

Major depressive disorder, sleep EEG and agomelatine: an open-label study



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Abstract

This open study evaluates the effect of agomelatine, a melatonergic receptor agonist and 5-HT_{2C} antagonist antidepressant, on sleep architecture in patients suffering from major depressive disorder. Fifteen outpatients with a baseline HAMD score ≥ 20 were treated with 25 mg/d agomelatine for 42 d. Polysomnographic studies were performed at baseline, day 7, day 14, and day 42. Sleep efficiency, time awake after sleep onset and the total amount of slow-wave sleep (SWS) increased at week 6. The increase of SWS was predominant during the first sleep cycle. The amount of SWS decreased throughout the first four sleep cycles from day 7 and delta ratio increased from day 14 onwards. No change in rapid eye movement (REM) latency, amount of REM or REM density was observed and agomelatine was well tolerated. In conclusion agomelatine improved sleep continuity and quality. It normalized the distribution of SWS sleep and delta power throughout the night.

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Introduction

Poor sleep constitutes one of the major complaints of patients suffering from a major depressive disorder (MDD).

Patients with affective disorders present reduced sleep efficiency and total sleep time, decreased slow-wave sleep (SWS), and altered rapid eye movement (REM) sleep. In addition, they present abnormal SWS distribution throughout sleep cycles compared to controls, with an initial reduction in delta sleep in the first non-REM (NREM) period, followed by either an increase in delta sleep in the second NREM period or no change (Armitage and Hoffmann, 2001; Kupfer et al., 1990).

Agomelatine is a new antidepressant (Kennedy and Emsley, 2006; Loo et al., 2002) with a novel pharmacological profile. It is a potent agonist at melatonergic

MT₁ and MT₂ receptors and an antagonist at serotonergic 5-HT_{2C} receptors. Animal studies indicate that interaction with both types of receptors contributes to agomelatine's antidepressant action (Bourin et al., 2004; Millan, 2003). Agomelatine has also been shown to resynchronize altered circadian rhythms both in an animal model of depression (Fuchs et al., 2006) and humans (Krauchi et al., 1997; Leproult et al., 2005).

The aim of this exploratory open study is to investigate the effects of agomelatine on sleep in MDD patients.

Methods

Patients

Inclusion and exclusion criteria

Male and female ambulatory patients fulfilling the diagnostic criteria for MDD, single or recurrent, according to DSM-IV criteria were recruited. A minimum severity score of 20 on the 17-item Hamilton Depression Rating Scale (HAMD) was required at baseline.

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Exclusion criteria were: significant suicide risk (defined as a score of >1 on item 3 of HAMD) or a serious suicide attempt within the past 6 months, a current depressive episode not having responded to two different previous antidepressant treatments, patients treated with ECT within the last 3 months prior to inclusion or requiring ECT at present, psychotherapy initiated <3 months before selection or phototherapy received within 2 wk before selection, a disease which could interfere with the study evaluations, shift work, recent transmeridian travel, alcohol or drug abuse or dependence within the past 12 months, and participation in another clinical trial in the past 3 months. Post-menopausal women (verified by FSH level), pregnant or breastfeeding women were excluded as were women of childbearing potential without effective contraception. Concomitant treatment with psychotropic drugs was not allowed. A washout period of at least five elimination half lives for benzodiazepines and non-benzodiazepine hypnotics, and of 2 wk for all antidepressants except fluoxetine (5 wk washout) was mandatory before inclusion. Patients with sleep apnoea (>15 apnoeas and hypopnoeas per hour of sleep) or periodic leg movements (>10 periodic leg movements per hour of sleep) were excluded.

Patient recruitment and procedures

Patients were recruited from the Garches Sleep Clinic, Hôpital Raymond Poincaré. Patients fulfilling the protocol requirements were shown the information and consent documents approved by the local ethics committee. All patients who gave written informed consent were included.

