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

Siegfried Kasper, MD, PhD; Göran Hajak, MD; Katharina Wulff, PhD; Witte J. G. Hoogendijk, MD, PhD; Angel Luis Montejo, MD, PhD; Enrico Smeraldi, MD; Janusz K. Rybakowski, MD; Maria-Antonia Quera-Salva, MD; Anna M. Wirz-Justice, PhD; Françoise Picarel-Blanchot, PhD; and Franck J. Baylé, MD

Objective: This study evaluates the efficacy of agomelatine, the first antidepressant to be an agonist at MT_1/MT_2 receptors and an antagonist at $5\text{-}HT_{2C}$ receptors, versus sertraline with regard to the amplitude of the circadian rest-activity cycle and depressive and anxiety symptoms in patients with major depressive disorder (MDD).

Method: Outpatients with *DSM-IV-TR*–defined MDD received either agomelatine 25 to 50 mg (n = 154) or sertraline 50 to 100 mg (n = 159) during a 6-week, randomized, double-blind treatment period. The study was conducted from 2005 to 2006. The main outcome measure was the relative amplitude of the individual rest-activity cycles, expressed as change from baseline to week 6 and collected from continuous records using wrist actigraphy and sleep logs. Secondary outcome measures were sleep efficiency and sleep latency, both derived from actigraphy, and efficacy on depression symptoms (17-Item Hamilton Depression Rating Scale total score and Clinical Global Impressions scale scores) and anxiety symptoms (Hamilton Anxiety Rating Scale total score and subscores).

Results: A significant difference in favor of agomelatine compared to sertraline on the relative amplitude of the circadian rest-activity cycle was observed at the end of the first week ($P = .01$). In parallel, a significant improvement of sleep latency ($P < .001$) and sleep efficiency ($P < .001$) from week 1 to week 6 was observed with agomelatine as compared to sertraline. Over the 6-week treatment period, depressive symptoms improved significantly more with agomelatine than with sertraline ($P < .05$), as did anxiety symptoms ($P < .05$).

Conclusions: The favorable effect of agomelatine on the relative amplitude of the circadian rest-activity/sleep-wake cycle in depressed patients at week 1 reflects early improvement in sleep and daytime functioning. Higher efficacy results were observed with agomelatine as compared to sertraline on both depressive and anxiety symptoms over the 6-week treatment period, together with a good tolerability profile. These findings indicate that agomelatine offers promising benefits for MDD patients.

Trial Registration: www.isrctn.org: ISRCTN49376288

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Corresponding author: *Siegfried Kasper, MD, PhD, Department of Psychiatry and Psychotherapy, Medical University Vienna, MUV, AKH, Währinger Gürtel 18-20, A-1090 Wien, Austria (biol-psychiatry@meduniwien.ac.at).*

Almost all patients with major depressive disorder (MDD) present with psychomotor dysfunction,[1] altered circadian rhythms[2] (eg, hormonal, body temperature, or cardiac rhythms are phase-advanced or -delayed[3]), and sleep disturbances.[4] There is a close link between the regulation of sleep and circadian rhythms and the regulation of mood.[5,6] Circadian rhythms are regulated by the suprachiasmatic nucleus, the biologic clock in the hypothalamus, which shows alterations in postmortem brain tissue of depressed patients.[7] Sleep disruption is a major symptom in depression, with over 90% of patients suffering from sleep complaints that affect daytime functioning.[8] Conversely, sleep disturbances are also a frequent residual symptom leading to high rates of incomplete remission and hence more relapses and higher risk of recurrence.[9,10] Consequently, sleep difficulties are often the key factor that causes depressed patients to seek medical help, and relief of sleep disturbances is important to encourage compliance with medication.[11]

Although effective antidepressant treatment generally improves sleep disturbances, agents such as selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors may modify sleep architecture, and some may even disturb sleep, particularly early in treatment.[11–13] Around 35% of patients treated with an SSRI are also coprescribed hypnotic drugs to relieve medication-induced sleep difficulties and anxiety.[14] Some antidepressants, including amitriptyline, trazodone, and mirtazapine, promote sedation and sleep, but may cause daytime drowsiness.[11,12]

Psychomotor retardation or agitation are considered to be core symptoms in depression, in particular in patients with melancholic features, so that psychomotor dysfunction is a key symptom for depressed patients. Psychomotor dysfunction in MDD is reflected in alterations of the 24-hour pattern of motor activity.[1,15,16]

Actigraphic measures appear to be potentially more objective than a retardation scale for evaluating psychomotor dysfunction. A recent study has proposed that the relative amplitude (RA), which is the ratio between daytime and nighttime activity, reflects such dysfunction.[17] Should the circadian rest-activity cycle already improve before the mood-lifting effects become apparent, this might initiate early global clinical improvement and thereby enhance adherence to treatment.

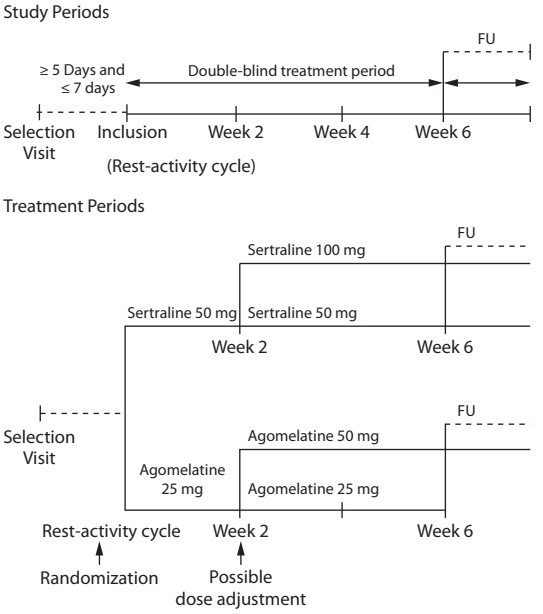
Agomelatine is the first melatonergic antidepressant acting as a potent MT_1/MT_2 receptor agonist with 5-HT_{2C} receptor antagonist properties.[18,19] Both properties contribute to the antidepressant activity of agomelatine.[20,21] Agomelatine has been shown to resynchronize altered circadian rhythms both in an animal model of depression[22] and in healthy young men.[23] Its efficacy in major depression has been demonstrated both in placebo-controlled trials[24–26] and in direct head-to-head comparisons.[27,28] Agomelatine has been shown to induce a rapid beneficial effect on subjective sleep and daytime functioning already at the first week after treatment initiation versus venlafaxine[27] and also to improve objective sleep disturbances in depressed patients.[29]

The current study was designed to compare the efficacy of agomelatine versus sertraline while paying closer attention to the circadian rest-activity cycle in outpatients with MDD. Sertraline was chosen as comparator due to its alerting properties[30] as well as its effects on sleep architecture in patients with depression[31] (with normalization of delta sleep ratio) that parallel those of agomelatine.[29]

It was supposed that agomelatine would improve the rest-activity cycle faster than sertraline, while a similar improvement in rest-activity overall over 6 weeks was expected with both treatments through alleviation of depression.

