another feasible effect of agomelatine on the SCN is related to sleep. MT₁-mediated effects in the SCN favor sleep initiation via the hypothalamic sleep switch, a mechanism characterized by typical on-off responses. This switch is thought to alternately activate either wake-related neuronal downstream pathways or promote sleep-related pathways.⁷²



Actions via the sleep switch do not seem to represent the exclusive route of melatonin-induced sleep onset. This is not surprising since sleep and sleep initiation are complex phenomena in which various brain areas are involved. The thalamus in particular contributes to the soporific effects of melatonin by promoting spindle formation, a characteristic feature of the transition from stage 2 sleep to deeper sleep stages.⁷³ This requires an additional thalamocortical interplay known to occur under these conditions. Moreover, the thalamus and other brain areas feedback to SCN.

In addition to sleep promotion, MT₁ and MT₂ receptors appear to be involved in the sedating and antiexcitatory effects of melatonergic drugs. This has been studied mainly in relation to anticonvulsant actions,^{74–79} which have been linked to a facilitatory role of melatonin on γ -aminobutyric acid (GABA) transmission.⁸⁰ The anticonvulsant activity of melatonergic agents seems to be mediated by MT₁ and/or MT₂ membrane receptors since similar effects were observed with the melatonergic agonist ramelteon.⁸¹ In mammals, the antiexcitatory actions may also be related to additional anxiolytic, antihyperalgesic, and antinociceptive effects of melatonergic agents.^{82–88}

A recent study indicates that agomelatine has anticonvulsant action in murine seizure models induced by pentylenetetrazole (PTZ) and pilocarpine. PTZ binds to the picrotoxin site of the GABA receptor complex and blocks GABA-mediated inhibition.⁸⁹ The agomelatine's main anticonvulsant effect is presumably mediated by GABA receptors and not via 5-HT_{2C} receptor inhibition, since 5-HT_{2C} antagonism was shown to enhance rather than to inhibit PTZ convulsions. In the case of pilocarpine (an agonist of muscarinic receptors) agomelatine's anticonvulsant effect at a high dose could be related to the demonstrated melatonergic action on the cholinergic system.⁹⁰

As in the retina,⁹¹ an antagonistic relationship between melatonergic receptors and the dopaminergic system may exist in the central dopaminergic system.^{92–94} This antagonism was detected in preclinical studies which looked at agomelatine's effects as an inhibitor of the apomorphine-induced turning in 6-hydroxydopamine-lesioned rats.⁹⁵

It has been hypothesized that agomelatine has a unique mechanism of action because its effects are mediated through MT₁/MT₂ melatonergic receptors and 5-HT_{2C} serotonergic receptors, acting differently

at different circadian phases of the day/night cycle.⁹⁶ Through this dual action agomelatine may promote and maintain sleep at night and helps to maintain alertness during daytime. Agomelatine given before sleep would have an immediate sleep promoting melatonergic effect that would prevail over its potentially anti-hypnotic 5-HT_{2C} antagonism.⁹⁶ In contrast, during the day, the drug's 5-HT_{2C} antagonism would predominate on melatonergic action, thus having an alerting action. 5-HT_{2C} receptors are concentrated in frontal cortex, amygdala, hippocampus and cortico-limbic structures that are involved in the regulation of mood and cognition.⁹⁷ They are also present in SCN,⁹⁸ and antidepressants decrease the number of 5-HT_{2C} receptors.⁹⁹

One criticism to this dual interpretation of agomelatine action is the large differences in affinity for the putative action on serotonergic receptors as compared to the melatonergic one; about 3 orders of magnitude greater concentration are needed to exert 5-HT_{2C} antagonism.⁵⁰ Moreover, both melatonin and ramelteon have been shown to display antidepressant-like effects even though they are not reportedly known to affect serotonergic receptors significantly.^{100–102}

Agomelatine has been classified as a neutral antagonist of 5-HT_{2C}, without inverse agonist properties.¹⁰³ This inhibition of 5-HT_{2C} receptor has been interpreted as grounds for direct action of drug antidepressants (Table 1). These have to be distinguished from indirect actions related to melatonergic adjustments of circadian rhythms, which are effective in subtypes of depression with an etiology of circadian dysfunction. More recently, a synergistic interaction of the signaling mechanisms between melatonergic and 5-HT_{2C} receptors has been assumed to explain the direct action of antidepressant agomelatine.¹⁰⁴ However, the precise nature of this type of synergy remains to be elucidated. Agomelatine has also been demonstrated to show robust anxiolytic properties, which appear to be higher than those of melatonin and can again be explained by a concerted action of melatonergic stimulation and 5-HT_{2C} inhibition (Table 1).

Preclinical Pharmacology

Table 1 summarizes published preclinical information on agomelatine activity. Agomelatine was found effective in several animal models of depression including learned helplessness, chronic mild stress,

