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Brief Report

Agomelatine adjunctive therapy for acute bipolar depression: preliminary open data

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Objectives: Agomelatine has been shown to be safe and efficient in the treatment of major depressive disorder at 25 mg daily. The aim of this study was to gather preliminary data regarding the antidepressant efficacy of agomelatine in patients with bipolar I disorder experiencing a major depressive episode.

Methods: Bipolar I patients on lithium (n = 14) or valpromide (n = 7), with a Hamilton Rating Scale for Depression (HAM-D-17) total score ≥ 18, were given adjunctive open-label agomelatine at 25 mg/day for a minimum of 6 weeks followed by an optional extension of up to an additional 46 weeks.

Results: Using intent-to-treat data, 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 one week of treatment. Nineteen patients entered the optional extension period for a mean of 211 days (range 6–325 days). Eleven patients completed the one-year extension on agomelatine. There were no dropouts due to adverse events during the acute phase of treatment (6 weeks). Six patients experienced serious adverse events during the one-year period. Three lithium-treated patients experienced manic or hypomanic episodes during the optional extension period, one of which was treatment-related.

Conclusions: These results indicate the effectiveness of agomelatine 25 mg in the treatment of depressed bipolar I patients co-medicated with lithium or valpromide. A randomized controlled trial is planned to confirm these results.

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Key words: agomelatine – antidepressant – bipolar I depression

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Bipolar disorder (BD) is a chronic and severe psychiatric condition that has a substantial impact on the quality of life of patients and is associated with a considerable economic burden on both patients and society (1). Depression is the predominant mood state in BD, but in comparison to unipolar depression, the treatment of BD has not been studied extensively and effective treatments are not well characterized (2).

Some guidelines support the use of an antimanic agent, such as lithium, or an antipsychotic agent, to control mania, plus a traditional antidepressant for the acute management of bipolar depression (3). However, controlled trials suggest that treatment with standard antidepressants may offer little therapeutic benefit beyond that achieved with adequate

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doses of mood stabilizers (4, 5). In addition, the standard antidepressant classes – the tricyclic antidepressants, the selective serotonin reuptake inhibitors (SSRIs), and the monoamine oxidase inhibitors (MAOIs) – along with bupropion all appear to increase the risk of precipitating mania or cycle acceleration (6–10). Furthermore, adverse events associated with tricyclics (anticholinergic effects) and MAOIs (dietary restrictions) limit their use.

It has been hypothesized that the pathophysiology of BD may be linked to a disruption of circadian periodicity, since most patients with bipolar depression experience phase advance in their melatonin rhythms relative to sleep (11). Successful antidepressant treatment is associated with normalization of these rhythms (12). These findings suggest that modulation of the melatonin receptors may provide a specific and effective way of treating BD. In this regard, agomelatine, a potent agonist of melatonin MT_1 and MT_2 receptors with 5-HT_{2C} antagonist properties, has been shown to reset the experimentally disrupted circadian rhythm in several behavioral animal models (13–17).

Placebo-controlled studies have shown agomelatine to be an effective acute treatment of major depressive disorder (MDD) at doses of 25 mg/day (18, 19). Agomelatine has been shown to rapidly improve sleep in depressed patients without causing residual daytime impairment (20), possesses good tolerability and safety in major depressive disorder, and does not exhibit discontinuation symptoms (21).

In order to gather preliminary data regarding the potential efficacy of agomelatine in depressed patients with BD I, open-label, adjunctive agomelatine 25 mg/day was administered for 6 weeks followed by an optional one-year extension.

Methods

Study design

This open study was carried out in eight centers throughout France. Eligible depressed patients received agomelatine 25 mg/day in the evening in addition to a mood stabilizer (lithium or valpromide) during an initial six-week period. Valpromide (diproylacetamide) is a prodrug of valproic acid. Patients were then offered continued treatment with adjunctive agomelatine for up to 46 weeks. Concomitant lithium or valpromide was continued. After a screening visit, ratings were conducted at baseline, and then at weeks 1, 2, 4 and 6. During the optional extension phase, ratings were conducted at weeks 12, 18, 24, 30, 36, 42 and 52. The study was approved by a national ethics committee and was carried out in accordance with the Declaration of Helsinki. All patients enrolled in the study provided written informed consent.