The primary objective was to demonstrate that agomelatine (25–50 mg/d) improved the circadian rest-activity cycle faster than sertraline in MDD outpatients. The secondary objectives were to assess the effect of agomelatine on sleep efficiency and sleep latency derived from actigraphy, assess its efficacy on depressive and anxiety symptoms compared with sertraline, and assess its tolerability.

Figure 1. Study Design[a]



[a]Dashed lines indicate periods of no treatment.
Abbreviation: FU = follow-up period.

For the purpose of high-resolution analysis, actigraphy was used as a method for objectively measuring subjects' circadian rest and activity patterns. The miniaturized wrist-worn devices used in this study allowed ambulatory measurements for several weeks in the patient's natural environment with minimal interference in the everyday lifestyle.[32] In sleep research and chronobiology, actigraphy has proved useful as a method to indirectly measure sleep and characterize the 24-hour sleep-wake cycle, but it has rarely been used to assess the effect of an antidepressant therapy in patients with MDD.[16]

METHOD

This was an international, double-blind, randomized exploratory study with parallel-group design conducted from 2005 to 2006 in 37 centers in 6 European countries (France, Germany, Austria, Spain, Italy, and Poland) in outpatients with MDD requiring antidepressant treatment. Figure 1 shows the study design.

The study was run in accordance with the principles of Good Clinical Practice E6 of the International Conference of Harmonization (CPMP/ICH/135/95) and the Declaration of Helsinki, Finland, 1964 (revised in Tokyo, 2004). The study was approved by the relevant local ethics committees and included only patients who had given their written informed consent.

There was a washout period according to previous drugs' half-lives. The duration of this washout period was at least 1 week, increasing to 2 weeks if the patient had previously received monoamine oxidase inhibitors and to a maximum of 5 weeks if the patient had previously been treated with fluoxetine or trazodone. Eligible patients were randomly assigned to receive agomelatine 25 mg/d or sertraline 50 mg/d for a 6-week treatment period. Four visits were scheduled: at week 0 (baseline) and then every 2 weeks at weeks 2, 4, and 6.

After 2 weeks, a dose increase to agomelatine 50 mg/d or sertraline 100 mg/d was possible in case of insufficient improvement according to predefined criteria. These criteria and the dose increase were applied centrally using an Interactive Voice Response System, and the investigator and the patient were blind to them. The dose of 50 mg/d of sertraline is the usually effective and optimal therapeutic dose that can be increased in 50-mg/d increments in patients who do not show an adequate therapeutic response in 2 to 4 weeks according to the manufacturer's recommendations.[33]

During the entire duration of the study, all patients took orally 2 tablets once a day in the evening, irrespective of the treatment and daily dosage allocated. The appearance and the taste of the study treatment were the same from inclusion to the end of the treatment period for all patients. The packaging and the labeling were identical.

Rater Training

Clinicians were all experienced and had met for training in procedures and to establish interrater consistency prior to the start of the trial. The investigators were trained before and during the study on the diagnosis of depression and the rating of the 17-Item Hamilton Depression Rating Scale (HDRS) using video recording of patients' interviews.

Patients

Male and female outpatients aged 18 to 60 years with a primary diagnosis of major depressive disorder, single or recurrent, of moderate or severe intensity according to *DSM-IV-TR* criteria,[34] confirmed by the Mini-International Neuropsychiatric Interview,[35] with an HDRS score ≥ 22 and a sum of ≥ 3 on HDRS items 5 ("insomnia: middle of the night") and 6 ("insomnia: early hours of the morning") were eligible for this study. They did not have seasonal pattern, psychotic features, or catatonic symptoms and were not postpartum, and their current episode had already lasted at least 4 weeks. Patients were excluded if they had a high risk of suicide or a previous suicide attempt within 6 months (score > 2 on HDRS item 3); bipolar disorder; anxiety symptoms such as current panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, or acute stress disorder; drug abuse or dependency within the past 12 months; previous depression resistance to antidepressants; treatment with electroconvulsive therapy or formal psychotherapy within 3 months; or light-therapy started within 2 weeks. Patients who screened positive on clinical screening evaluation for sleep disorders, including obstructive sleep apnea and restless legs syndrome, were excluded. Patients with neurologic disorders (dementia, seizure, and stroke), obesity with functional impairment, serious or not stabilized organic disease (neoplasia, cardiovascular or pulmonary disease, or uncontrolled type 1 or type 2 diabetes) were also excluded. Other antidepressants, hypnotics, anxiolytics, and neuroleptic agents were prohibited during the study and for a variable period before inclusion, depending on half-life. When the washout period of hypnotics or anxiolytics was applicable for the study, the treatment had to be stopped at selection visit at the latest.

Actigraphy

Patients' rest-activity patterns derived from arm movements were continuously measured with a sampling interval of 2 minutes using activity monitors (Actiwatch Plus by Cambridge Neurotechnology Ltd. [CNT], Cambridgeshire, United Kingdom) from selection to week 6.[17,36,37] Patients wear the actigraphs on their nondominant wrist continuously except when showering or bathing. Patients were required to press an event marker button on the actigraph when they were ready to sleep and immediately on awakening, so the event was captured in the actogram recording. In addition, the patients were required to fill out a daily sleep agenda indicating "bed time" and "get up time" after activity monitoring. These data were crosschecked in order to ascertain correct sleep time and awakening data. Actigraphy data were downloaded to a computer, and actograms showing the rest-activity patterns were generated with the Actiwatch Activity and Sleep analysis software version 7 (CNT). Diary information was then added manually for each day (42 days per person) to the printed actograms to verify concordance with the marker in the actigraphy data, to determine "bed time" and "get up time," and to edit gaps from removing the watch for shower/bathing.

Efficacy Measurements

Efficacy on the circadian rest-activity cycle. Reading out of actigraphs was centralized and carried out blind. The actigraphic analysis programs extracted both "circadian" and "sleep" characteristics. The circadian parameters were obtained with the Non-Parametric Circadian Rhythms Analysis (NPCRA), which consisted of overlaying all single-day data (about 7 days from midnight to midnight) to generate an "average day" profile of activity for each week of the study. The relative amplitude (RA) of the patient's circadian rest-activity cycle obtained from these actigraphy recordings was chosen to assess changes in circadian organization of sleep and wakefulness patterns with treatment. The RA of the rest-activity cycle was calculated as the difference between the average activity level during the 10 most active hours (M10) and the 5 least active hours (L5) of

a 24-hour period, divided by the sum of M10 and L5. The measure theoretically ranges from 0 to 1.

$$RA = \frac{M10 - L5}{M10 + L5}$$

The difference between M10 and L5 gives an indication of the amplitude of the rhythm. Higher values of the RA indicate a rhythm of higher amplitude, which is considered healthy and expected in nondepressed subjects.