**Table I.** Preclinical investigations on agomelatine.

Animal model	Animal	Agomelatine dose (mg/kg)	Response obtained	Inference	Reference
Animal model of delayed sleep-phase syndrome	Wistar rats	1–3	Agomelatine and melatonin phase advanced the onset activity toward the onset of darkness	Chronobiotic activity	105
EEG recording in rats	Wistar rats	3	Agomelatine and melatonin reduced the power density in NREM sleep in the low frequency range (1–8 Hz) but did not affect the vigilance states and brain temperature	Effects on sleep	106
Circadian resynchronization in rats	Wistar rats	1–100	Agomelatine altered the direction of re-entrainment of rat activity rhythms in the same manner as melatonin	Chronobiotic activity	107
EEG recording in trypanosome infected rats	Wistar rats	3	Agomelatine and melatonin restored a normal sleep pattern during the infection, increasing the length of synchronized sleep episodes	Chronobiotic activity	108
Wheel-running activity monitoring	Wistar rats	0.5–10	Agomelatine was as effective as melatonin to entrain free-running rhythms; agomelatine showed dose-dependent response	Chronobiotic activity	109
Modulation of rat dopaminergic activity by agomelatine	Wistar rats	5	Agomelatine inhibited apomorphine-induced turning in lesioned rats and inhibited ³ H-diazepam binding in striate membranes	Antidopaminergic action via GABA-ergic mechanisms	95
Wheel-running activity monitoring	Mice, Syrian hamsters	10–25	Agomelatine showed dose dependent phase shifting effects, also improving motor activity	Chronobiotic activity	110
Locomotor activity and body temperature rhythms	Adult Long Evans rats	1–10	Entrainment of circadian rhythms by agomelatine requires intact SCN but not the pineal gland	Chronobiotic activity	111
Autoradiography	Wistar rats	10	Agomelatine was able to down-regulate melatonin receptors in the rat pars tuberalis	Down regulation of melatonin receptors	112
In vivo electrophysiological monitoring of SCN activity	Syrian hamsters	1	Chronic drug treatments did not alter sensitivity of SCN cells in vivo or in vitro	Chronic agomelatine pretreatment does not result in desensitization of SCN	113
“Jet-lag” paradigms	Arvichantis rodents	20	Agomelatine accelerated by about 30% resynchronization to the new LD cycle	Chronobiotic activity	114
Discrimination reinforcement test	Wistar rats, monkeys	5	Subjects preferred diazepam or non melatonergic drugs to agomelatine	Non-addictive properties of agomelatine	115
Running-wheel activity and body temperature rhythms	Long Evans rats	0.25–0.50 mg/kg/h	Agomelatine and melatonin entrained the free-running circadian rhythms of rats	Exerts chronobiotic activity	116
Circadian resynchronization in old hamsters	Golden hamsters	10	agomelatine accelerated by approximately 25% resynchronization of the circadian activity rhythm.	Chronobiotic activity	117
Prolactin secretory mechanisms	Sprague Dawley rats	1	Agomelatine and melatonin exert inhibitory effects on prolactin secretion by stimulating tuberoinfundibular dopaminergic neurons	Effects on prolactin	118



Wheel-running activity rhythms	Rats	20	Agomelatine treatment resulted in prolonged overstimulation of melatonin receptors, attenuating the effects of light on the circadian timing system. Young hamsters fed with agomelatine showed larger phases than old ones	Chronobiotic activity	119
Wheel-running activity rhythm	Golden hamsters	Variable amounts in diet		Chronobiotic activity	120
5-HT _{2C} receptor antagonism	Wistar rats	25–40	Agomelatine but not melatonin antagonizes the penile erections induced by the stimulation of 5-HT _{2C} receptors	Activity of agomelatine as 5-HT _{2C} receptor antagonist	121
5-HT _{2C} receptor antagonism	Wistar rats	10–80	In contrast to melatonin, agomelatine behaves as an antagonist at 5-HT _{2C} receptors, increasing extracellular levels of DA and NA in frontal cortex and accelerating the firing rate of adrenergic cell bodies in the locus coeruleus	Activity of agomelatine as 5-HT _{2C} receptor antagonist	50
Desensitization of 5-HT _{1A} autoreceptors in dorsal raphe nucleus and hippocampus	Wistar rats	10	Agomelatine did not change the density of 5-HT _{1A} receptors, their coupling with G proteins or electrophysiological response to receptor stimulation	Antidepressant effect	122
Elevated plus-maze	Wistar Rats	10–75	Increased percentage of open arm entries	Anxiolytic effect	86,123
Vogel-test		10–75	Increased number of punished responses		
Conditioned ultrasonic vocalization test		10–75	Increased number of punished responses		
Punishment drinking test		40	Increased number of shocks	Potentiates the effect of diazepam	124,125
Punishment drinking test		20–40	Induced clear cut anxiolytic effect	Potentiates the effect of diazepam	
Elevated plus maze		20	Induced clear cut anxiolytic effect	Anxiolytic activity	126
Social interaction test	Sprague-Dawley rats	2.5–10	Increased the time devoted to active social interaction	Anxiolytic activity	127
Vogel conflict test	Wistar rats	2.5–80	Elicited a dose-dependent increase in punished responses	Anxiolytic activity	
Plus- maze test		40–80	Increased the percentage of entries into open arms	Anxiolytic activity	
Ultrasonic vocalization test		80	No significant activity	No anxiolytic activity	128
Learned helplessness test		10	Reduced the number of escape failures	Antidepressant activity	
Chronic mild stress test		10–50	Reversed the induced sucrose consumption	Antidepressant activity	129
Forced swimming test	Rats	4–64	Decreased duration of immobility in a dose dependent manner	Antidepressant activity	
Forced swimming test	Mice	4–32	Decreased the duration of immobility in dose dependent manner	Antidepressant activity	129
Porsolt forced swim test	Adult transgenic mice	10	Consistent reversal of the decreased immobility	Antidepressant activity	
Elevated plus-maze	Adult transgenic mice		Spent significantly less time in open arms	Antidepressant activity	

(Continued)



Table I. (Continued)