Eligible patients were entered into a 42-d open-label acute treatment trial and received 25 mg agomelatine orally once a day at 20:00 hours. An 18-wk optional treatment period for patients much improved at day 42 was offered.

At selection, an ECG, haematology and biochemistry tests were performed, as well as urine sampling for benzodiazepines, zopiclone, zolpidem and barbiturates screening. This screening was also performed before each recording.

The study was planned including regular follow-up with evaluation just before drug intake, e.g. day 1 (the first day of intake), days 7, 14, 28, 41 and 42. At each visit, the severity and evolution of depression was assessed by the HAMD 17-item score. A responder was defined as a patient with an improvement in HAMD score of $\geq 50\%$ in relation to the HAMD score at baseline.

Subjective daytime alertness (feeling wide awake at awakening and daytime sleepiness) was evaluated using an auto-questionnaire with five possible answers: very rarely, rarely, sometimes, often, very often (Laredo et al., 2002) administered at days 1 and 42.

Any adverse event spontaneously mentioned by the patient was recorded at each visit. All unused medication was returned in the original package at each visit, and drug intake was regularly checked.

Polysomnography

Patients had a total of six nights of polysomnography (PSG). PSG recordings were performed either at the patient's home or at the sleep laboratory depending on the patient's choice. All PSGs were performed under the same conditions; two patients chose recordings at hospital and 13 chose recordings at home. The first PSG recording was used for evaluating the absence of sleep apnoea or periodic leg movements and served as an adaptation to the recording conditions. The second recording (baseline) was performed the night following the inclusion visit (day 1), the eve of the first agomelatine intake. The following recordings were performed after 1 wk (day 7), 2 wk (day 14) and 6 wk of treatment (day 41, adaptation night and day 42). Recordings were realized with Pamela (Medatec, Brussels, Belgium) with a sampling rate of 100 Hz, and included the following channels: EEGs (C3-A2, C4-A1), two EOGs and one chin EMG. Electrode impedances were maintained at <5 k Ω . EEG signals were high-pass filtered with a time constant of 1.0 s and low-pass filtered at 35 Hz. During the first night (day 1) an extra montage set was used with recordings of pulse oximetry, nasal flow, thoracic and abdominal bands and tibialis EMG for primary sleep-disorder screening.

Data analysis

Polysomnography

Sleep and wake was manually scored by 30-s epochs following international criteria (Rechtschaffen and Kales, 1968) and short EEG arousals were scored according to the American Sleep Disorders Association criteria (ASDA, 1992). Sleep cycles were analysed according to Feinberg and Floyd criteria (Feinberg and Floyd, 1979). Following sleep scoring the following variables were tabulated: time of sleep onset [calculated according to Kupfer criteria (Kupfer et al., 1994)]; total sleep period (TSP) (time from sleep onset to final wake-up); total sleep time (TST) (all epochs scored as

sleep during TSP). Sleep efficiency was computed as the ratio of TST to TSP $\times 100$ and time awake after sleep onset as minutes awake between sleep onset and sleep offset. The following parameters were also calculated: duration in minutes of each sleep stage (stage 1, stage 2, stages 3–4 or SWS and REM) and their percentage in relation to TSP, and number of short ASDA arousals per hour of sleep. Two different analyses were used to calculate REM sleep latency: time in minutes from sleep onset to first epoch of scored REM sleep, and REM sleep latency minus intervening time awake (corrected REM latency). REM density was the average number of ocular movements per epoch. Time of minimum heart rate and heart rate frequency was measured at each recording.

During the first PSG recording apnoeas (AASM Task Force, 1999) and leg movements were scored as per international criteria (ASDA, 1993).

Quantitative EEG analysis

Quantitative EEG analysis was performed with the PRANA software (PhiTools, Strasbourg, France). For each analysed recording, artefacts were removed by an expert. Power spectral analysis was performed on successive 2-s windows using a fast Fourier Transformation (FFT) algorithm. To evaluate the pattern of change of the first two NREM sleep episodes, the delta sleep ratio (Kupfer et al., 1990) was computed as the quotient of the average EEG delta power (0.5–4 Hz) during the first NREM sleep episode to the corresponding average during the second NREM sleep episode.

