Agomelatine Versus Venlafaxine XR in the Treatment of Anhedonia in Major Depressive Disorder

A Pilot Study

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Abstract: The primary aim of the present study was to compare the effects of agomelatine (AGO) and venlafaxine XR (VLX) on anhedonia in patients with major depressive disorder. Secondary end points were to test its antidepressant and anxiolytic efficacy.

Sixty patients were enrolled and randomly assigned to two different treatments: AGO (25-50 mg/d; n = 30 subjects) or VLX (75-150 mg/d, n = 30 subjects). Psychopathological assessment was performed at baseline and after 8 weeks of treatment with the Snaith Hamilton Rating Scale (SHAPS), the Hamilton Depression Rating Scale, the Hamilton Anxiety Rating Scale, and the Clinical Global Impression for anhedonia, depression, anxiety, and global improvement, respectively.

Both groups showed a significant reduction in time for the SHAPS, the Hamilton Depression Rating Scale, and the Hamilton Anxiety Rating Scale. A significant between-group difference was observed for SHAPS scores: patients treated with AGO showed a more relevant reduction compared with that in VLX-treated patients. Moreover, only patients treated with AGO showed a statistically significant improvement in Clinical Global Impression scores.

In this study, AGO showed significantly greater efficacy on anhedonia and similar antidepressant efficacy to the serotonin-norepinephrine reuptake inhibitor VLX in patients with major depressive disorder during an 8-week treatment period. Anhedonia has been considered a potential trait marker related to vulnerability for depression. Therefore, the efficacy of AGO on this dimension holds particular importance in the treatment of patients with anhedonic features.

Key Words: major depressive disorder, anhedonia, agomelatine, venlafaxine

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By the year 2020, depression is expected to reach second place in the ranking of Disability-Adjusted Life Years (DALYs) calculated for all ages and both sexes.[1] Anhedonia, defined as a loss of interest and lack of reactivity to pleasurable stimuli, is considered to be a core symptom for the diagnosis of major depressive disorder (MDD), predicts poor outcome 12 months later,[2] is a common residual symptom after treatment,[3] and is associated with dysfunctions within the brain reward system.[4] Therefore, the efficacy of agomelatine (AGO, S20098, N-[2-{7-methoxynaphth-1-yl}ethyl]acetamide) on this dimension may hold particular importance in the treatment of patients with anhedonic features.

At present, a large number of effective antidepressant drugs exist. However, treatment efficacy is often suboptimal; approximately 30% of patients with a diagnosis of MDD do not respond and less than 60% achieve remission.[5] A recent survey indicated that only 57.3% of patients received any form of treatment, and the treatment was judged to be adequate in less than half of these cases.[6] The main problems with antidepressant treatment are acute and long-term adverse effects such as gastrointestinal disorders, nausea, sleep disturbances, weight gain, and sexual dysfunctions; lack of adequate response; slow onset of action; interaction with other drugs; and need for polypharmacotherapy. These therapeutic deficits emphasize the need for alternative drugs that are effective, well tolerated, and with a rapid onset of action and improved safety profile.

In this scenario, a new therapeutic strategy is AGO. Unlike other antidepressants, AGO has a novel neurochemical mechanism because it is an agonist of MT1 and MT2 melatonergic receptor agonist and a selective antagonist of the 5-HT2C receptor. Agomelatine was first reported in literature in 1992, among a series of synthetic naphthalene melatonin analogs. It was intended to serve as a drug that would easily cross the blood-brain barrier and synchronize circadian rhythm.[7,8] Agomelatine's antidepressant action is mainly attributed to its synergistic action on both melatonergic and 5-HT2C receptors.[9] This synergistic action could be matched up with physiologic circadian rhythms, with the melatonergic action prevailing during the night and the serotoninergic action prevailing during the day.[10] Evidence from clinical studies[11–17] suggests that, compared with placebo, AGO has antidepressant and antianhedonic properties—alleviates anxiety symptoms associated with depression and provides relief of symptoms early on. In addition, the tolerability and safety profile of AGO includes a low propensity to cause sexual dysfunction,[18] absence of discontinuation symptoms on withdrawal,[19] and improvement in sleep quality.[20,21]

The primary goal of the present study was to compare the effects of AGO on anhedonia with those of a well-established antidepressant, the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine XR (VLX), in patients with MDD. A secondary outcome was testing its antidepressant and anxiolytic efficacy.