Animal model	Animal	Agomelatine dose (mg/kg)	Response obtained	Inference	Reference
Chronic social stress	Tree shrews	40	Agomelatine treatment caused the subordinate animals to remain under psychosocial conflict situations without stress and normalized the activity of the HPA axis	Antidepressant activity	130
Social defeat model of anxiety	Wistar rats	5–10	Anxiolytic-like action of the antidepressant agomelatine after a social defeat needs the integrity of the SCN	Anxiolytic effect	131
5-HT _{2C} receptor antagonist	Wistar rats	10–80	In contrast to melatonin, and reflecting blockade of 5-HT _{2C} receptors, agomelatine was active in several models of anxiolytic properties in rodents. The anxiolytic profile of agomelatine differs from that of benzodiazepines	Activity as 5-HT _{2C} receptor antagonist	126
Radial-arm water maze (RAWM) memory model	Rats	10	Agomelatine blocked the predator stress-induced impairment of spatial memory	Memory improvement	132
Ibotenate-induced periventricular leukomalacia and cerebral palsy model	Newborn mice	5	Agomelatine and melatonin promoted secondary lesions repair when given within the first 2h following the excitotoxic insult	Neuroprotective properties	133
24 hour-polygraphic recordings of sleep-wake episodes	Wistar rats	10–40	Agomelatine phase enhanced duration of REM and SWS sleep and decreased wake state, effects not shared by melatonin, ramelteon or the 5-HT _{2C} antagonist S32006	EEG profile reflecting co-joint agonist and antagonist properties at melatonergic and 5-HT _{2C} receptors	134
Neuronal cell proliferation, maturation, and survival	Wistar rats	40	Agomelatine increased the ratio of mature vs. immature neurons and enhanced neurite outgrowth of granular cells neurogenesis in the ventral hippocampus. Only the 5-HT _{2C} receptor antagonism mimicked the effects of agomelatine on cell proliferation	Activity as 5-HT _{2C} receptor antagonist	135
Expression of brain-derived neurotrophic factor	Sprague-Dawley rats	40	Agomelatine augmented expression in prefrontal cortex. Neither melatonin nor the 5-HT _{2C} antagonist S32006 mimic the effects of agomelatine	Effect on neuroplasticity	136
Glucocorticoid receptor-impaired (GR-i) mice	Mouse	40	Agomelatine and fluoxetine treatments reversed down-regulated hippocampal cell proliferation and brain-derived neurotrophic factor mRNA expression in GR-i mice. GR mRNA down-regulation was reversed only by agomelatine with increased survival of newly formed cells	Effect on neuroplasticity	137
Progenitor cell proliferation in the dentate gyrus	Wistar rats	40	Agomelatine or the 5HT _{2C} receptor antagonist SB242084 stimulated progenitor cell proliferation in the dentate gyrus. The effect was dependent on the daily corticosterone rhythm	Neuroprotective effect	138



Stress-induced increase of glutamate release in prefrontal/frontal cortex	Sprague-Dawley rats	40	Only agomelatine, but not melatonin or the 5-HT _{2C} antagonist S32006, prevented the stress-induced increase of glutamate release	Antidepressant activity	139
H/Rouen mouse genetic model of depression	Mice	10–50	Locomotor activity in a novel environment and anhedonia were reduced by agomelatine or fluoxetine	Antidepressant activity	140
Daily footshock stress	Rats	40	Agomelatine abolished stress-induced expression of synapsin I, a regulator of synaptic transmission and plasticity, in all layers of the medial prefrontal cortex and in the outer and middle molecular layers of the hippocampal dentate gyrus	Effect on neuroplasticity	141
Prenatal restraint stress model	Sprague-Dawley rats	10–50	Chronic agomelatine treatment corrected the increased immobility in the forced swim test, the anxiety-like behavior in the elevated plus maze, the reduced hippocampal levels of phosphorylated—CREB and mGlu2/3 and mGlu5 metabotropic glutamate receptors, and the reduced neurogenesis in the ventral hippocampus	Antidepressant activity	142
Expression of brain-derived neurotrophic factor, fibroblast growth factor, and activity-regulated cytoskeleton-associated protein	Sprague-Dawley rats	40	Agomelatine up-regulated expression in the hippocampus but not in the prefrontal cortex	Effect on neuroplasticity	143
Chronic mild stress model	Wistar rats	40	Agomelatine counteracted the decrease in hippocampal cell survival induced by chronic mild stress	Neuroprotective effect	144
Wheel-running activity in olfactory bulbectomized rats	Sprague-Dawley rats	10–50	Agomelatine reversed the bulbectomy-induced hyperactivity, an effect shared by the 5-HT _{2C} antagonist, S32006 but not by melatonin	Antidepressant activity	145
Stress-induced response in elevated plus-maze and acoustic startle response after exposure to predator scent	Sprague-Dawley rats	50	The long-term abnormalities in circadian expression of Period 1 and Period 2 genes in response to stress is normalized by agomelatine administered immediately after exposure	Chronobiotic activity	71
Pentylenetetrazole (PTZ), pilocarpine, picrotoxin, strychnine or electroshock-induced convulsion models	Mice	25–75	Agomelatine increased latency to convulsion in the PTZ and pilocarpine models at doses of 25–50 mg and 75 mg respectively. No activity on picrotoxin, strychnine or electroshock-induced models	Anticonvulsant effect mediated by GABA receptors (PTZ) and muscarinic receptors (pilocarpine)	89



forced swimming, transgenic mice with decreased glucocorticoid receptor (GR) expression, H/Rouen mouse model of depression, footshock stress, pre-natal restraint stress, psychosocial stress, olfactory bulbectomy and stress-induced increase of glutamate release in prefrontal/frontal cortex (Table 1). In some cases, for example stress-induced increase of cortical glutamate release, only agomelatine but not melatonin or 5-HT_{2C} antagonists prevented antidepressant activity,¹³⁹ supporting the conjoint action on both effects ascribed to agomelatine. In other cases, for example wheel-running activity in olfactory bulbectomized rats, agomelatine effect was shared by 5-HT_{2C} antagonists but not by melatonin, indicating an antidepressant action mediated exclusively by 5-HT_{2C} receptor antagonism.¹⁴⁵

An interesting animal model of depression is the transgenic mouse with decreased GR expression, called GR-i mouse. It is based on the evidence indicating that malfunction of GR system can be instrumental in depression. The antidepressant activity of agomelatine was assessed in this transgenic mouse model by using a forced swimming test.¹²⁹ In the same model, agomelatine was investigated for anxiolytic properties in the elevated plus maze. The effects of agomelatine were compared to those of desipramine or melatonin. Treatment with agomelatine reversed the decreased immobility in forced swimming test seen in transgenic mice, the effect being comparable to that of melatonin or desipramine. Both the number of open arm entries and the total time spent in open arms of the elevated plus maze were greatly increased in transgenic mice and agomelatine was effective in reversing the GR-i behavioral changes noted in the elevated plus maze.¹²⁹ In the same study, agomelatine accelerated readjustment of circadian cycles of temperature and activity of transgenic mice following an induced phase-shift, the effect of agomelatine being more potent than that of melatonin.¹²⁹ This resynchronizing effect of agomelatine is of therapeutic value since the internal desynchronization of circadian rhythms is presumably implicated in the pathophysiology of depressive disorders.¹⁴⁶ Therefore, the antidepressant action of agomelatine can depend partly on its chronobiotic properties. In the same GR-i mouse model, both agomelatine and fluoxetine reversed down-regulated hippocampal cell proliferation and brain-derived neurotrophic factor (BDNF) mRNA

expression. GR mRNA down-regulation was reversed only by agomelatine with increased survival of newly formed cells.¹³⁷