Efficacy on sleep. Assessment of objective sleep changes with treatment was also obtained from the actigraphy recordings. A second program yields a number of actigraphy-derived "sleep" parameters. The sleep analysis algorithm of the CNT software was used to establish sleep onset, sleep end, sleep latency, sleep efficiency, and mean length of wake bouts for each night. Efficacy of treatments was assessed on sleep efficiency (the percentage of time spent asleep while in bed), sleep latency (the latency from bed time until sleep onset), and mean length of wake bouts, which is determined by dividing the total duration of wake during the sleep period by the corresponding number of wake bouts.

Subjective sleep was assessed using the Leeds Sleep Evaluation Questionnaire (LSEQ),[38] a standardized validated self-rating scale for the measurement of sleep difficulties in a clinical setting. The questionnaire consists of 10 items, each quantified by a 100-mm visual analog scale (VAS), grouped into 4 scores evaluating the ease of getting to sleep (made up of 3 VAS component items), the perceived quality of sleep (2 VAS items), the ease of awakening (2 VAS items), and the integrity of behavior following wakefulness (3 VAS items assessing whether patients feel more alert and less clumsy after getting up).

The LSEQ questions assess the changes experienced during treatment relative to the patient's condition before receiving the study treatment; therefore, there is no evaluation at baseline. In the absence of a formal baseline assessment, the midpoint of the scale, 50 mm, representing no change from prestudy condition, may be considered as the baseline.[39] The LSEQ questionnaire was completed by the patient at weeks 2, 4, and 6.

For clarity, the scores for each item were subtracted from 100 mm, so that higher numerical scores indicate an improvement in sleep with treatment.

Efficacy on depressive and anxiety symptoms. The efficacy of study medication on depression and on anxiety was assessed by the investigator during patient visits using the HDRS 17-item scale[40] and the Hamilton Anxiety Rating Scale (HARS),[41] respectively. In addition, treatment efficacy on the severity of illness and patient global improvement was assessed using the Clinical Global Improvement scale (CGI)[42] item 1 (severity of illness) and item 2 (global improvement), respectively. Responders were defined by a decrease of at least 50% in the HDRS total score from baseline. Patients with a HDRS total score less than or equal to 6 at last value were considered as remitters. According to the global improvement score, patients with a score of 1 or 2 were considered as responders, and patients with a score of 1 were considered as remitters.

Safety Evaluation

Adverse events reported by the patient were recorded at each visit. Somatic complaints expressed by the patient spontaneously or upon inquiry by the investigator were assessed and recorded. The investigator established the diagnosis if conditions permitted and specified the date of onset, the outcome, the measures taken, and the date of remission or stabilization. The investigator also evaluated the event in terms of severity, relationship, and seriousness.

At week 0 and week 6, the following measures were carried out: body mass index (BMI), calculated from body weight; blood pressure; and heart rate. A 12-lead electrocardiogram was performed at week 0 and in case of withdrawal from the study. Biochemistry and hematology parameters were assessed at week 0 and week 6 and in case of withdrawal from the study.

Compliance

Compliance was assessed by counting returned tablets. It was assessed at each visit and global compliance was calculated over the week 0–week 6 period.

Statistical Analysis

Two efficacy sets were defined: (1) the actigraphy analysis set (AAS), defined, for objective sleep criteria analyses, as all randomized patients who took at least 1 dose of study treatment and had 1 reliable baseline value and at least 1 reliable postbaseline value for the RA, and (2) the full analysis set (FAS), defined, for other efficacy criteria analyses, as all randomized patients who took at least 1 dose of study treatment and had at least 1 postbaseline efficacy assessment (other than actigraphic) over the 6-week treatment period.

As main analysis, treatment groups were compared in the AAS using a mixed-effects model with repeated measures (MMRM) including factors treatment, time, and treatment-by-time interaction as fixed effects and RA at baseline (week 0) as covariate: (1) in terms of evolution of mean RA (expressed as change from baseline) over time (weeks 1, 2, 3, 4, 5, and 6) and (2) at the first 3 postbaseline time points (weeks 1, 2, and 3). The Hochberg procedure[43] was used for the comparison between treatment groups at week 1, week 2, and week 3 in order to take into account the multiplicity of tests. A similar analysis was performed for the average activity level during the 10 most active hours (M10) and during the 5 least active hours (L5) (complementary analyses).

The main analysis model was also used in the AAS for mean sleep efficiency, mean sleep latency, and length of wake bouts (all expressed in terms of change from baseline)

in order to study the overall treatment effect over the 6-week treatment period and the treatment effect (*P* value to be compared to 5%) at each postbaseline time (weeks 1, 2, 3, 4, 5, and 6) (complementary analyses).

The difference between agomelatine and sertraline groups on HDRS total score was estimated in the FAS using a 2-way analysis of covariance with factors treatment, center (as random effect), and week 0 (baseline) HDRS total score as covariate, at week 2 (complementary analysis) and to the last postbaseline value. The same analysis was performed for the HDRS core of depression score (defined by Bech as the sum of items 1, 2, 7, 8, 10, and 13) and the HDRS total score excluding sleep items, both expressed as change from baseline to the last postbaseline value (complementary analyses). A χ^2 test was performed for the response to treatment at week 2 (post hoc analysis) and taking into account the last postbaseline value, and for remission in terms of last postbaseline value (post hoc analysis).

A 2-sided Student *t* test for independent samples was performed in the FAS to compare the treatment groups on HDRS insomnia items score (sum of items 4, 5, and 6) at week 2 and week 6 and for last postbaseline value, on CGI items 1 and 2 in terms of last postbaseline value, and on LSEQ getting to sleep and quality of sleep scores at week 2 and in terms of last value for LSEQ item 1 (post hoc analyses). The difference between the agomelatine and sertraline groups on HARS total score, subscores, and total score excluding the sleep item was estimated in the FAS using a 1-way covariance analysis with baseline as covariate, for the change from baseline to the last postbaseline value (post hoc analyses).

The safety descriptive analysis was performed on the safety set, defined as all included patients who took at least 1 dose of study treatment.