MATERIALS AND METHODS

Subjects

Outpatients aged 18 to 60 years with a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision*

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(American Psychiatry Association, 2000) diagnosis of MDD (as determined by the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [SCID-I]) were enrolled in the study. All patients included in the study understood and signed the informed consent. Patient enrollment began in January 2010 and was complete by November 2010. Exclusion criteria were the presence of a medical condition that could either interfere with the assessment of the drug treatment or be unsafe for the patient (ie, cirrhosis, renal impairment, unstable hypertension, hypotension, diabetes mellitus, convulsions), history of bipolar disorder, schizophrenia, schizoaffective disorder, eating disorder, obsessive-compulsive disorder, substance dependence, concomitant use of other antidepressant drugs (in this case, a washout period of 7 days was required), and pregnancy and breastfeeding or noneffective contraception. The study was approved by the institutional review board and was conducted in accordance with the principles of good clinical practice and the *Declaration of Helsinki* (1964) and subsequent revisions. All participants provided written informed consent before enrollment.

Study Design

This was an 8-week open-label parallel-group pilot study conducted at two sites: the University "G. D'Annunzio" in Chieti and the Neuropsychiatric Clinic "Villa Maria Pia" in Rome. Patients' medical and family history was collected and then recorded in a specific Case Report Form. The study was performed on outpatients with MDD. In case of prior intake of antidepressants (SSRIs, TCAs, MAOIs, or other new-generation antidepressants), a pharmacological washout period of 7 days was instituted.

After screening to assess eligibility, patients were randomly started on AGO at a dose of 25 mg/d (n = 30) or on VLX 75 mg/d (n = 30). As for AGO, the dosage regimen involved the administration of 25 mg/d, a single dose at 8:00 P.M. In case of no clinical response and based on the clinician's judgment, after 2 weeks, the dosage could be increased to 50 mg/d, administered in a single dose. As for VLX, the dosage regimen involved the administration of 75 mg/d, a single dose at 8:00 A.M. In case of no clinical response, and based on the clinician's judgment, after 2 weeks, the dosage could be increased to 150 mg/d, administered in a single dose. Randomization was nonadaptive, balanced, and stratified on the center. After recruitment of a patient, an interactive computer-based system allocated a therapeutic unit number.

The medical examinations—carried out at baseline (T0) and then at 1 (T1), 2 (T2), and 8 (T3) weeks—were performed by medical doctors and consisted in the registration of vital signs and any other concomitant medication and in the assessment of the severity of any adverse effects. Treatment outcome, in terms of improvement on anhedonia (Snaith Hamilton Rating Scale [SHAPS]),[22] depression and anxiety scores (Hamilton Depression Scale [HAM-D]; Hamilton Anxiety Scale [HAM-A]),[23,24] was assessed at visits T1, T2, T3.

Both at the beginning and at the end of the treatment period, a general clinical assessment was performed by the examiner, along with an evaluation of global improvement (Clinical Global Impression [CGI]).

Effectiveness Assessments

Consistent with the study objectives, the primary end point was to assess improvement on anhedonia scores (SHAPS). In particular, scores collected on examination at the end of the treatment period (8 weeks, T3) were compared with baseline scores (T0). Secondary end points concerned improvement, at T3, of the overall clinical condition (CGI) and of depressive and anxious symptoms, as reflected by scores on HAM-D and HAM-A scales, respectively. Safety parameters were monitored with electrocardiography, urinalysis, and hematological and clinical chemical analyses of blood samples (including liver enzymes) at the start and at the end of the study. Self-reported adverse events provided a measure of safety and tolerability.

Statistical Analysis

Primary and secondary efficacy analyses were performed on the intent-to-treat population, which included all randomly assigned patients who took at least 1 dose of study medication. Student t and χ^2 tests were used to compare sociodemographic and clinical data. Psychometric data were analyzed at baseline and at different times by means of analysis of variance for repeated measures using the last-observation-carried-forward method. The analysis of variance was used with the SHAPS, HAM-D, HAM-A, and CGI scores at different times to verify the presence of significant changes during the time course considered. Tests were 2-tailed, with significance set at $P < 0.05$.