Patients

Male and female in- or out-patients, aged ≥18 years, were enrolled in the study if they fulfilled the criteria for BD I (without rapid cycling) with a current major depressive episode according to DSM-IV with a score ≥18 on the 17-item Hamilton Rating Scale for Depression (HAM-D). In addition, patients had to be on mood stabilizing medication (lithium or valpromide) for at least six months and to have experienced at least two mood episodes (at least one manic or mixed episode) during the past 10 years. Patients were required to have therapeutic blood levels of lithium: for patients aged < 65 years: 0.5–0.8 mmol/L, immediate release form, 0.8–1.2 mmol/L, extended release form; for patients aged ≥65 years: 0.3–0.5 mmol/L, immediate release form. The minimum dosage of valpromide required was 600 mg/day.

Patients with any type of mood disorder other than BD I and those using psychotropic or central nervous system (CNS)-active medication (unless an adequate washout period had been observed) were excluded from the study. Resistant depression, defined as non-response to two consecutive treatments of at least four weeks with two different classes of antidepressant drugs, was excluded. In 10 patients, the depressive episode started while already on antidepressant treatment. Two other patients had an antidepressant trial for the current episode before being selected for the study and nine patients did not receive any antidepressant treatment for the current episode.

Compliance with treatment was assessed by tablet count at each study visit.

Efficacy evaluations

HAM-D. The severity of depressive symptoms was assessed with the 17-item HAM-D, which was rated by investigators at every study visit. The primary efficacy outcome was the HAM-D response to treatment, defined as a change of ≥50% from baseline score over the six-week period in the intention-to-treat population (ITT). Secondary analyses included: score at each visit and remission (defined as a HAM-D total score ≤ 6).

Montgomery–Åsberg Depression Rating Scale (MADRS) and Clinical Global Impression (CGI). Secondary outcomes defined as *a priori* were the MADRS response to treatment (defined as a ≥50% decrease from the baseline score) and

CGI-Severity (CGI-S) and CGI-Improvement (CGI-I) scores. Investigators rated the MADRS at every visit from week 0 to week 6 and the CGI at every study visit.

Safety evaluations

Clinical examinations, including blood pressure, heart rate and body weight, were carried out at inclusion, week 6, week 52 and the follow-up visit. Laboratory values were measured at the selection visit, week 6 and week 52.

The Young Mania Rating Scale (YMRS) was completed at each visit from inclusion to week 52.

The YMRS total score value at each visit, last post-baseline value and change between last post-baseline value and baseline value were explored. All adverse events (AEs) reported by participants were assessed and recorded at each study visit. The severity of AEs was graded by the investigators as mild, moderate or severe using their own clinical judgment. Serious AEs were predefined using standard criteria and the judgment of the investigator.

Statistical analyses

The number of subjects to be enrolled was calculated, according to Fleming's design (22), to be 17. For the first six-week study period, efficacy data were analyzed for the ITT group. The ITT group was defined as all enrolled patients who had taken at least one dose of agomelatine and who had a HAM-D score at baseline and one post-baseline score in the initial six-week period. In the optional treatment period, all results were analyzed for the ITT population. During the optional period, the ITT population only included patients who had decided to continue with study treatment. All safety results were analyzed in the safety set, defined as all patients known to have taken at least one dose of agomelatine. Data were analyzed using descriptive statistics and 95% confidence intervals (CIs).

Results

Patients

Twenty-one patients were included in the study: 14 received agomelatine + lithium and 7 received agomelatine + valpromide. Patients' baseline characteristics and disposition are presented in Table 1 and Fig. 1, respectively. Twenty patients completed the six-week period [mean ± standard deviation (SD) 40.1 ± 6 days of treatment]. Of 19 entering the 46-week optional extension, 11 patients completed the one-year extension. Overall the mean treatment duration was 231.3 ± 139.5 days (range 13–364 days).

Five inpatients were included in the study and four of them (three treated with lithium and one with valpromide) were discharged during weeks 0–6. One lithium-treated patient remained hospitalized throughout the study treatment period. In- and outpatients had similar baseline profiles and final HAM-D total scores but the response to treatment tended to appear later in those hospitalized.