Statistical analysis

Statistical analysis was carried out using the SAS software version 8.2 (SAS Institute Inc., Cary, NC, USA). An intention-to-treat analysis was performed for all 15 patients having taken at least one dose of study medication. Evolution of sleep parameters at each visit in relation to baseline was investigated using two-tailed Wilcoxon signed-ranks test. The evolution of stages 3–4 (SWS) at each visit throughout the different sleep cycles was studied using the two-tailed Friedman test.

Results

Patients involved in the study

Fifteen patients were included during a 20-month period. One patient withdrew at day 41 for inefficacy, and refused day-42 PSG after having performed his day-41 recording. As the group was small, it was

decided to include these night-41 data with those obtained on night 42 for analysis.

Thirteen patients continued the optional treatment period of 24 wk. Nine patients completed the optional period and four patients withdrew during this optional period, one for inefficacy and three because of recovery.

There were eight women and seven men (mean age, 36.5 ± 11.3 yr). Twelve patients had recurrent depressive episodes according to DMS-IV criteria, and none had melancholic features or seasonal pattern. The mean number of previous depressive episodes by patient was 2.3 ± 1.1 .

Efficacy on depression and safety

Depressive symptoms improved over time with a HAMD 17-item score progression as follows: 22 ± 2 (baseline), 17 ± 3 (day 7), 14 ± 4 (day 14), 11 ± 5 (day 28) and 9 ± 5 (last evaluation). Since the group was small no statistical analysis was performed on the HAMD score. However, the percentage of responders at consecutive visits were: 0% (day 7), 13% (day 14), 53% (day 28) and 67% (day 42).

This improvement of depressive symptoms was obtained without report of serious adverse events during the study. The most frequently reported adverse event was sleepiness 1 h after drug intake. This event was always considered as mild or moderate and did not lead to withdrawal from the trial.

Effect on subjective daytime alertness

Eleven patients reported difficulties in becoming wide awake in the morning (often or very often) at baseline compared to only two at day 42. Thirteen patients complained of daytime sleepiness often or very often at baseline vs. two patients at day 42.

Effect on objective sleep parameters

Polysomnographic results are presented in Table 1. Sleep efficiency increased and intra-sleep awakening decreased progressively from day 7, the differences from baseline were close to significance at day 14 ($p = 0.068$ and $p = 0.076$ respectively) and were significant at last evaluation ($p = 0.050$ and $p = 0.041$ respectively). SWS duration and percentage of sleep period time on SWS (stages 3–4) were significantly increased at last evaluation compared to baseline ($p = 0.037$ and $p = 0.022$ respectively).

The increase in the amount of SWS during the first cycle compared to baseline was close to significance at day 14 ($p = 0.058$), still with an important trend at last

Table 1. Polysomnographic results [values are mean \pm S.D. (median)]