The anxiolytic properties of agomelatine have been explained through its antagonist action on 5-HT_{2C} receptors,^{126,147,148} which are highly concentrated in frontal cortex, hippocampus, and basal ganglia, all associated with mood, motor, and cognitive functions.^{149,150} In the case of melatonin, its anxiolytic action can be demonstrated in animal models involving exploratory behavior.^{151–153} Melatonin's anxiolytic action involves GABA-related mechanisms. Although melatonin reduces the use of benzodiazepines in human beings for induction of sleep, it may not act via expression of its anxiolytic properties.¹⁵⁴

By using a combined neurochemical and behavioral approach, the anxiolytic action of agomelatine was compared to that of melatonin, the selective 5-HT_{2C} receptor antagonist (SB243.213), and the benzodiazepine agonist clorazepate.¹²⁶ In the social interaction test model, agomelatine increased the time spent in social interaction by pairs of unfamiliar rats introduced into a novel environment. This action was mimicked by clorazepate and by SB243.213. In the Vogel conflict procedure, agomelatine exerted an anxiolytic activity with a maximal effect comparable to that of clorazepate and SB243.213. In the plus-maze test, agomelatine only moderately augmented the percent of entries into the open arm when compared to clorazepate, while SB243.213 was inactive. The anxiolytic action of agomelatine differed from that of benzodiazepines by its lack of inhibitory influence on the corticolimbic release of serotonin and norepinephrine, a finding that may explain the therapeutic efficacy of agomelatine in the treatment of depressive and anxious states.¹⁵⁵

In another study, agomelatine (40 mg/kg) was more effective than melatonin (20 or 40 mg/kg) in the punished drinking test in rats, but was as effective as melatonin (80 mg/kg), the finding being interpreted as an indication of a major 5HT_{2C} antagonist activity property of agomelatine.¹²⁴ However, neither melatonin (40–80 mg/kg) nor agomelatine (20–40 mg/kg) counteracted response suppression during the period associated with the safety signal withdrawal, nor did they affect rats' behavior in the elevated-plus-maze. Co-administration of melatonin or agomelatine with diazepam, at a dose inactive on its own (0.25 mg/kg),



induced anxiolytic effect in the punished drinking test and the elevated-plus-maze.¹²⁴ It was thus concluded that although melatonin or agomelatine were devoid of anxiolytic action per se, they potentiated the anxiolytic effect of diazepam.¹²⁴ The anxiolytic effect of melatonin or agomelatine depended upon the experimental procedures and time of administration.^{151–153}

The anxiolytic activity of agomelatine was compared to that of melatonin and two anxiolytics, diazepam and buspirone.⁸⁶ The drugs were tested 2 hours before and 2 hours after the dark phase of the diurnal cycle. Morning and evening agomelatine administration increased animals' responses in the elevated plus maze and Vogel tests. Melatonin (10–75 mg/kg) enhanced open arms exploration in the evening experiment. The melatonin antagonist S22153 enhanced the action of morning and evening agomelatine administration in the Vogel and conditioned ultrasonic vocalization tests, while in the elevated plus maze test, S22153 inhibited effects of evening but not morning melatonin or agomelatine administration. The results indicate the involvement of both the melatonin and the 5-HT_{2C} receptors in the mechanism of anxiolytic-like action of agomelatine.⁸⁶

It must be noted that the doses of agomelatine effective in underscoring the involvement of 5-HT_{2C} receptor antagonist properties in preclinical pharmacology studies were 10–40 mg/kg in rats (Table 1). Calculation of the equivalent dose in humans made on the basis of the body surface area normalization method¹⁵⁶ yields a human equivalent dose of 114–456 mg/day for a 70 kg person, which is greater than those used clinically. It is therefore important to find out whether agomelatine causes functional blockade of 5-HT_{2C} receptors in the human brain at standard clinical doses.

A recent paper does not support such a conclusion.¹⁵⁷ The acute administration of agomelatine to normal human volunteers did not reproduce the increase in slow wave sleep (SWS) reported for drugs with 5-HT_{2C} receptor antagonist properties,¹⁵⁸ thus suggesting that, at clinical doses, agomelatine does not cause any functional blockade of brain 5-HT_{2C} receptors in humans.

Neuronal plasticity is associated with depression, probably as a result of modified expression of proteins important for cellular resiliency. It is therefore important to establish whether antidepressant drugs are able to regulate these mechanisms in order to

achieve relevant clinical effects. Clinical studies have shown that stress-related depressed patients have a reduced hippocampal volume.^{159–161} This reduction in hippocampal size was attributed to a decrease in granule cell neurogenesis and to neuronal atrophy due to increased exposure to corticosteroids via excitatory amino acids.¹³⁰ The dentate gyrus of the hippocampal formation is a site of continuous neurogenesis during adult life in mammals, including humans.¹⁶² Treatment of animals with antidepressants and mood-stabilizing drugs increased the formation of neurons in the dentate gyrus. Indeed, the antidepressant effect on neurogenesis gives the basis for the neuroplasticity hypothesis of major depression.^{163,164} This effect was shared by agomelatine.^{165,166} The effect of agomelatine was selective since it only induced cell proliferation and neurogenesis in the ventral part of dentate gyrus, a region implicated in the response to emotion and anxiety, therefore providing the basis for explaining both the antidepressant and anxiolytic properties of the drug. More recently, a number of preclinical studies have reported that agomelatine increases expression of several neuroplasticity-associated molecules in the same regions (Table 1).^{136,138,141–144} Although these effects have generally been attributed to 5HT_{2C} receptor antagonism, BDNF expression was found to be stimulated by the pure MT₁/MT₂ agonist ramelteon in cerebellar granule cells of wild-type, MT₁, or MT₂ knockout mice.¹⁶⁷ This was also seen with melatonin, but rather surprisingly only in MT₂ knockouts.¹⁶⁷