Efficacy over six weeks

HAM-D. At the end of the six-week period, 81% (last evaluation: 17/21) of patients were responders

Table 1. Baseline characteristics of patients with bipolar I depression treated with adjunctive agomelatine (intention-to-treat population)

Mean ± SD (range)	Included set (n = 21)	Agomelatine + lithium (n = 14)	Agomelatine + valpromide (n = 7)
Age (years)	51.2 ± 15.2 (19–76)	49.1 ± 13.4 (27–69)	55.3 ± 18.8 (19–76)
Sex: male/female	7/14	6/8	1/6
Duration of bipolar disorder (years)	18.6 ± 12.9 (2.5–42.9)	19.1 ± 12.8 (2.5–42.9)	17.7 ± 14.3 (2.7–40.7)
Positive family history	14	9	5
First episode (manic/depressive)	8/13	5/9	3/4
Number of manic episodes[a]	1.9 ± 1.0 (0–4)	2.0 ± 0.9 (1–4)	1.6 ± 1.1 (0–3)
Number of mixed episodes[a]	0.5 ± 0.8 (0–3)	0.3 ± 0.6 (0–2)	0.9 ± 1.1 (0–3)
Number of depressive episodes[a]	3.9 ± 2.3 (1–13)	2.9 ± 2.3 (1–10)	5.7 ± 4.1 (2–13)
Duration of current depressive episode (days)	34.1 ± 28.8 (11–125)	39.4 ± 33.3 (12–125)	23.6 ± 12.7 (11–41)
HAM-D score	25.2 ± 3.9 (18–33)	24.9 ± 4.0 (18–33)	25.7 ± 4.0 (20–33)
MADRS score	29.7 ± 6.4 (21–41)	30.6 ± 6.8 (22–41)	27.9 ± 5.6 (21–35)
CGI Severity of Illness	5.0 ± 0.9	4.7 ± 0.9	5.3 ± 0.8

SD = standard deviation; HAM-D = Hamilton Rating Scale for Depression; MADRS = Montgomery–Åsberg Depression Rating Scale; CGI = Clinical Global Impression.
[a]In the past 10 years.

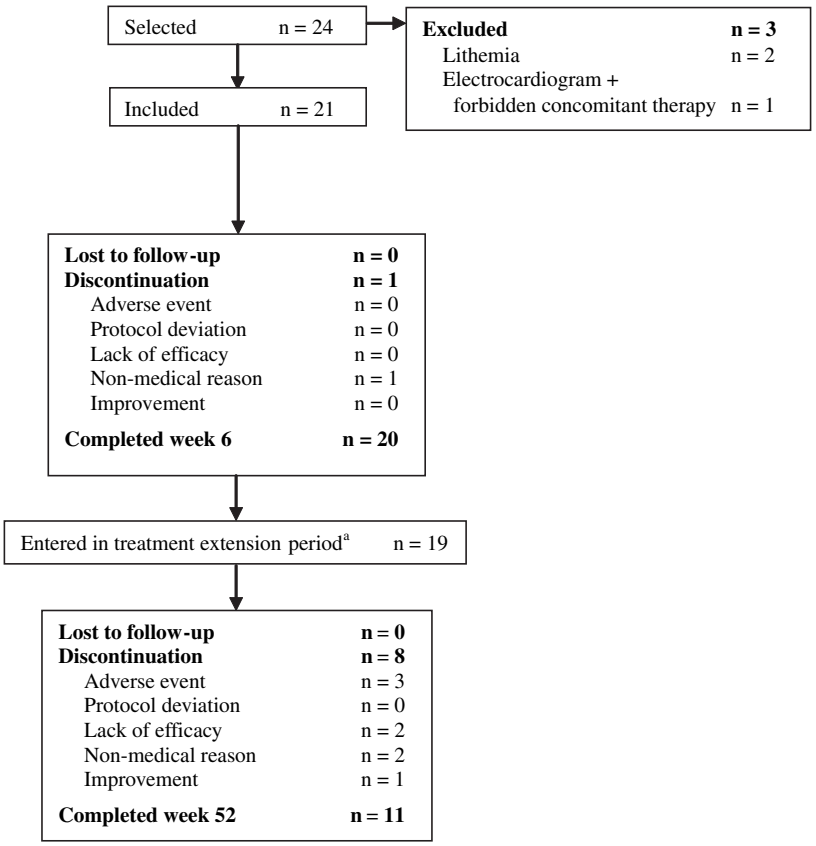

Fig. 1. Patient disposition.
[a]One patient stopped at week 6 due to lack of efficacy.