	Baseline	Day 7	Day 14	Last
HAMD total score	21.8 \pm 1.5 (22)	17.4 \pm 3.2 (18)	13.9 \pm 3.5 (14)	9.2 \pm 5.5 (8)
TST (min)	363 \pm 60 (363)	408 \pm 83 (404)	386 \pm 74 (372)	392 \pm 95 (377)
WASO (min)	48 \pm 31 (42)	40 \pm 22 (39)	39 \pm 45 (28)	29 \pm 27 (19)
Sleep efficiency (%)	88 \pm 7 (90)	92 \pm 5 (91)	91 \pm 8 (93)	93 \pm 7 (95)
Stage 1 (% TSP)	5.3 \pm 2.9 (5)	5.3 \pm 2.0 (5)	4.7 \pm 2.6 (3)	5.2 \pm 3.2 (5)
Stage 2 (% TSP)	45.7 \pm 8.5 (47)	47.2 \pm 7.1 (46)	47.9 \pm 8.1 (49)	47.4 \pm 6.2 (48)
Stages 3–4 (% TSP)	15.9 \pm 4.2 (17)	16.2 \pm 4.7 (16)	17.3 \pm 4.6 (16)	19.4 \pm 4.7 (20)
Stages 3–4 (min)	66 \pm 20 (73)	71 \pm 23 (63)	72 \pm 14 (74)	80 \pm 20 (75)
REM (% TSP)	21.5 \pm 5.9 (22)	22.4 \pm 4.4 (23)	21.2 \pm 6.6 (21)	20.8 \pm 5.2 (20)
REM latency (min)	71 \pm 40 (61)	53 \pm 29 (52)	66 \pm 34 (59)	66 \pm 27 (54)
REM latency (min) (corrected)	61 \pm 33 (55)	49 \pm 27 (44)	64 \pm 33 (57)	63 \pm 26 (54)
Mean REM density	2.5 \pm 1.0 (2.4)	1.9 \pm 0.8 (1.9)	2.9 \pm 2.3 (2.1)	2.6 \pm 1.5 (2.1)
Time of sleep onset (hours:min)	23:59 \pm 0:52 (00:03)	23:26 \pm 0:54 (23:37)	23:36 \pm 1:03 (23:27)	00:01 \pm 1:37 (23:27)
Time of sleep onset in REM (hours:min)	01:13 \pm 1:03 (01:10)	0:23 \pm 1:00 (0:25)	0:41 \pm 1:12 (0:40)	01:06 \pm 1:35 (0:46)
Time of minimum heart rate	4:47 \pm 1:41 (5:10)	4:24 \pm 1:37 (4:18)	3:55 \pm 2:03 (4:30)	4:16 \pm 1:59 (4:34)
Delta power ratio	0.88 \pm 0.35 (0.93)	1.08 \pm 0.51 (1.07)	1.23 \pm 0.56 (1.19)	1.16 \pm 0.57 (1.30)

No. of patients: 15 (baseline), 15 (day 7), 14 (day 14), 15 (last evaluation) for all parameters except for time of minimum heart rate [no. of patients: 13 (baseline), 13 (day 7), 11 (day 14), 13 (last evaluation)].

S.D., Standard deviation; TST, total sleep time; SPT, sleep period time (time from sleep onset to morning awakening); WASO, intra-sleep awakening or time awake in minutes between sleep onset and sleep offset; sleep efficiency = (TST/TSP) \times 100; REM latency corrected, REM sleep latency minus intervening time awake.

Significant results ($p < 0.05$) in bold.

evaluation ($p = 0.135$). This change in SWS was supported by the analysis of the delta ratio using power spectral analysis: there was a progressive increase in comparison to baseline that started at day 7 and reached statistical significance at day 14 ($p = 0.007$).

Treatment did not influence REM sleep latency, amount of REM sleep, mean overnight REM density or REM density during each sleep cycle.

Time of sleep onset and time of REM sleep onset advanced significantly from baseline at day 7 ($p = 0.013$, and 0.009 respectively), and time of minimum heart rate advanced significantly from baseline to at day 14 ($p = 0.003$) and at the last evaluation ($p = 0.033$). The repartition of stages 3–4 throughout the first four sleep cycles changed over time. The amount of stages 3–4 decreased progressively throughout the first four sleep cycles from day 7 (see Figure 1).

Discussion

The aim of the present study was to explore the effect of agomelatine on sleep EEG parameters of MDD patients.