RESULTS

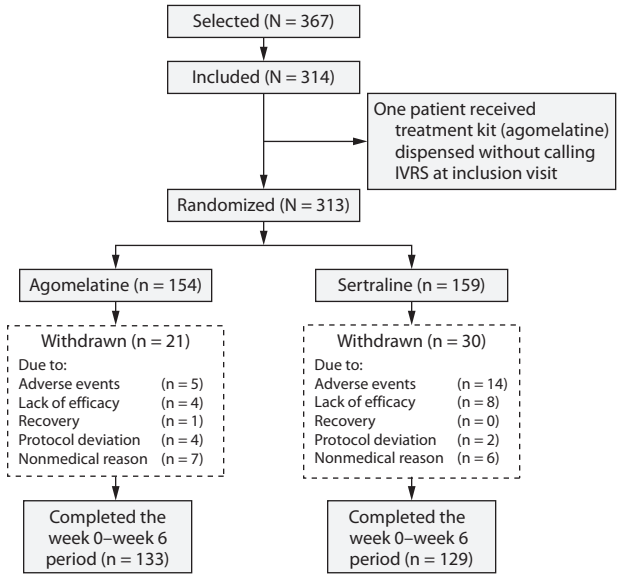
Patients

Three hundred seventy-two patients were screened, and 313 patients were randomly assigned to receive agomelatine (154 patients) or sertraline (159 patients) for 6 weeks. The randomized patients were aged from 18 to 60 years, with a mean ± SD age of 43.9 ± 10.3 years, and 70.6% were female. According to the *DSM-IV-TR* criteria, all patients had major depressive disorder, mainly of moderate intensity (74.4% of patients), with a mean HDRS score of 26.3 ± 2.9. Most patients (70.3%) had a recurrent episode, the mean number of previous episodes was 2.9 ± 2.8, and the mean duration of the current episode was 4.7 ± 4.2 months.

The flow of patients from baseline to week 6 is depicted in Figure 2.

From week 0 to week 6, 51 patients (16.3%) withdrew from the study (21 [13.6%] in the agomelatine group, 30 [18.9%] in the sertraline group). The reasons for withdrawal were mainly adverse events (6.1%), nonmedical reasons (4.2%), and lack of efficacy (3.8%). The rate of withdrawal was lower in the agomelatine group than in the sertraline group, in particular due to adverse events (3.2% of patients in the agomelatine group and 8.8% in the sertraline group) and lack of efficacy (2.6% and 5.0%, respectively). In the subgroup of patients with an increase in daily dose at week 2 (25.3% of randomized patients in the agomelatine group and 24.5% in the sertraline group), no patient was withdrawn from the study between week 2 and week 6 in the agomelatine group, while 6 patients withdrew in the sertraline group, of which 4 withdrew for lack of efficacy. In all, 262 patients completed the week 0 to week 6 period, ie, 133 (86.4%) in the agomelatine group and 129 (81.1%) in the sertraline group.

Figure 2. Disposition of Included Patients



Treatment compliance was 94.3% in the agomelatine group and 93.0% in the sertraline group.

The baseline demographic and clinical characteristics of patients in the FAS are presented by treatment group in Table 1. There was no relevant difference between the 2 treatment groups at baseline. In the AAS, used for the analysis of the primary efficacy criterion and actigraphy-derived sleep parameters, baseline characteristics and main efficacy parameters were similar to those observed in the randomized patients. The mean ± SD values of RA at baseline were 0.87 ± 0.08 in the agomelatine group and 0.85 ± 0.11 in the sertraline group without difference between groups (*P* = .105, complementary analysis).

Six randomized patients (4 in the agomelatine group and 2 in the sertraline group) were not included in the FAS due to absence of treatment intake or no postbaseline efficacy assessment for rating scale and questionnaires. The FAS comprised 150 patients treated with agomelatine

Table 1. Main Demographic Data and Characteristics of MDD at Selection in the Full Analysis Set

Parameter	Agomelatine (N = 150)	Sertraline (N = 157)	All (N = 307)
Age, y			
Mean ± SD	43.3 ± 10.3	44.4 ± 10.2	43.8 ± 10.2
Minimum–maximum	19–60	18–60	18–60
Sex, n (%)			
Male	41 (27.3)	51 (32.5)	92 (30)
Female	109 (72.7)	106 (67.5)	215 (70)
No. of depressive episodes			
Mean ± SD	2.8 ± 2.3	3.0 ± 3.2	2.9 ± 2.8
Minimum–maximum	1–20	1–30	1–30
Median	2.0	2.0	2.0
Duration of current MDE, mo			
Minimum–maximum	0.5–21.8	0.9–20.4	0.5–21.8
Median	3.1	3.1	3.1
Illness characteristic (*DSM-IV* criteria), n (%)			
Recurrent episode	104 (69.3)	113 (72)	217 (70.7)
Severity			
Moderate	110 (73.3)	117 (74.5)	227 (73.9)
Severe without psychotic features	40 (26.7)	40 (25.5)	80 (26.1)
Melancholic features	34 (22.7)	44 (28)	78 (25.4)

Abbreviations: MDD = major depressive disorder, MDE = major depressive episode.

and 157 treated with sertraline. The AAS comprised 233 patients (73% of the FAS: agomelatine 117 [76%], sertraline 116 [73%]).

Efficacy on the Circadian Rest-Activity Cycle

The mean change from baseline to week 1 in RA of the rest-activity cycle was statistically significant in favor of agomelatine as compared with sertraline (between-group difference: −0.027; 95% CI, −0.0478 to −0.0067; $P = .010$ compared to .017, Hochberg procedure).

In the AAS, evolution of the mean RA over time was statistically significantly different between the agomelatine group and the sertraline group (treatment-by-time interaction, $P = .023$). In the agomelatine group, the mean RA remained stable over time, whereas in the sertraline group the mean RA decreased between week 0 and week 1. From week 2 onward, the mean RA in the sertraline group became similar to that of the agomelatine group without statistically significant difference between treatment groups ($P = .184$ at week 2 and $P = .521$ at week 3).

The mean ± SD average activity during the 10 most active hours (M10) increased between baseline and last postbaseline value in the agomelatine group (386.6 ± 6914.9), whereas it decreased in the sertraline group (−430.5 ± 5934.2), with a statistically significant difference between treatments in the evolution of the mean M10 over time (treatment-by-time interaction, $P = .006$).

The mean ± SD average activity during the 5 least active hours (L5) decreased in both groups between baseline and last postbaseline value: −120.8 ± 1302.8 in the agomelatine group and −366.8 ± 1367.1 in the sertraline group, with a difference between the groups over time close to statistical significance (treatment-by-time interaction, $P = .121$).

Efficacy on Actigraphy-Derived Sleep Parameters

As soon as week 1 and up to the end of the treatment period, mean sleep efficiency increased in the agomelatine group and decreased in the sertraline group, with a statistically significant difference at each time point in favor of agomelatine (overall difference between treatments, $P < .001$). After 6 weeks of treatment, the change from baseline in sleep efficiency was 1.59 ± 5.10% for agomelatine and −1.18 ± 7.09% for sertraline, with a statistically significant difference between groups in favor of agomelatine ($P < .001$) (Figure 3).