to agomelatine treatment. At week 1, 47.6% of patients (10/21) responded to agomelatine, with the number of responders increasing over time: 12 (57.1%) patients by week 2; 15 (75%) by week 4; and 17 (85%) by week 6. Response rates in patients taking agomelatine + lithium and agomelatine + valpromide were 78.6% (11/14, ITT) and 85.7% (6/7, ITT), respectively. Changes from baseline in HAM-D total scores after six weeks of treatment are shown in Table 2. Remission criteria were reached in 40% (week 6, 8/20) of patients (38.1%, 8/21 at last observation) (Fig. 2). Seven of the 14 patients (50%, ITT) taking lithium and one of the 7 patients (14.3%, ITT) on valpromide were in remission at the last post-baseline observation.

MADRS and CGI. At the end of the six-week period, 74% (14/19) (15/21, 71.4% at last observation) of patients were responders to agomelatine treatment. Response rates were 78.6% (11/14) in patients receiving agomelatine + lithium and 57.1% (4/7) in those receiving agomelatine + valpromide. The response to agomelatine treatment occurred early in about a third of the ITT population, with the number of responders increasing over time: 7 patients (33.3%) at week 1; 11 (52.4%) at week 2; 14 (70%) at week 4; and 14 (73.7%) at week 6. The mean change in MADRS score at week 6 (Table 2) reflected the improvements seen with the HAM-D. Ratings on CGI subscales were improved by week 6 compared with baseline, regardless of the concomitant mood stabilizer taken (Table 2).

Long-term efficacy

Nineteen patients continued treatment with agomelatine beyond week 6 (13 patients receiving lithium and 6 valpromide); 11 of them (52%) continued the treatment up to one year. Numbers of remitters by visit over the full one-year study period are presented in Fig. 2. At the end of the study, 84.2% of the patients who continued in the optional period were responders to agomelatine treatment (last evaluation: 16/19), of whom 10 (76.9%) were receiving lithium and 6 (100%) were taking valpromide. The final mean HAM-D total score at week 52 was 2.3 ± 3.5 (last: 5.2 ± 5.3) for all patients combined, 2.0 ± 2.4 (last: 6.1 ± 6.3)

Table 2. Efficacy measures over the six-week study period (FAS, last post-baseline value)

Measure Mean ± SD (95% CI)	Included set (n = 21)	Agomelatine + lithium (n = 14)	Agomelatine + valpromide (n = 7)
HAM-D			
Baseline	25.2 ± 3.9	24.9 ± 4.0	25.7 ± 4.0
Last	8.2 ± 6.3	7.1 ± 5.6	10.4 ± 7.5
Change	−17.0 ± 5.3 (−19.4, −14.6)	−17.9 ± 3.9 (−20.1, −15.6)	−15.3 ± 7.3 (−22.1, −8.5)
Response rate	81.0%	78.6%	85.7%
Remission rate	38.1%	50.0%	14.3%
MADRS			
Baseline	29.7 ± 6.4	30.6 ± 6.8	27.9 ± 5.6
Last	10.0 ± 9.0	8.6 ± 7.8	12.7 ± 11.3
Change	−19.7 ± 8.2 (−23.4, −16.0)	−21.9 ± 5.9 (−25.4, −18.5)	−15.1 ± 10.5 (−24.9, −5.4)
CGI-S			
Baseline	5.0 ± 0.9	4.7 ± 0.8	5.4 ± 0.8
Last	2.8 ± 1.5	2.4 ± 1.3	3.6 ± 1.7
CGI-I			
Week 1	2.5 ± 1.0	2.4 ± 1.0	2.7 ± 1.0
Last	1.9 ± 0.9	1.6 ± 0.5	2.4 ± 1.3

CI = confidence interval; HAM-D = Hamilton Rating Scale for Depression; Response rate = ≥ 50% reduction in the HAM-D total score; Remission rate = HAM-D ≤ 6; MADRS = Montgomery–Åsberg Depression Rating Scale; CGI-S = Clinical Global Impression-Severity; CGI-I = Clinical Global Impression-Improvement.