RESULTS

Patients and Disposition

A total of 92 patients were screened, of whom 32 were excluded from the study (Fig. 1). Sixty patients were finally enrolled and randomly assigned to VLX or AGO treatment (30 patients for each group). There were no significant differences between the baseline characteristics of patients who did not pass the screening compared with those who were included in the study. The mean age of the population (61% were women) was 40.2 years (SD, 9.4 years). The two groups of randomized patients did not vary with respect to demographical characteristics, anhedonia (SHAPS), depression (HAM-D), and anxiety (HAM-A) scores at baseline. Similarly, the number of prior episodes (AGO, 2.6 vs VLX, 2.5) and the duration (in months) of the current episode (AGO, 3.2 [SD, 2.2] vs VLX, 3.3 [SD, 2.4]) were comparable between the groups.

Efficacy

In the AGO group, a significant reduction in SHAPS ($F = 20.74$; $P < 0.001$), HAM-D ($F = 11.87$; $P < 0.001$) (Fig. 2), and

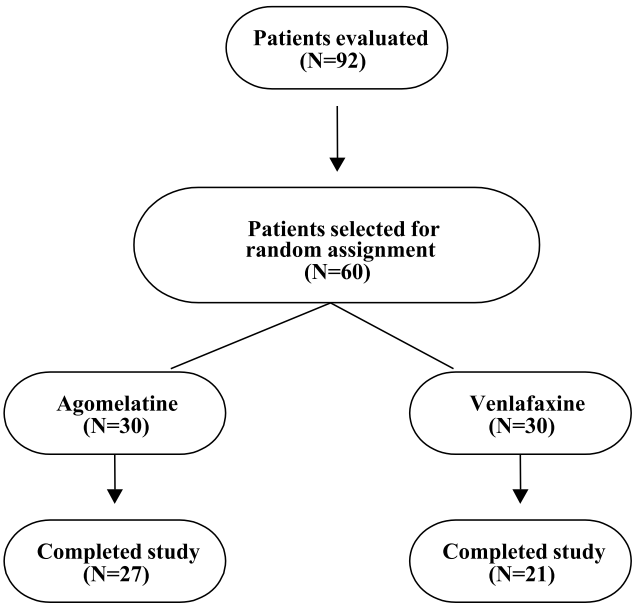

FIGURE 1. Diagram of subject flow by treatment group.

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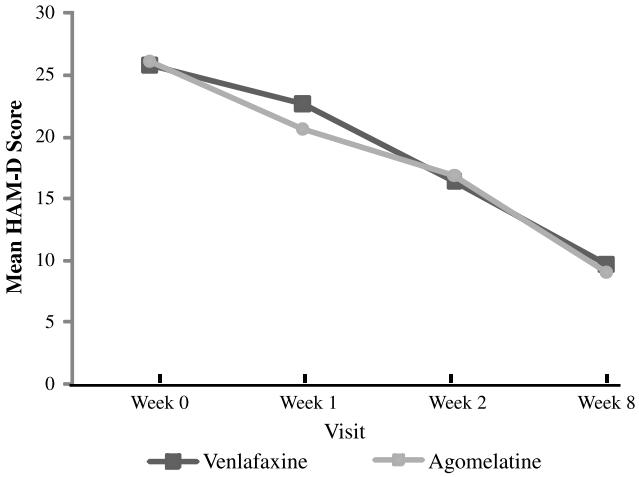

FIGURE 2. Hamilton Rating Scale for Depression (HAM-D): total scores by study visit.

HAM-A (F = 12.52; $P < 0.005$) scores was observed at last assessment (T3), with respect to the baseline (T0) scores. For the SHAPS scores only, a significant reduction was already observed after 1 week of treatment (T1): Tukey post hoc test $P < 0.05$. Likewise, the VLX group showed a significant mean reduction in SHAPS (F = 3.27; $P < 0.5$), HAM-D (F = 18.26; $P < 0.001$) (Fig. 2) and HAM-A (F = 12.02; $P < 0.001$) scores. The mean change from baseline at last assessment in the two groups of patients is described in Figure 3. A significant difference between groups was observed for SHAPS scores (Fig. 4), but not for those of HAM-D and HAM-A.