Similarly, as soon as week 1 up to week 6, the mean sleep latency decreased in the agomelatine group, while an increase was observed in the sertraline group (−2.35 ± 15.75 minutes for agomelatine and +6.52 ± 22.57 minutes for sertraline, $P < .001$), with a statistically significant difference in favor of agomelatine at each time point up to the end of treatment (Figure 3).

The mean length of wake bouts decreased with agomelatine and increased with sertraline as soon as week 1 (−0.84 ± 19.78 minutes for agomelatine and +6.92 ± 30.13 minutes for sertraline, $P = .004$), and the difference was also statistically significant at week 6 ($P = .018$).

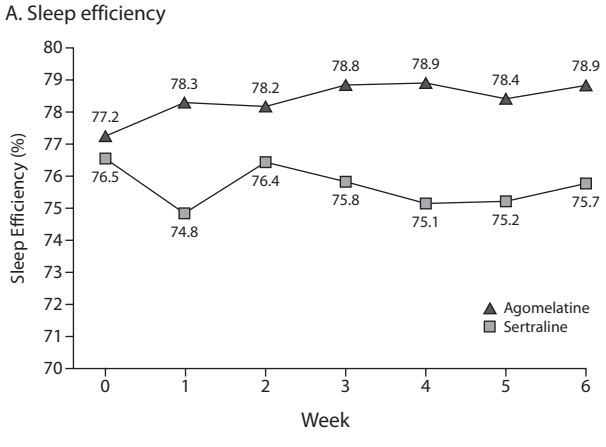
Efficacy on Subjective Sleep

In the FAS, the 4 mean scores in the LSEQ decreased during the 6-week period in both treatment groups. At week 2, the first time point measurement, a significantly greater improvement in the LSEQ getting to sleep score was observed with agomelatine (61.61 ± 16.63 mm) than with sertraline (54.21 ± 16.99 mm) (between-group difference of 7.40; 95% CI, 3.38–11.41; $P < .001$). At last value, the mean score remained numerically higher in the agomelatine group without reaching a statistically significant difference between treatments. The quality of sleep score also showed significantly greater improvement at week 2 with agomelatine (60.60 ± 18.25 mm) compared with sertraline (54.39 ± 19.99 mm) (between-group difference of 5.21; 95% CI, 0.67–9.75; $P = .025$). At last value, the improvement in the mean score was similar in the agomelatine group (67.63 ± 19.51 mm) and in the sertraline group (64.61 ± 20.92 mm) without relevant difference between treatments.

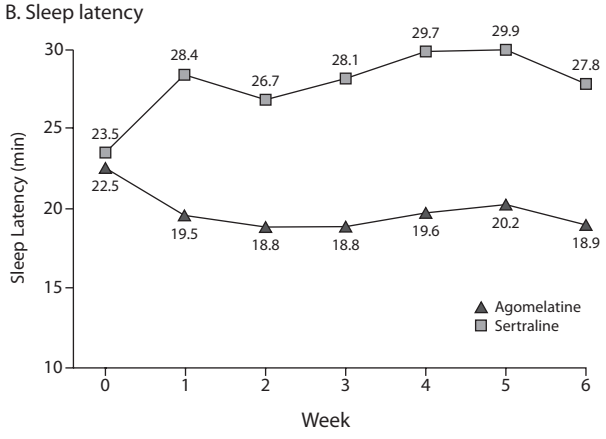
In the FAS, a similar improvement in the LSEQ measures of ease of awakening and integrity of behavior was observed over the whole treatment period with both treatments (Figure 4).

In the FAS, the HDRS insomnia items score (sum of items 4, 5, and 6) decreased between baseline and the last value with a statistically significant between-treatment difference in favor of agomelatine of 0.67 (95% CI, 0.26–1.08; $P = .001$).

Figure 3. Baseline and Difference in Sleep Efficiency (A) and Sleep Latency (B) Between Treatment Groups Over Each Postbaseline 7-Day Period in the Actigraphy Analysis Set



	0	1	2	3	4	5	6
P value	…	< .0001	.018	.001	< .001	.007	.001
Agomelatine n	117	117	112	112	105	99	88
Sertraline n	114	113	101	93	87	79	71



	0	1	2	3	4	5	6
P value	…	< .001	< .001	< .001	< .001	.003	.005
Agomelatine n	117	117	112	112	105	99	88
Sertraline n	114	113	101	93	87	79	71

This superiority of agomelatine over sertraline was also present at week 2 (between-treatment difference of 0.43; 95% CI, 0.04–0.81; $P = .030$) and at week 6 (between-treatment difference of 0.40; 95% CI, 0.01 to 0.79; $P = .043$).

Efficacy on Depressive Symptoms

Hamilton Depression Rating Scale. In the FAS, as soon as the second week of treatment, a mean decrease in the HDRS total score from baseline was observed for both groups from 26.1 ± 2.8 to 18.9 ± 6.4 for agomelatine and from 26.5 ± 3.0 to 20.3 ± 5.8 for sertraline, with a trend in favor of agomelatine in the difference between treatments (difference of 1.06; 95% CI, −0.08 to 2.21; $P = .069$). The percentage of responders at week 2 was significantly higher in the agomelatine group (20.0%) than in the sertraline group (10.9%), with a statistically significant difference between treatments in favor of agomelatine of 9.10% (95% CI, 1.05–17.16; $P = .027$).

After 6 weeks of treatment, agomelatine was superior to sertraline in the mean decrease in the HDRS final score (HDRS total scores of 10.3 ± 7.0 and 12.1 ± 8.3, respectively), with a difference between treatments in favor of agomelatine of 1.68 (95% CI, 0.15–3.20; $P = .031$) at last value (Table 2). At last observation, the HDRS score excluding items relating to sleep (items 4, 5, and 6) was 8.6 ± 6.0 in the agomelatine group and 9.7 ± 6.8 in the sertraline group, for a difference between treatments of 1.03 (95% CI, −0.22 to 2.29; $P = .107$). The decrease from baseline in the core symptoms as defined by Bech showed a numerical advantage for agomelatine (−7.9 ± 4.0) as compared to sertraline (−7.6 ± 4.6), with a difference between treatments of 0.33 (95% CI, −0.45 to 1.11; $P = .406$).

The percentage of responders over the 6 weeks of treatment was 70% in the agomelatine group and 61.5% in the sertraline group with an estimated difference of 8.5% (95% CI, −2.12 to 19.05; $P = .119$) at last value. The percentage of remitters (HDRS total score ≤ 6) after 6 weeks of treatment, was 32.7% in the agomelatine group and 28.8% in the sertraline group at last value with an estimate difference of 3.82 (95% CI, −6.52 to 14.16; $P = .469$).