Clinical Pharmacology

Starting from a double blind, multinational, placebo controlled trial of agomelatine conducted in 711 MDD patients,¹⁵⁵ ten similar studies have been published thus far (N = 3827, Table 2). Collectively, these studies indicate that agomelatine at doses of 25–50 mg/day is effective in reducing the depressive symptoms in patients with MDD. The effectiveness of agomelatine in severely depressed patients is particularly significant inasmuch as this patient group tend to be resistant to classical antidepressants.¹⁵⁵ Agomelatine has few adverse effects and is associated with early resolution of depressive symptoms.¹⁸⁹ The superior efficacy of agomelatine over other antidepressants, including paroxetine,^{155,169} venlafaxine,¹⁷⁶ fluoxetine,¹⁸³ and sertraline¹⁸² is supported by several investigations (Table 2).



Table 2. Clinical studies on agomelatine.

Condition	Type of study	N	Agomelatine (daily dose)	Duration of treatment	Response	Reference
Healthy volunteers	Cross-over design polysomnography (PSG) study. Comparison of agomelatine vs. melatonin	8	5 or 100 mg; melatonin 5 mg	Single injection	A single dose of melatonin or agomelatine increases REM sleep propensity and advances sleep termination without affecting NREM duration	64
Healthy volunteers	Double-blind, placebo-controlled crossover trial	8	5 or 100 mg; melatonin 5 mg	Single injection	Agomelatine or melatonin induced an earlier dim-light melatonin onset (DLMO), an earlier increase in distal skin temperature, and an earlier decrease in core body temperature, heart rate, and proximal skin temperature	65
MDD (DSM-IV)	Double blind, placebo controlled trial	711	25 mg, 20 mg paroxetine used as study validator	49 ± 15 days	Agomelatine decreased HAM-D score from 27.4 ± 3.1 to 12.8 ± 8.2	155
MDD (DSM-III-R)	Randomized controlled trial	28	5–100 mg	4 to 8 weeks	Total MADRS scores decreased from 30.7 ± 3.5 to 14.8 ± 6.4 in the 5 mg group vs. a decrease from 31.6 ± 4.7 to 18.6 ± 14.8 in the 100 mg group	168
MDD	Randomized controlled trial	192	25 mg, 20 mg paroxetine used as study validator	14 weeks	Discontinuation Emergent Signs and Symptoms (DESS) checklist. Patients treated for 12 weeks with agomelatine and continued to 2 weeks on the same drug, showed similar discontinuation symptoms to those "continued" to placebo while the paroxetine (20 mg/day) discontinued group experienced more	169
MDD DSM-IV	Randomized, double-blind, placebo controlled trial	212	25 or 50 mg	6 weeks	Agomelatine reduced the HAM-D score from 26.5 ± 2.8 to 14.1 ± 7.7	170
MDD	Open-label PSG study	15	25 mg	6 weeks	Sleep efficiency, time awake after sleep onset and the total amount of slow-wave sleep increased at week 6. No change REM sleep	171
SAD	Open-label trial	37	25 mg	14 weeks	Treatment with agomelatine yielded a response rate of 75.7% (SIGH-SAD < 50% of baseline value)	172
MDD	Double-blind, placebo controlled, parallel randomized, group trial	235	25 mg (augmented to 50 mg after 2 weeks of non-response)	6 weeks	Agomelatine and placebo reduced the HAM-D score from 27.4 ± 2.7 to 13.9 ± 7.7 and 17.1 ± 7.9, respectively	173
MDD	Pooled analysis of 3 positive placebo-controlled trial	717	25 or 50 mg	6–8 weeks	Agomelatine and placebo reduced the HAM-D score from 27.2 ± 3.7 to 14.0 ± 8.0 and 17.2 ± 6.5, respectively	174
MDD	Single-blinded, PSG trial	30	25 mg	6 weeks	Agomelatine improved NREM sleep phases	175



MDD	Placebo-controlled randomized trial; 2 arms. Agomelatine vs. venlafaxine	332	25–50 mg; 75–150 mg venlafaxine (variable dose)	6 weeks	176	Agomelatine and venlafaxine reduced HAM-D score from 25.9 ± 3.2 and 26.0 ± 3.3 to 9.9 ± 6.6 and 11.0 ± 7.4 , respectively. Sleep quality was subjectively better among patients treated with agomelatine
Depressed Bipolar I co-medicated with lithium or valpromide	Open-label trial	21	25 mg	A minimum of 6 weeks followed by an optional extension of up to an additional 46 weeks	177	81% of patients met criteria for marked improvement ($>50\%$ improvement from baseline in HAM-D score) at study endpoint. Patients were severely depressed at study entry (HAM-D of 25.2) and 47.6% responded as early as at 1 week of treatment
Generalized anxiety disorder	Randomized, double-blind, placebo-controlled trial	121	25 or 50 mg	12 weeks	178	Analysis of covariance of change in the last Hamilton Anxiety Rating Scale total score from baseline demonstrated significant superiority of agomelatine 25 to 50 mg as compared with placebo ($E = -3.28 \pm 1.58$; 95% confidence interval = -6.41 to -0.15); clinical response, symptoms of insomnia and improvement in associated disability, were consistent with the efficacy of agomelatine
Healthy volunteers	Placebo-controlled trial. Agomelatine vs. paroxetine	92	25–50 mg, 20 mg paroxetine	8 weeks	179	Score in PRSEXDQ-SALSEX of sexual acceptability was significantly lower in agomelatine group as compared to paroxetine group
MDD	Double-blind trial. Agomelatine vs. venlafaxine	277	50 mg, titrated to a target dose of 150 mg venlafaxine	12 weeks	180	Agomelatine showed antidepressant efficacy and a superior sexual side effect profile vs. venlafaxine
MDD	Randomized, placebo controlled trial	339	25 or 50 mg	24 weeks	181	Agomelatine prevented major depressive episode. The cumulative relapse rate at 6 months for agomelatine-treated patients was 21.7% vs. 46.6% for placebo. Agomelatine was also superior to placebo in preventing relapse in the subset of patients with baseline 17-item HDRS total score ≥ 25
MDD	Randomized, double-blind, placebo-controlled trial. Agomelatine vs. sertraline	313	25–50 mg, sertraline 50–100 mg	6 weeks	182	Agomelatine and sertraline reduced HAM-D score from 26.1 ± 2.8 and 26.5 ± 3.0 to 10.3 ± 7.7 and 12.1 ± 8.3 , respectively. Favorable effect of agomelatine on the relative amplitude of the circadian rest-activity/sleep-wake cycle at week 1. Higher efficacy results were observed with agomelatine on anxiety symptoms