Patients treated with AGO showed a statistically significant improvement in scores on the CGI ($t = 2.94$; $P < 0.05$). For the VLX group, the improvement was not statistically significant ($t = 1.44$; $P = 0.18$).

Dropouts, Safety, and Tolerability

There were no statistically significant differences between AGO and VLX groups in the proportion of patients who completed the study: 27 in the AGO group, 21 in the VLX group. Common adverse events (whether or not considered treatment related) occurred in 1 (3.2%) patient of the AGO group and in 11 (39.2%) patients of the VLX group. The overall rate of study discontinuation caused by adverse events was 3.2% (n = 1) in the AGO group and 17.8% (n = 5) in the VLX group. Nausea and vomiting (n = 6), dizziness (n = 2), and hypotension (n = 3) were the most common effects across the VLX group, with 5 cases of nausea and vomiting being the events that led to patient withdrawal from the study. Confusion (n = 1) was the adverse event that led to patient withdrawal from the study in the AGO group. No clinically relevant differences between groups were seen in the mean change from baseline for any vital signs, electrocardiograms, and hematology or clinical chemistry parameters, including liver enzymes. Mean change in weight from baseline to end of treatment was −0.2 kg in the AGO group, +1.5 in the VLX group.

At drug discontinuation, we observed no side effects caused by drug suspension in either group.

DISCUSSION

In this study on patients with MDD, AGO's antidepressant efficacy proved to be similar to that of the SNRI VLX during an 8-week treatment period. With regard to anhedonia, the study's main efficacy criterion, analyzed on an intention-to-treat basis, at week 1 and week 8, AGO showed significantly better efficacy compared with that of VLX, as manifested by the greater reduction in SHAPS scores.

Agomelatine led to significantly greater improvements on CGI scores at the last observation compared with VLX, which is renowned for its potent antidepressant activity and efficacy.[25]

This is the first study to assess AGO's impact on anhedonia versus an active comparator. A previous open study we conducted[16] demonstrated AGO's efficacy in treating this dimension. The term "anhedonia," first introduced by Ribot[26] and defined as the inability to experience pleasure, refers to both a state symptom in various psychiatric disorders and a personality trait.[27] Anhedonia is considered crucial for the diagnosis of depression and has been considered a potential trait marker related to vulnerability for depression.[28] In addition, it represents a core psychopathological symptom and a therapeutic target of alcohol dependence[29,30] that frequently occurs in comorbidity with depressive disorders and also seems to be relevant in alcohol protracted withdrawal syndrome.[31]

Therefore, the efficacy of AGO on this dimension holds particular importance in the treatment of patients with anhedonic features.

However, although in vivo data indicate that AGO enhances the levels of dopamine in the frontal cortex, in nucleus accumbens, at the moment, there are no data available in the literature.[17] About this important issue, other studies are required to confirm a possible effect of AGO on dopamine circuits.

Nevertheless, as for other antidepressant drugs, the specific effect of circadian rhythm resynchronization may contribute to the regulation of hedonic capacity.[32,33] However, this is just a speculative hypothesis that merits exploration by further studies.

Agomelatine's safety profile compared favorably with that of VLX. Fewer patients withdrew, and there were fewer withdrawals because of adverse events in the AGO group. In particular, AGO treatment was associated with a lower incidence of nausea, vomiting, and dizziness.

The improvements in anhedonia scores detected as early as 1 week after treatment initiation with AGO are a beneficial characteristic of AGO, especially given the usually relatively slow onset of antidepressant efficacy with current agents.

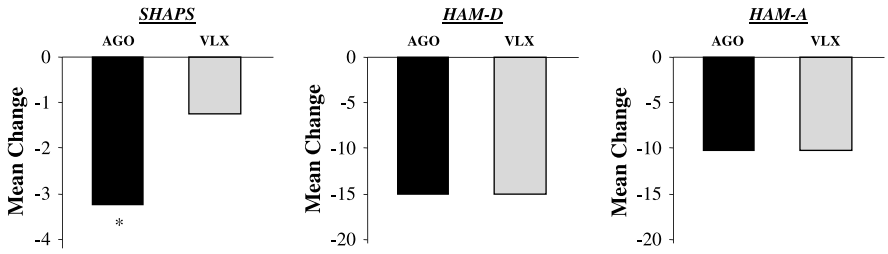

FIGURE 3. Snaith Hamilton Pleasure Scale (SHAPS) for anhedonia, Hamilton Depression Rating Scale (HAM-D), and Hamilton Anxiety Rating Scale (HAM-A) mean change from baseline at the last assessment (T3). *$P < 0.01$ (significant differences between groups).