Clinical Global Impressions scale. In the FAS, over the 6 weeks of treatment, the mean decrease from baseline to the last value in CGI severity of illness score was significantly higher with agomelatine (from 4.7 ± 0.7 to 2.5 ± 1.1) than with sertraline (from 4.7 ± 0.7 to 2.8 ± 1.3) (difference of 0.28; 95% CI, 0.01–0.56; $P = .043$). The CGI global improvement score decreased on average significantly more in the agomelatine group from week 2 to the last value (1.8 ± 1.0) as compared with the sertraline group (2.1 ± 1.2) (difference of 0.29; 95% CI, 0.04–0.54; $P = .023$).

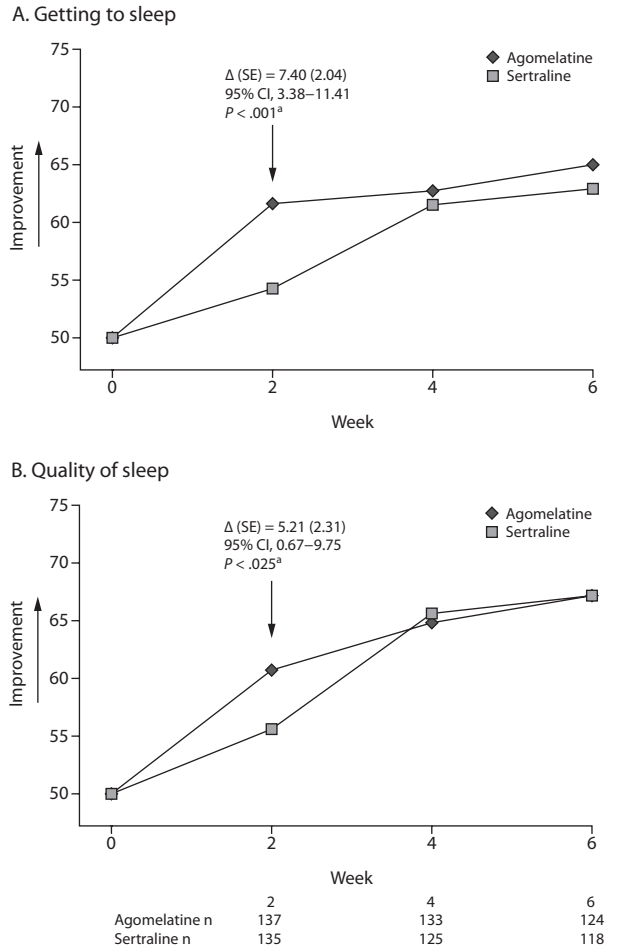
After 6 weeks of treatment, the percentages of responders were 83.3% with agomelatine and 76.9% with sertraline, and the percentages of remitters were 46.7% with agomelatine and 37.8% with sertraline.

Efficacy on Anxiety Symptoms

In the FAS, over the 6-week period, the HARS total score decreased significantly more at last value in the agomelatine group (mean decrease of −14.5 ± 9.8) as compared with the sertraline group (mean decrease of −13.1 ± 11.0) (difference of 2.34; 95% CI, 0.43–4.26; $P = .017$).

The decrease from baseline to last value in the HARS score excluding sleep item was also significantly higher for agomelatine (−12.4 ± 9.1) than for sertraline (−11.4 ± 10.0) (difference of 1.89; 95% CI, 0.16–3.62; $P = .033$). Results of superiority of agomelatine over sertraline were also

Figure 4. Change in LSEQ Getting to Sleep (A) and Quality of Sleep (B) Scores (mm) From Baseline to Last Postbaseline Value Over the Week 0–Week 6 Period in the Full Analysis Set



[a]*P* value, treatment effect: 2-sided Student *t* test for independent samples.
Abbreviation: LSEQ = Leeds Sleep Evaluation Questionnaire.

Table 2. Change in HDRS Total Score From Baseline to Last Postbaseline Assessment Over the 6-Week Period (week 0–week 6) in the Full Analysis Set

HDRS Total Score	Agomelatine (N = 150)	Sertraline (N = 157)
Baseline value (week 0)		
n	150	156
Mean ± SD	26.1 ± 2.8	26.5 ± 3.0
Last postbaseline value		
n	150	156
Mean ± SD	10.3 ± 7.0	12.1 ± 8.3
Last postbaseline – baseline value		
n	150	156
Mean ± SD	−15.8 ± 7.3	−14.4 ± 8.7
	Statistical Result[a]	
E (SE)[b]	1.68 (0.77)	
95% CI[c]	0.15–3.20	
P value[d]	.031	

[a]Two-way analysis of covariance with treatment and center (as random effect) as factors and week 0 HDRS total score as covariate.
[b]Estimate (standard error) of the difference between adjusted treatment group means: sertraline minus agomelatine.
[c]95% CI of the difference.
[d]*P* value of treatment effect.
Abbreviation: HDRS = Hamilton Depression Rating Scale.

Table 3. Most Frequently Reported Emergent Adverse Events (≥5.0% of patients in any treatment group), Expressed as Percentage of Affected Patients Among Exposed Patients During the Double-Blind Treatment Period in the Safety Set

Emergent Adverse Event	Agomelatine (N = 152)	Sertraline (N = 159)
Headache	8.6	10.1
Dry mouth	5.3	5.0
Diarrhea	3.9	5.7
Fatigue	5.9	1.3
Hyperhydrosis	0.0	5.0

observed at the last value on the HARS psychic anxiety (difference of 1.26; 95% CI, 0.11–2.40; $P = .031$) and the HARS somatic anxiety score (difference of 1.00; 95% CI, 0.11–1.90; $P = .028$).

Safety

In the safety set, the incidence of emergent adverse events (EAEs) was 48.0% (N = 73) with agomelatine and 49.1% (N = 78) with sertraline. EAEs reported by more than 5% of the patients are reported in Table 3. The most common reported adverse events in both groups were headache, dry mouth, and diarrhea. Fatigue was more frequently reported in the agomelatine group (5.9%) than in the sertraline group (1.3%), and hyperhidrosis was reported in the sertraline group (5%) and not in the agomelatine group. The total number of EAEs leading to treatment discontinuation was 4.5 times higher with sertraline (18 patients [11.3%]) than with agomelatine (4 patients [2.6%]), mainly due to psychiatric disorders such as anxiety, depression, loss of libido, agitation, insomnia, and sleep disorder (5.7% vs 0%, respectively). Regarding the course of biologic parameters over time, no clinically relevant changes were observed with either treatment except for γ-glutamyl transferase (GGT), with a mean increase of 8.0 ± 110.0 U/L in the agomelatine group related to high values in 1 alcoholic patient with GGT > 30 times the upper limit of normal (ULN), aspartate aminotransferase > 6 ULN, alanine aminotransferase > 3 ULN, bilirubin > 1 ULN, and high values for glucose and triglycerides. No relevant changes in vital signs (weight, blood pressure, heart rate, and ECG) were observed in either treatment group. No deaths occurred during the trial.