(Continued)



Table 2. (Continued)

Condition	Type of study	N	Agomelatine (daily dose)	Duration of treatment	Response	Reference
MDD	Randomized, double-blind, placebo-controlled trial. Agomelatine vs. fluoxetine	415	25–50 mg, fluoxetine 20–40 mg	8 weeks	Agomelatine and fluoxetine reduced HAM-D score from 28.5 ± 2.7 and 28.7 ± 2.5 to 11.1 ± 7.3 and 12.7 ± 8.5 , respectively. The percentage of responders at last post-baseline assessment was higher with agomelatine on both HAM-D17 (decrease in total score from baseline $\geq 50\%$; 71.7% agomelatine vs. 63.8% fluoxetine) and CGI-improvement (score 1 or 2; 77.7 vs. 68.8%). There was a significant between-group difference in HAM-D sleep sub score in favor of agomelatine	183
MDD	Randomized, double-blind, placebo-controlled trial	482	25 or 50 mg	8 weeks	Agomelatine 25 mg, agomelatine 50 mg and placebo reduced HAM-D score from 26.8 ± 0.3 , 26.8 ± 0.3 and 26.4 ± 0.2 to 15.0 ± 0.6 , 15.9 ± 0.7 and 17.1 ± 0.6 , respectively. Both agomelatine doses were effective	184
MDD	Randomized, double-blind, placebo-controlled trial	511	25 or 50 mg	8 weeks	Agomelatine 25 mg, agomelatine 50 mg and placebo reduced HAM-D score from 26.7 ± 0.3 , 27.1 ± 0.3 and 27.1 ± 0.3 to 15.9 ± 0.6 , 14.1 ± 0.6 and 16.6 ± 0.7 , respectively. Significant antidepressant efficacy of agomelatine 50 mg, including a positive effect on sleep as compared to placebo	185
MDD	Randomized, double-blind, placebo-controlled PSG study. Agomelatine vs. escitalopram	138	25–50 mg, escitalopram 10–20 mg	24 weeks	Agomelatine reduced sleep latency from week 2 onward. REM sleep latency was increased by escitalopram. Agomelatine preserved the number of sleep cycles, whereas it was decreased by escitalopram. Agomelatine improved morning condition, and reduced daytime sleepiness as compared to escitalopram. 17-item Hamilton depression rating scale total score was reduced in both groups.	186
MDD	Open-label trial	30	25–50 mg	8 weeks	Significant improvements were seen on HAM-D, Hamilton Anxiety Scale, anhedonia (Snaith Hamilton Rating Scale), and sleep quality (Leeds Sleep Evaluation Questionnaire)	187
Healthy volunteers	Double-blind, placebo-controlled trial	48	25–50 mg	8 days	Emotional processing evaluated by the Emotional Test Battery. Agomelatine (25 mg) decreased subjective ratings of sadness, reduced recognition of sad facial expressions, improved positive affective memory and reduced the emotion-potentiated startle response	188



Agomelatine is unique because it has a chronobiological basis for its action and acts differentially at different circadian phases of the sleep/wake cycle.⁹⁶ While it promotes and maintains sleep at night, it also maintains alertness during the day. These effects are in contrast to traditional antidepressants which elevate the mood of depressed patients during daytime, an effect that is sustained at night and which causes impairment in sleep quality.¹⁹⁰

Agomelatine has been used in the treatment of bipolar affective disorder I and has been administered as an adjunctive to either lithium or valpromide for 46 weeks.¹⁷⁷ In this open label study, patients with severe Hamilton Anxiety Rating Scale (HAM-D) score higher than 25 showed clinical responses as early as one week after starting agomelatine therapy; 19 patients opted for an extension period up to 211 days (6–325 days) and 11 patients completed a one year extension period of treatment. There was no dropout from the study due to adverse events.¹⁷⁷

Interestingly a randomized, placebo-controlled study suggested that the pure MT₁/MT₂ melatonergic agonist ramelteon (8 mg/day) can also be beneficial for treatment of ambulatory bipolar I disorder patients.¹⁰¹ Although ramelteon and placebo had similar rates of reduction in rating symptoms of insomnia, mania, and global severity of illness, ramelteon treatment was associated with an improvement in a global rating of depressive symptoms. These findings underline the interpretation that activation of MT₁/MT₂ receptors alone may be sufficient to induce antidepressant activity.^{100–102}

Agomelatine has a low relapse rate (21.7%) when compared to placebo (46.6%), 6 months after continuous treatment.¹⁹¹ This may well be because agomelatine targets residual symptoms such as anxiety or sleep disturbances. The early clinical response to agomelatine therapy was confirmed in another open-label study in which 24 patients suffering from MDD received agomelatine 25–50 mg for 8 weeks.¹⁸⁷ Agomelatine was found effective in reducing HAM-D scores and improving anhedonia seen in depression. Agomelatine not only has an early onset of action but also exhibits excellent safety and tolerability.^{192–194}

In a randomized, double-blind, placebo-controlled trial in 121 patients with generalized anxiety disorder, the analysis of covariance of change in the last Hamilton Anxiety Rating Scale total score from

baseline demonstrated significant superiority of agomelatine 25 to 50 mg as compared with placebo.¹⁷⁸ As discussed above, together with a 5-HT_{2C} action, a GABAergic modulating action may account for the reported anxiolytic effects of agomelatine. While melatonin-like drugs have been reported to overlap the activity of GABA agonists (such as diazepam), neither agomelatine nor melatonin substituted benzodiazepines in anxiety-stressed rats trained to discriminate the different drugs. This suggests that the melatonergic anti-anxiety effect may be not additive as compared to the diazepam's effect, therefore becoming a core feature when it comes to choosing the correct drug for substance abusers and other addictive-behavior populations.