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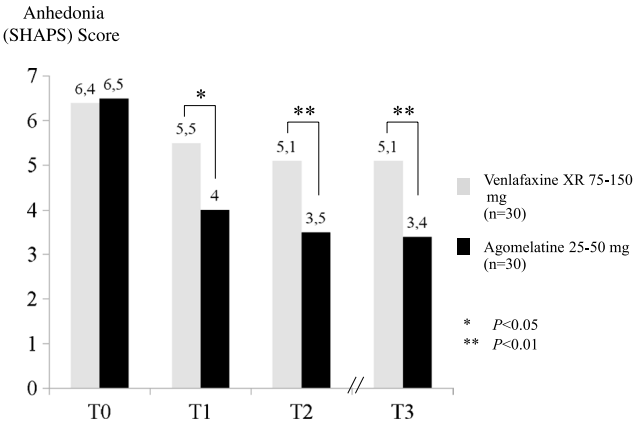

FIGURE 4. Anhedonia scores at different times for patients treated with agomelatine or venlafaxine.

The results of this study need to be interpreted with caution because of its limitations. First, the small sample size does not allow for firm conclusions to be drawn. Second, the open design is a weakness that temper the interpretation of the results.

The flexible dosing regimen used in this study for VLX was midway the recommended dose range for outpatients in European countries. The choice of using VLX, a well-established antidepressant, at a max dosage of 150 mg/d, not including the maximum recommended dose of 225 mg/d, was based on previous studies comparing AGO with VLX at these ranges of dosage.[34,35] However, we cannot exclude that some patients would have benefited from a higher VLX dose.

In conclusion, AGO showed significantly greater efficacy on anhedonia and similar antidepressant efficacy to the SNRI VLX in patients with MDD. The original effect of AGO on anhedonia represents a novel contributing property in the class of antidepressant agents.

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AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