DISCUSSION

This is the first study to compare the effect of 2 antidepressants, agomelatine and sertraline, with different mechanisms of action, on circadian rhythm, the sleep-wake cycle as measured by the *relative* amplitude (RA) of MDD

patients. Wrist actigraphy was used to gather objective data on patients' sleep-wake organization and sleep quality. The continuous recording of wrist movements permitted to measure wake-activity (continuous high movement) and sleep/rest (reduced amount of movement) across a 24-hour period over many weeks.

In the present study, we measured the RA of the circadian rest-activity cycle, which provides a normalized value of the amplitude of the circadian rhythm and allows individual comparisons. Relative amplitude was explored as a way to measure the impact of agomelatine in resetting the circadian rhythms of depressed patients. Our hypothesis was that nocturnal disturbances of sleep onset, continuity, and/or awakening, together with daytime retardation and napping, lead to a reduced RA, and that improvement of the former leads to increase of the latter. This would not necessarily apply to agitated patients—improvement would go in the opposite direction (though again, this would depend on the quality of their sleep). In this study, the mean change in RA from baseline to week 1 was significantly in favor of agomelatine as compared with sertraline. Overall, RA remained relatively stable with agomelatine, whereas sertraline appeared to show a drop in RA during the first week of treatment and then joined agomelatine from week 2 onward. From week 2, RA remained quite stable and similar in the 2 groups until the end of the study, even though depressive state significantly improved over this time period, so there was not a 1-to-1 correlation. This lack of correlation showed that the RA was not sensitive in this population of depressed outpatients and probably not adequate for assessing the circadian changes in this population with a high level of RA at baseline.

It is of interest to note that patients presenting a low RA were most severely depressed, leading us to assume that such a marker should be more appropriate to inpatients with melancholic features. This is in accordance with the results seen in the only study[16] investigating the circadian rest-activity cycle in 26 inpatients with MDD (including 5 bipolar patients) throughout a 4-week tricyclic antidepressant treatment (clomipramine, maprotiline, or trimipramine at 150 mg/d) together with a stable and moderate hypnotic treatment. The authors described low amplitude of the circadian rest-activity rhythm at treatment onset and found a positive relationship between clinical course and the 24-hour change in activity level. However, the small number of patients and the possible interaction between hypnotics and activity level limit the conclusions that can be drawn from these findings.[16] Further studies using actigraphy and analyzing RA are in progress to better understand this criterion in MDD patients undergoing pharmacologic therapy and to confirm that it may be affected in these conditions.

The definition of the RA criteria in choosing the 5 best hours of the night and the 10 best hours during the day must be challenged, as it potentially reduces too much the differences between patients' conditions and then the sensitivity of change.

Generally speaking, there are few data available to explore how RA is sensitive to depression-induced psychomotor disturbances and to antidepressant treatment. Wrist actigraphy has predominantly been used in sleep research and chronobiology, where the technique has proved useful in the indirect and noninvasive measurement of sleep[32,44–47] and characterization of the sleep-wake cycle.

Although actigraphy is not a direct measure of sleep, it allows estimation of objective sleep data (eg, sleep latency, sleep efficiency). These actigraphy-derived "sleep" variables are mostly well correlated with polysomnographic sleep electroencephalographic (EEG) data in healthy subjects,[47] even though they are naturally not exactly identical. A patient lying quietly in bed awake for hours cannot be differentiated from someone sleeping, solimitations of the sleep data need to be kept in mind. Notwithstanding this caveat, actigraphy has the advantage of measuring "sleep" for weeks (which cannot be done with the EEG), thus averaging behavior over longer time periods and thereby increasing reliability.

The favorable results on sleep efficiency and sleep latency for agomelatine compared to sertraline are largely statistically and clinically significant. The actigraphy analysis revealed a significant decrease in sleep latency and the duration of wake bouts, together with a significant increase in sleep efficiency from week 1 to week 6, in agomelatine-treated patients as compared with sertraline-treated patients.

In addition, according to the LSEQ, patients treated with agomelatine found it easier to get to sleep and judged the quality of their sleep improved already at week 2, while similar improvement in the ease of awakening and integrity of behavior following wakefulness occurred only later than week 2 in patients treated with sertraline. The similar improvement from week 2 to week 6 in both groups emphasizes that the positive effect of agomelatine on daytime functioning is in parallel with the vigilance-enhancing effects characteristic of sertraline.[48]

Finally, according to the HDRS sleep items, insomnia was alleviated with agomelatine when compared with sertraline at weeks 2 and 6. Together, these different scores support the beneficial properties of agomelatine on sleep architecture and daytime functioning in MDD patients that have been seen in previous studies.[27,29]

The present findings confirm the antidepressant efficacy[25,26,49,50] and antianxiety properties[25] of agomelatine in MDD patients. The superiority of agomelatine over sertraline seen on the HDRS and CGI may be partially explained by the greater improvement of the sleep items, which are a core component of depressive state. A difference in favor of agomelatine compared to sertraline, though not significant, was still present when the sleep items were deleted from the HDRS total score, while a significant difference in favor of agomelatine was sustained when the sleep item was deleted from the HARS total score.

Such superiority results were seen in a head-to-head fluoxetine study[51] on HDRS total score and in a venlafaxine comparison study on CGI improvement[27] and may be viewed as demonstrating better effectiveness of agomelatine compared to those antidepressants. The effectiveness of agomelatine may be related to the combination of the antidepressant effect, some additional properties on sleep and daytime condition, and the tolerability profile. These results are of particular interest since sertraline has recently been suggested to be better than other new-generation drugs in terms of efficacy and acceptability.[52]

The superiority results may also be related to the selected population of the study, for whom the sum of HDRS items 4 and 5 had to be at least of 3. This was done in order to optimize the chance to get a low RA and not to select a population potentially more responsive to agomelatine. Furthermore, those 2 items were shown to be sensitive to antidepressant effect in general[53] as the 6 items defining the Bech core symptoms.[54]

We are aware of some limitations of our study. One aspect that can be viewed as a limitation is the use of an exploratory parameter as primary efficacy criterion. Relative amplitude has been shown not to be sensitive to change and probably not fully adequate to characterize the circadian rest-activity cycle of depressed outpatients over 6 weeks of treatment. Agomelatine has distinctive pharmacologic properties on melatonin receptors, and it is legitimate to find different ways or markers for estimating the clinical impact of such differences. This large study using extensive actigraphy recording during 7 weeks was done for this purpose, and additional analysis of the total night or day time would allow use of a better marker than RA. The present study provides some strong evidence of an early effect on both sleep and awakening state on classical actigraphic parameters not translated on RA.

Furthermore, the dose regimen of sertraline cannot be viewed as optimal considering that it was administered in the evening.[33] However, this administration is in accordance with the prescribing information given by the manufacturer, which does not specify the time of administration.