One remarkable effect of agomelatine is to reduce sleep complaints in depressed patients. As already stated, sleep disturbances constitute one of the prominent features of depressive illness and are among the diagnostic criteria of DSM-IV for MDD.¹⁹⁵ Patients suffering from MDD or bipolar disorder exhibit marked difficulties in initiation and maintenance of sleep, poor quality of sleep, and frequent nocturnal and early morning waking.¹⁹⁶ The NIMH Epidemiological Catchment Area study of sleep disturbances and psychiatric disorders identified sleep disturbances as a highly significant risk factor for subsequent development of depression.¹⁹⁷

Hence an ideal antidepressant should be able to decrease sleep onset latency (SOL) and wake-time after sleep onset (WASO), and should promote a feeling of well-being and alertness during the daytime. Sleep promoting effects of most antidepressants have been found to be either limited or non-existent. The effectiveness of agomelatine in reducing the sleep complaints of depressed patients has been ascertained. Altered intra-night temporal distribution of REM sleep with increased amounts of early REM sleep and reduction in SOL to REM sleep are the specific EEG sleep patterns that are associated with depression.⁵ Hence prevention of sleep disturbances would help to reduce the risk of relapse or recurrence of depressive disorders. The treatment of depressive patients with agomelatine for 6 weeks increased the duration of non-REM (NREM) sleep without affecting REM sleep, thereby causing improvements in both sleep quality and continuity.¹⁷¹ In a study that compared the effect of agomelatine (25 mg) with the antidepressant



venlafaxine, agomelatine promoted sleep earlier and scored higher on the “criteria of getting into sleep”, as assessed by the Leeds Sleep Evaluation Questionnaire.¹⁹⁸ The improvement in sleep quality was evident from the first week of treatment with agomelatine, whereas venlafaxine did not produce any beneficial effect. This is important clinically inasmuch as improvement in sleep disturbances often precede that of depressive symptoms.^{175,199} Agomelatine has also been shown to be effective in reducing circadian rhythm disturbances in patients with MDD.¹⁸²

Agomelatine is thus a dual action drug that can produce rapid antidepressant effects while also improving sleep quality. This is important clinically inasmuch as improvements in sleep among depressed patients are associated with a reduced rate of recurrence of depressive symptoms and, conversely, complaints of poor sleep in depressed patients are associated with a poor response to subsequent antidepressant treatment.^{198,200} Another study provides strong support for the superior chronobiological effects of agomelatine in patients with MDD.¹⁸² As compared to sertraline, agomelatine increased the relative amplitude of the circadian rest-activity cycle by the end of week one and in parallel there were improvements in sleep efficiency and in sleep latency from weeks one to six. Over a six week treatment period, depression and anxiety symptoms improved more with agomelatine than with sertraline.

Despite the foregoing, the relationship of sleep symptoms to depression and agomelatine treatment needs to be further examined. In particular, are those patients with a specific sleep pattern such as early morning waking or difficulty with sleep initiation more likely to respond to agomelatine than those without that pattern? If so, would it be possible to use the sleep pattern of depressed patients to predict the likelihood of response? The answer to these questions does not appear to have been addressed in any of the published papers to date. A second issue that has not been considered is that existing depression rating scales include sleep symptoms as part of the scale. For instance, the 17 item Hamilton Rating Scale for depression includes three items related to insomnia and later expanded versions added diurnal variation. Analysis of depression ratings separate from sleep symptoms is warranted to determine what part of the change is simply an improvement in sleep.

Safety

Agomelatine has an excellent safety and tolerability record, showing no difference from placebo except for dizziness (5.9% vs. 3.5%; $P < 0.05$).²⁰¹ Emergent adverse events, including gastrointestinal, cardiovascular, and body weight effects, were generally lower than sertraline or venlafaxine in active comparative trials. Moreover, antidepressant-induced sexual dysfunction was significantly lower than the specific serotonin reuptake inhibitors (paroxetine, sertraline and fluoxetine) or venlafaxine in both spontaneous reports and using structured instruments.²⁰¹ There were transient increases in transaminases, with an incidence similar to that of venlafaxine primarily when administered a higher dose of 50 mg per day. These were isolated, occurred mainly in the first month, and without clinical signs, and were reversible. In a study with the active comparator paroxetine, there was no evidence of discontinuation symptoms as compared to placebo.¹⁶⁹

A most notable effect of agomelatine is its almost absent effect on sexual function. Many antidepressants that are currently in use cause increased impairment of sexual function and a negative impact on quality of life. Most antidepressants have been shown to affect all phases of sexual activity, including desire, arousal, orgasm, and ejaculation. However, patients treated with agomelatine experienced significantly less sexual dysfunction than those treated with the placebo.¹⁸⁰

Because it is chiefly metabolized in the liver it should not be administered to patients with liver disease.²⁰² Agomelatine is contraindicated in patients receiving concomitant potent CYP1A2 inhibitors such as fluvoxamine or ciprofloxacin. However, paroxetine and fluconazole, which are moderate 1A2 and potent 2C9 inhibitors respectively, have little effect on agomelatine levels.²⁰²

Increases in alanine aminotransferase and/or aspartate aminotransferase (3 times the upper limit of normal) have been noted in 1.1% of patients treated with agomelatine vs. 0.7% of patients treated with placebo. These increases were isolated and reversible and occurred without any clinical signs of liver damage.²⁰¹ In two recent studies,^{184,185} newly occurring, clinically notable aminotransferase elevations were respectively seen in 2.4% and 4.5% of patients in the agomelatine 50 mg group, but not in the agomelatine



25 mg or placebo groups. These transaminase elevations were not associated with clinical signs of liver damage and one of the incidental reasons for the transient elevation of aminotransferases could be the higher prevalence of hepatobiliary disorders at baseline in the agomelatine 50 mg group (3.1%) compared with the agomelatine 25 mg and placebo groups (0.6% each). In any event, it is recommended that liver function tests should be performed in all patients at initiation of treatment and then periodically after around 6, 12, and 24 weeks, and thereafter when clinically indicated. Any patient who develops increased serum transaminases should have their liver function tests repeated within 48 hours. Therapy should be discontinued if the increase in serum transaminases exceeds 3 times the upper limit of normal and liver function tests should be performed regularly until serum transaminases return to normal.