REFERENCES

1. World Health Organization. *The Global Burden of Disease: 2004 Update*. Geneva, Switzerland: World Health Organization; 2008:43–51.
2. Spijker J, Bijl RV, de Graaf R, et al. Determinants of poor 1-year outcome of *DSM-III-R* major depression in the general population: results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Acta Psychiatr Scand*. 2001;103:122–130.
3. Taylor DJ, Walters HM, Vittengl JR, et al. Which depressive symptoms remain after response to cognitive therapy of depression and predict relapse and recurrence? *J Affect Disord*. 2010;123:181–187.
4. Keedwell PA, Andrew C, Williams SC, et al. The neural correlates of anhedonia in major depressive disorder. *Biol Psychiatry*. 2005;58:843–853.
5. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*. 2006;163:1905–1917.
6. Kessler RC, Berglund P, Demler O, et al. National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*. 2003;289:3095–3105.
7. Dolder CR, Nelson M, Snider M. Agomelatine treatment of major depressive disorder. *Ann Pharmacother*. 2008;42:1822–1831.
8. Yous S, Andrieux J, Howell HE, et al. Novel naphthalenic ligands with high affinity for the melatonin receptor. *J Med Chem*. 1992;35:1484–1486.
9. Papp M, Gruca P, Boyer PA, et al. Effect of agomelatine in the chronic mild stress model of depression in the rat. *Neuropsychopharmacology*. 2003;28:694–703.
10. Millan MJ. Multi-target strategies for the improved treatment of depressive states: conceptual foundations and neuronal substrates, drug discovery and therapeutic application. *Pharmacol Ther*. 2006;110:135–370.
11. Lôo H, Hale A, D'haenen H. Determination of the dose of agomelatine, a melatoninergic agonist and selective 5-HT(2C) antagonist, in the treatment of major depressive disorder: a placebo-controlled dose range study. *Int Clin Psychopharmacol*. 2002;17:239–247.
12. Kennedy SH, Emsley R. Placebo-controlled trial of agomelatine in the treatment of major depressive disorder. *Eur Neuropsychopharmacol*. 2006;16:93–100.
13. Olié JP, Kasper S. Efficacy of agomelatine, an MT1/MT2 receptor agonist with 5-HT2C antagonistic properties, in major depressive disorder. *Int J Neuropsychopharmacol*. 2007;10:661–673.
14. Zajecka J, Schatzberg A, Stahl S, et al. Efficacy and safety of agomelatine in the treatment of major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled trial. *J Clin Psychopharmacol*. 2010;30:135–144.
15. Carney RM, Shelton RC. Agomelatine for the treatment of major depressive disorder. *Expert Opin Pharmacother*. 2011;12:2411–2419.
16. Di Giannantonio M, Di Iorio G, Guglielmo R, et al. Major depressive disorder, anhedonia and agomelatine: an open-label study. *J Biol Regul Homeost Agents*. 2011;25:109–114.
17. De Berardis D, Di Iorio G, Acciavatti T, et al. The emerging role of melatonin agonists in the treatment of major depression: focus on agomelatine. *CNS Neurol Disord Drug Targets*. 2011;10:119–132.
18. Sapetti A. Agomelatine: an antidepressant without deterioration of sexual response. *J Sex Marital Ther*. 2012;38:190–197.
19. Montgomery SA, Kennedy SH, Burrows GD, et al. Absence of discontinuation symptoms with agomelatine and occurrence of discontinuation symptoms with paroxetine: a randomized, double-blind, placebo-controlled discontinuation study. *Int Clin Psychopharmacol*. 2004;19:271–280.
20. Lam RW. Sleep disturbances and depression: a challenge for antidepressants. *Int Clin Psychopharmacol*. 2006;21:25–29.
21. Kupfer DJ. Depression and associated sleep disturbances: patient benefit with agomelatine. *Eur Neuropsychopharmacol*. 2006;16(suppl 5):639–643.
22. Snaith RP, Hamilton M, Morley S, et al. A scale for the assessment of hedonic tone: the Snaith-Hamilton Pleasure Scale. *Br J Psychiatry*. 1995;167:99–103.
23. Hamilton M. The assessment of anxiety states by rating. *Brit J Med Psychol*. 1959;32:50–55.
24. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56–62.
25. Mann JJ. The medical management of depression. *N Engl J Med*. 2005;353:1819–1834.
26. Ribot T. *La Psychologie Des Sentiments*. Paris, France: Felix Alcan; 1896.
27. Loas G, Pierson A. Anhedonia in psychiatry: a review. *Ann Med Psychol*. 1989;147:705–717.

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28. Meehl PE. Hedonic capacity: some conjectures. *Bull Menninger Clin*. 1975;39:295–307.
29. Martinotti G, Di Nicola M, Di Giannantonio M, et al. Aripiprazole in the treatment of patients with alcohol dependence: a double-blind, comparison trial vs naltrexone. *J Psychopharmacol*. 2009;23:123–129.
30. Martinotti G, Andreoli S, Reina D, et al. Acetyl-L-carnitine in the treatment of anhedonia, melancholic and negative symptoms in alcohol dependent subjects. *Prog Neuropsychopharmacol Biol Psychiatry.* 2011;35(4):953–958.
31. Martinotti G, Di Nicola M, Reina D, et al. Alcohol protracted withdrawal syndrome: the role of anhedonia. *Subst Use Misuse.* 2008;43:271–284.
32. Farina B, Della Marca G, Mennuni G, et al. The effects of reboxetine on human sleep architecture in depression: preliminary results. *J Affect Disord*. 2002;71:273–275.
33. Coogan AN, Thome J. Chronotherapeutics and psychiatry: setting the clock to relieve the symptoms. *World J Biol Psychiatry.* 2011;12:40–43.
34. Kennedy SH, Rizvi S, Fulton K, Rasmussen J. A double-blind comparison of sexual functioning, antidepressant efficacy, and tolerability between agomelatine and venlafaxine XR. *J Clin Psychopharmacol*. 2008;28(3):329–333.
35. Lemoine P, Guilleminault C, Alvarez E. Improvement in subjective sleep in major depressive disorder with a novel antidepressant, agomelatine: randomized, double-blind comparison with venlafaxine. *J Clin Psychiatry.* 2007;68(11):1723–1732.

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