The absence of a placebo arm may be considered as a limitation, but a placebo arm would have introduced other strong bias in the recruitment of a representative depressed population.[55]

The use of the LSEQ is recognized as valuable to assess sleep during treatment as perceived by the patient[11] even if the absence of formal baseline assessment may be questionable as a potential for recall bias. The LSEQ was developed to assess aspects of sleep in studies involving psychopharmacologic agents and is a validated and sensitive method to assess changes in subjective sleep and behavior at awakening.[38] The LSEQ shows high internal consistency and good test-retest reliability and has been used extensively in many clinical trials to assess the effects of antidepressants on sleep during the treatment of depression.[56] The results of the present study are consistent with previous findings as an early improvement is observed at week 2 (first measure) on getting to sleep and quality of sleep. The tolerability profile of agomelatine was reasonable, as already reported,[25,27,28,57] and compared favorably with that of sertraline. The frequencies of emergent adverse effects were low, and no clinically relevant changes were observed in vital signs or in the course of biologic parameters over time, except for γ-glutamyl transferase related to higher hepatic values in 1 alcoholic patient. Fewer patients withdrew and there were 3 times fewer withdrawals due to adverse events in the agomelatine group than in the sertraline group. The only reported adverse event more frequent with agomelatine, which mainly occurred within the first 2 weeks, was fatigue, with frequencies of 5.9% in agomelatine-treated patients and 1.3% in sertraline-treated patients. This difference did not have an impact on the course of the RA.

In summary, this study shows a favorable effect of agomelatine on the relative amplitude of the circadian rest-activity/sleep-wake cycle in depressed patients at week 1, expressing early improvement in sleep and daytime functioning. Early beneficial effect on the sleep/wake cycle may contribute to higher efficacy results on both depressive and anxiety symptoms as observed with agomelatine versus sertraline in the study condition over the 6-week treatment period. Additional analysis of this large data set of actigraphy in MDD at baseline may reveal further information about circadian rhythm and sleep characteristics of subgroups as putative predictors of treatment response.

Drug names: clomipramine (Anafranil and others), fluoxetine (Prozac and others), mirtazapine (Remeron and others), sertraline (Zoloft and others), trimipramine (Surmontil and others), venlafaxine (Effexor and others).

Author affiliations: Department of Psychiatry and Psychotherapy, Medical University Vienna, Austria (Dr Kasper); Department of Psychiatry, Psychosomatics and Psychotherapy, University of Regensburg, Regensburg, Germany (Dr Hajak); Circadian and Visual Neuroscience, Nuffield Laboratory of Ophthalmology, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom (Dr Wulff); Department of Psychiatry, VU University Medical Center, Amsterdam, the Netherlands (Dr Hoogendijk); Hospital Universitario de Salamanca, Salamanca, Spain (Dr Montejo); Department of Clinical Neuroscience, Ospedale San Raffaele, Milan, Italy (Dr Smeraldi); Department of Adult Psychiatry, Poznań University of Medical Sciences, Poznań, Poland (Dr Rybakowski); Sleep Unit, Raymond Poincaré Hospital, Garches, France (Dr Quera-Salva); Centre for Chronobiology, Psychiatric University Clinics, Basel; Switzerland (Dr Wirz-Justice); Institut de Recherches Internationales Servier (IRIS), Courbevoie, France (Dr Picarel-Blanchot); and Centre Hospitalier Sainte-Anne, Paris, France (Dr Baylé).

Agomelatine Study Group participants: The following members participated in this study with the authors of this report. From Austria: Margot Schmitz, MD, Wien. From France: Jean-François Arnaud, MD, Paris; Bernadette Bouyssou, MD, Altkirch; Joël Carrera, MD, Bordeaux; Michel Costes, MD, Centre Psychothérapique, Fontaine; Bernard Jomard, MD, Centre Médico-Psychologique, Bourg en Bresse; Fabrice Lanvin, MD, Lens; Béatrice Lognos, MD, Saint Georges D'Orques; Grégoire Martocq, MD, Cournonterall; Jean-Marc Perez, MD, Montpellier; Brigitte Ridel, MD, Nantes; Geneviève Saint-Mard, MD, Paris; Danielle Sire, MD, Dole; Sophie Vincent, MD, Nice. From Germany: Bettina Bergtholdt, MD, Emovis Institut für emotionale Gesundheit GmbH, Berlin; Hermann-Josef Gertz, MD, Universitätsklinikum Leipzig Klinik und Poliklinik für Psychiatrie, Leipzig; Dieter Kunz, MD, Psychiatrische Universitäts Klinik der Charite im St Hedwig Krakenhaus, Berlin; Eckart Rüther, Klinik für

Psychiatrie und Psychotherapie der Georg-August-Universität Göttingen, Göttingen; Klaus-Christian Steinwachs, MD, Praxis Dr. Steinwachs Neurologie und Psychiatrie, Nürnberg; Markus Gastpar, MD, Klinik für Psychiatrie und Psychotherapie der Universität Duisburg – Essen, Essen. From Italy: Giuseppe Bersani, MD, Servizio Speciale di Medicina Psicosomatica e Psicofarmacologia Clinica Policlinico Umberto I, Rome; Filippo Bogetto, MD, Università di Torino Dipartamento di Neuroscienze Clinica Psichiatrica, Torino; Carlo Faravelli, MD, Azienda Ospedaliera Careggi Clinica Neuropsichiatrica Policlinico Careggi, Firenze; Giovanni Muscettola, MD, Azienda Universitaria Policlinico Federico II di Napoli Dipartimento di Psichiatria psicoterapia audiologica psicologica, Napoli; Eugenio Aguglia, MD, Clinica Psichiatrica Università degli studi di Trieste, Trieste. From the Netherlands: Joanneke van der Linde, MD, Parnassia, Den Haag; R. Verkes, MD, Universitair Medisch Centrum Sint-Radboud Locatie Psychiatrie; Nijmegen. From Poland: Leszek Bidzan, MD, Private practice "Syntonia," Gdynia; Jerzy Landowski, MD, SPSK nr1, Akademickie Centrum Kliniczne Akademii medycznej w Gdańsku, Klinika Chorób Psychicznych i Zaburzeń Nerwicowych, Gdańsk. From Spain: José Francisco Montilla, MD, Centro de Especialidades "Los Angeles," Madrid; Pilar Rico, MD, Centro de Especialidades "Los Angeles," Madrid; Cristina del Alamo, MD, Centro de Salud Mental, Madrid; Mónica Pastor, MD, Centro de Salud Calahorra Consulta de Salud Mental, LOGROÑO - La Rioja; José Otero, MD, Centro de Salud de Villalba, Madrid; Diego Palao, MD, Hospital General de Vic Servicio de Psiquiatría, Barcelona; María Jesús del Yerro, MD, Centro de Salud Mental de Carabanchel Servicio de Psiquiatría, Madrid; Santiago Vega, MD, Centro de Salud Mental de Usera, Madrid.

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