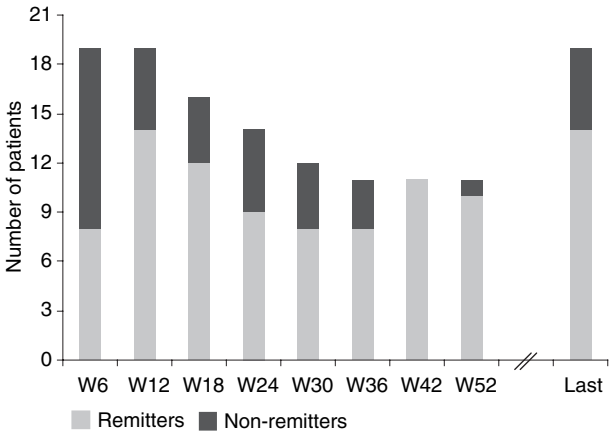

Fig. 2. Number of remitters for the entire one-year study period in patients with bipolar I depression treated with adjunctive agomelatine. Remission is defined as a Hamilton Rating Scale for Depression total score of ≤6. W = week.

for patients taking lithium and 2.6 ± 4.7 (last: 3.2 ± 4.4) for those on valpromide. After one year of treatment, 73.7% of all patients who continued in the optional period were in remission (last evaluation: 14/19), as were 69.2% (9/13, last observation) of lithium-treated patients (100%, 6/6, week 52) and 83.3% (5/6, last observation) of valpromide-treated patients (80%, 4/5, week 52). All CGI parameters improved further during the optional study period. The last post-baseline CGI values were: 2.3 ± 1.6 for CGI-S (2.5 ± 1.9 with lithium and 1.8 ± 1.0 with valpromide) and 1.7 ± 1.2 for CGI-I (1.8 ± 1.4 with lithium and 1.5 ± 0.8 with valpromide).

Safety

None of the patients were hospitalized for a major depressive episode (MDE) during the initial six-week treatment period. During the optional period, one patient taking lithium was hospitalized for an MDE at week 36.

Overall, 15 patients (71.4%) experienced at least one emergent adverse event (EAE) during weeks 0–52, with equal frequency in both subsets (lithium/valpromide). During the six-week period, no patients experienced an EAE leading to study discontinuation. During the optional period, three lithium-treated patients withdrew from the study (one for agitation, one for mania and one for hypomania). Twelve serious AEs occurred during weeks 0–52, four of which were considered by the investigator to be related to treatment (Table 3). Specifically, two patients experienced manic or hypomanic episodes under treatment: one patient presented a manic episode after 47 days of treatment (YMRS = 40) and one patient had a hypomanic episode after 33 weeks of treatment. Another patient presented a manic episode 18 days after he discontinued agomelatine + lithium for personal reasons (YMRS = 42). All the patients who presented as manic/hypomanic were lithium-treated patients, had experienced more than two previous manic episodes in the past and had had BD for over 20 years. No suicide

Table 3. Serious adverse events in patients with bipolar I depression receiving adjunctive agomelatine over one year

	Event description	Events (n)	Related to treatment[a]
Agomelatine + lithium			
1 patient	Anxiety	2	No, Yes
	Insomnia	1	Yes
	Hypomania	1	Yes
1 patient	Mania	1	Yes
1 patient	Mania[b]	1	No
1 patient	Agitation	1	No
	Breast abscess	1	No
Agomelatine + valpromide			
1 patient	Social problem[c]	1	No
	Bereavement reaction	1	No
	Agitation	1	No
1 patient	Traffic accident	1	No

[a]According to investigator's judgment.
[b]Occurred 17 days after the patient interrupted agomelatine and lithium treatment for personal reasons.
[c]Occurred between selection and inclusion visit.

attempts and no deaths were reported during the entire study.

YMRS. In the safety set, the mean YMRS total score was 3.81 ± 2.86 at baseline, 2.67 ± 2.52 (week 6: 2.80 ± 2.50) after six weeks of treatment and 5.86 ± 11.88 after one year of treatment (week 52: 1.18 ± 1.47).

Higher scores in the optional period were linked to the manic episodes that happened during the week 6–52 period.

Laboratory tests and vital signs

No clinically relevant changes were observed in hematological, biochemistry parameters or vital signs.