Place in Therapy

The ultimate goal of antidepressant therapy is the symptomatic and functional recovery that helps a return to normal everyday life. However, a large proportion of patients fail to achieve a complete and sustained recovery from depression and are left with residual symptoms and/or psychosocial impairments that make relapse or recurrence more likely, making poorer quality of life a reality.^{203,204}

Most treatment guidelines recognize a symptom-free state as the best definition of disease remission, despite the fact that functional recovery often lags behind symptomatic improvement. Results from one large, prospective study of more than 7000 patients with at least one axis I disorder found that impairment in psychosocial functioning was apparent even in patients whose last episode occurred more than one year prior.²⁰⁵ In another study, which investigated the association between psychosocial impairment and recurrence of depression, it was demonstrated that for each 1-point increase in functional impairment score, the risk of disease recurrence increased by approximately 12%.²⁰⁶

Given the importance of all three dimensions of functioning (emotional, cognitive and social) in everyday activities such as work, and the impact that impaired functioning may have on a patient's life, it is clear that more attention should be paid to functioning when assessing treatment's response.

Social functioning, a central component to a patient's quality of life, is defined as an individual's ability to carry out normal social roles.²⁰⁶ In depression, loss of interest in activities, loss of self-esteem, loss of energy, and depressed mood compromises social functioning and affects the patient's ability to maintain relationships and to remain in employment.²⁰⁷ Relationships at home are affected, with spouses and relatives reporting strains in their relationship with the patient, and feelings of burden and distress are common. In turn, less family support for the patient with depression may be associated with a greater risk of the patient drinking alcohol to cope.

In community-based studies, patients with depression reported less enjoyable and less intimate day-to-day social interactions than non-depressed controls. Indeed, in a long-term study of 371 patients with major depression that examined their relationships with spouse/partner, functional disability related to work/employment, and overall psychosocial function, psychosocial impairment increased as the severity of depressive symptoms increased.²⁰⁵ Even a low-level of symptomatology was associated with a significant increase in psychosocial impairment.

Agomelatine rapidly improves social functioning. When the results from three published trials of agomelatine vs. placebo in patients with depression (agomelatine, N=358; placebo, N=363) were pooled,²⁰⁸ item-by-item Hamilton Depression Rating Scale analysis showed significant benefit with agomelatine over placebo for 10 of 17 items, including the 'work and activities' item (difference in item score: 0.32; $P < 0.001$, vs. placebo at weeks 6 to 8), thus highlighting agomelatine's capacity to improve social functioning.

In addition, agomelatine efficacy has been shown to correlate with recovery in personal, social, and professional functioning in the 8 week VALID trial in patients (N = 111) with depression.²⁰⁹ As early as the end of the first week, significant improvements from baseline were observed in Montgomery-Asberg Depression Scale scores and the work/school, social life, and family life sub-scores of the Sheehan Disability Scale. These significant improvements were maintained throughout the entire 8 week study period, with a return to normal levels of social functioning by the end of the study.²⁰⁹

The effects of agomelatine have been recently confirmed in results from the largest observational



trial of the agent conducted to date, the CHRONOS program.²¹⁰ This “real world” trial included 6276 patients with moderate or severe depression who were given agomelatine monotherapy (25–50 mg/day) for 8 weeks. As early as the first week of treatment, a significant reduction from baseline in HAM-D17 total score was apparent; this continued improvement was seen throughout the remainder of the trial. Crucially, rapid and continual improvement in social function (items 7 and 8 of the HAM-D17 scale: work/activities and retardation [psychomotor activity]) was also seen in this population, from week 1 through to the end of week 8. By week 8, 81% of patients had responded to treatment with agomelatine and 59% were considered to be in remission. According to the CGI—Severity scale, there was a consistent decrease in the proportion of patients with moderate, severe, or very severe depression during the study, from 100% of patients at baseline to 75% at week 1 and 7% at week 8.²¹⁰

Conclusions

The novel antidepressant drug agomelatine is an agonist of MT₁ and MT₂ melatonin receptors and an antagonist of 5-HT_{2C} receptors. Pre-clinical studies demonstrated that agomelatine may exert its antidepressant activity via its interaction with both types of receptors. Agomelatine’s mechanism of action differs from all other antidepressants on the market since it is a chronobiotic improving the extent of the sleep/wake cycle, which in turn improves sleep and quality of everyday performance. Agomelatine’s efficacy in improving sleep and in resynchronizing the disturbed circadian rhythms makes it a very useful antidepressant. In clinical trials, patients experience improvements in social functioning and relief of symptoms at the first week of treatment, and these effects are maintained and even improved during the treatment period. Agomelatine improves the three functional dimensions of depression—emotional, cognitive, and social—hence it can be a ready to use drug for our anxiety-disturbed society.

Author Contributions

Analysed the data: DPC, MFV, DEV. Wrote the first draft of the manuscript: DPC. Contributed to the writing of the manuscript: MFV, DEV. Agree with manuscript results and conclusions: DPC, MFV, DEV.

Jointly developed the structure and arguments for the paper: DPC, MFV, DEV. Made critical revisions and approved final version: DPC, MFV, DEV. All authors reviewed and approved of the final manuscript.

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Competing Interests

Author(s) disclose no potential conflicts of interest.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

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