The major findings of the study are that agomelatine, besides its antidepressant activity, demonstrated

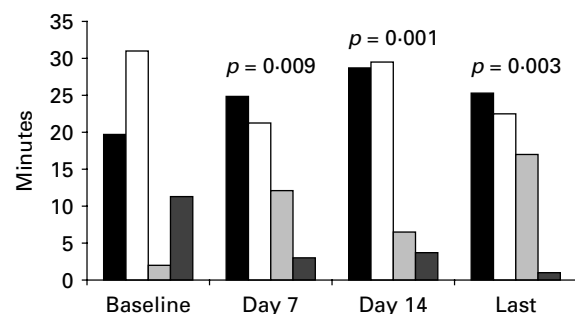


Figure 1. Distribution of slow-wave sleep (stages 3–4 in minutes) in the first four sleep cycles at each visit. No. of patients, 11 (baseline), 14 (day 7), 14 (day 14), 11 (last evaluation). Patients who did not have four cycles were not included in this analysis. Values are expressed in medians. The duration of stages 3–4 in minutes decreased progressively throughout the first four cycles from day 7. ■, Cycle 1; □, cycle 2; ▣, cycle 3; ■, cycle 4 (p values two-tailed Friedman test).

sleep-promoting properties and redistributed SWS and slow-wave activity to the first sleep cycle without suppressing REM sleep. This normalization of SWS distribution occurs very early with this compound. These changes are associated with a simultaneous displacement of the lowest heart rate point which has

been considered as a marker of circadian rhythm (Taillard et al., 1990).

Other antidepressants with 5-HT₂ receptor antagonist properties, such as trazodone, nefazodone, mirtazapine, amitriptyline have also demonstrated sleep-promoting effects (Willson and Argyropoulos, 2005) but may also induce daytime sleepiness whereas agomelatine improved daytime alertness.

It must be emphasized that agomelatine did not suppress REM sleep. Although dose-dependent suppression of REM sleep has been seen with both tricyclics, selective serotonin reuptake inhibitors and venlafaxine, other antidepressants, such as trimipramine, nefazodone, and trazodone do not produce apparent REM sleep inhibition (Willson and Argyropoulos, 2005).

SWS was higher at baseline in our study than in most sleep laboratory studies in depression. This could reflect the young age of our population and the use of home recordings for most of the patients (13/15), as the amount of SWS in the present study at baseline is similar to that found by Hicks et al. (2002) in depressive patients with ambulatory recordings.

Despite this, agomelatine increased SWS, an effect also seen in other compounds producing 5-HT₂ blockade such as trazodone (Mouret et al., 1988) and ritanserin. Ritanserin massively enhances SWS in humans (Declerck et al., 1987), and increases deep SWS and EEG power density, mainly delta activity, in rats (Kantor et al., 2002). Furthermore, the increase of SWS and slow-wave power activity by agomelatine was more evident during the first NREM sleep period as reflected by traditional sleep scoring and by the power density analysis on the delta band.

In several studies, the delta ratio has been reported to be increased after treatment with other antidepressants such as sertraline, amitriptyline and clomipramine (Ehlers et al., 1996; Jindal et al., 2003). It could be argued that this is due to their REM suppression effect, leading to a delay in the first REM sleep. This is not the case for agomelatine.

Thus, it seems that agomelatine, by increasing SWS and activity especially during the first sleep cycle, improves the deficiency of the homeostatic system of sleep regulation known to be impaired in depression (Borbely et al., 1984). This is in agreement with a study demonstrating impairment of the cyclic alternating pattern (CAP) during NREM sleep in depressed patients at baseline and the very fast and significant improvement of this pattern within the first 15 d of treatment (Lopes et al., In Press).

Finally, although the study was not designed to show the chronobiotic activity of agomelatine

(Krauchi et al., 1997), the advance of sleep onset and time of minimum heart rate seen after treatment are in favour of a chronobiotic effect with reorganization of the sleep structure.

The study confirms the results of a large double-blind study that showed an early subjective positive improvement of sleep using the Leeds questionnaire (Guilleminault, 2005). This study had the limitation of being an open study and it should be replicated with a larger patient population and a double-blind protocol.

In conclusion, the results of this study showed an early effect of agomelatine on sleep improvement with a redistribution of SWS. Further controlled studies investigating sleep and daytime alertness are needed.

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Statement of Interest

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