Discussion

The results of this study suggest marked improvement was experienced by severely depressed patients with BD I treated with agomelatine in combination with lithium or valpromide.

As agomelatine is a melatonin agonist, it seems important to differentiate the depression symptoms from sleep symptoms: scores for HAM-D sleep items [4-5-6] decreased from 4.1 ± 1.6 to 1.9 ± 1.6 between weeks 0 and 6 but HAM-D core depression items also decreased from 13.7 ± 2.3 to 3.4 ± 3.6 over the same period.

The high overall response rate and early time to first response assessed by both the HAM-D and MADRS scores support the clinical efficacy of agomelatine. Remission, assessed by stringent HAM-D criteria, was encouraging, with an overall remission rate at week 6 of 38%. The remission rate was also encouraging in patients taking lithium (50%). The six-week efficacy of agomelatine 25 mg/day in bipolar I depression observed in this study appears to be similar to that found in a study of patients with predominantly unipolar depression, in which the mean total HAM-D score in 137 patients was reduced from 27.4 to 12.8 after eight weeks of treatment, with a response rate of 61.5% (18). Results observed during the overall treatment period confirmed the global improvement of MDE.

In this open study, the efficacy and safety of agomelatine treatment was sustained during the optional extension period. This is consistent with recommendations by some that antidepressants should be continued for at least one year before being tapered off (23). Agomelatine was associated with good safety and acceptability in this study. This is reflected by the low number of AEs, the absence of hospitalizations during the six-week treatment period, and the fact that almost all patients in the ITT population entered the optional period and 11 (59%) continued with the study for one year. The limitations of this study include its open design, the absence of a placebo arm, and the relatively small sample size. Nevertheless, the strength of the findings is supported by the high response rates achieved.

In BD I, choosing a suitable antidepressant invariably involves considering the potential risk of precipitating mania (10). In this study, there were no manic episodes during the initial treatment period, which compares favorably with rates reported for other antidepressants over similar treatment periods (imipramine 6–11%, bupropion 11%, tranylcypromine 40%) (24). In a recent 10-week trial in 64 patients with BD, who were treated with bupropion, sertraline or venlafaxine in combination with a mood stabilizer, Post and colleagues reported seven switches to hypomania and six to full mania (25). During the voluntary one-year continuation phase, 10 switches to hypomania and 6 to mania were observed in 42 patients. The one-year switch rate observed in the current study (14.3%, total: 3/21; two under treatment and one after 18 days of agomelatine + lithium discontinuation) is similar to that found with venlafaxine (13%) and far lower than that reported for tricyclic antidepressants (up to 50%) (24). It also compares favorably with the anti-epileptic, lamotrigine, for the one-year incidence of manic episodes (31%) (26).

In this study, three patients (14.3%), all receiving lithium, developed manic symptoms during

the optional treatment period and deserve detailed consideration. One patient deviated from the protocol by abruptly ceasing to take treatment (first lithium, then agomelatine), which is likely to have precipitated the manic switch. Such abrupt cessation of treatment is well known to trigger mania, and it is recommended that antidepressants are tapered off while the mood stabilizer is continued (2). The episode of hypomania occurred in one patient with a suspicion of Lewy body dementia. The third switch, to dysphoric mania, occurred in a female patient who had severe depression (HAM-D, 28; MADRS, 37; YMRS, 10) when enrolled in the study. Although she was in remission at week 4, her HAM-D score increased to 10 at week 6 and she proceeded to develop dysphoric mania at week 7.

In conclusion, these results indicate that agomelatine 25 mg may have a good efficacy and safety profile in the treatment of depressed BD I patients co-medicated with lithium or valpromide, and that this efficacy may be sustained over the long-term. These findings on the efficacy and safety of agomelatine have led to the design and conduct of large, double-blind, placebo-controlled trials.

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Appendix

The Agomelatine Bipolar Study Group includes: M Abbar, MD, CHU-Hôpital Caremeau, Nimes; C Gay, MD, Hôpital Sainte Anne, Paris; A Jouan, MD, Le Mans; S Vincent, MD, Nice; L Waintraub, MD, Hôpital Paul Brousse, Villejuif; M Beyadh, MD, Hôpital André Breton, St. Dizier; and J Meynard, MD, CH Lafon-Hôpital Marius Lacroix, La Rochelle.