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ARTICLE

Efficacy of agomelatine and escitalopram on depression, subjective sleep and emotional experiences in patients with major depressive disorder: a 24-wk randomized, controlled, double-blind trial

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Abstract

In the present randomized, controlled, double-blind trial (12 wk treatment plus double-blind extension for 12 wk), 25–50 mg/d agomelatine (n=164) and 10–20 mg/d escitalopram (n=160) were compared for short- and long-term efficacy, subjective sleep and tolerability. The effects of these drugs on emotional experiences were also compared in patients having completed the Oxford Questionnaire on the Emotional Side-Effects of Antidepressants (agomelatine: n=25; escitalopram: n=20). Agomelatine and escitalopram similarly improved depressive symptoms, with clinically relevant score changes over 12 and 24 wk and notable percentage of remitters (week 12: 60.9 and 54.4%; week 24: 69.6 and 63.1% respectively). Over the 12 and 24-wk treatment periods, the 'global satisfaction on sleep' scores increased in both treatment groups and did not differ between groups. Satisfaction with sleep–wake quality was high in both groups; the 'wellness feeling on waking' was more improved with agomelatine than with escitalopram (p=0.02). In patients with pronounced sleep complaints, quality of sleep and feeling on waking were significantly more improved with agomelatine than with escitalopram (p=0.016 and p=0.009, respectively). Emotional blunting was less frequent on agomelatine than on escitalopram. Indeed, 28% of patients on agomelatine *vs.* 60% on escitalopram felt that their emotions lacked intensity and 16% of patients on agomelatine *vs.* 53% on escitalopram felt that things that they cared about before illness did not seem important any more (p=0.024). The tolerability profile of agomelatine was found to be superior to that of escitalopram and the incidence of patients with at least one emergent adverse event leading to treatment discontinuation was lower in the agomelatine group than in the escitalopram group (5.5 *vs.* 10.6%). The findings suggest that agomelatine displays additional long-term clinical benefits on sleep–wake quality and emotional experiences over escitalopram in the management of depression.

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Introduction

Up to 90% of patients who suffer from an acute major depressive episode (MDE) report changes in their sleep–wake profile. They usually describe difficulties in initiating and maintaining sleep during the night and fatigue during the day (Brunello et al., 2000; Armitage, 2007). Despite the efficacy of currently available antidepressant treatments, residual symptoms are common among individuals treated for major depressive disorder (MDD) and again the most frequently reported residual symptoms are those associated with sleep disturbance and fatigue (Menza et al., 2003). The most recent reports concern selective serotonin reuptake inhibitors (SSRIs; Nierenberg et al., 2010; Iovieno et al., 2011) and these complaints are associated with a higher risk of relapse, chronicity and functional impairment.

Agomelatine has a novel pharmacology among antidepressants (de Bodinat et al., 2010); its antidepressant efficacy, demonstrated at doses of 25–50 mg/d in patients with MDD (Olie and Kasper, 2007; Goodwin, 2009), has been compared previously with other antidepressants of different classes (Lemoine and Guilleminault, 2007; Hale et al., 2010; Kasper et al., 2010). In agreement with its chronobiological properties, agomelatine relieves sleep–wake complaints of depressed patients and its efficacy in improving subjective and objective sleep parameters as well as daytime functioning compared favourably with venlafaxine (Lemoine and Guilleminault, 2007), sertraline (Kasper et al., 2010) and escitalopram (Quera-Salva et al., 2011). This difference remains of interest to understanding the mechanism of action of agomelatine in relieving depression.

The tolerability profile of agomelatine is superior to that of available antidepressants, with an absence of discontinuation symptoms upon withdrawal (Montgomery et al., 2004) and a low risk of sexual dysfunction (Kennedy et al., 2008; Montejo et al., 2010). The latter finding raised the question of emotional experience more generally. Patients with sexual dysfunction attributed to antidepressants, particularly SSRIs, have reported that they also experienced a restricted range of emotions and a blunted emotional response to everyday events (Opbroek et al., 2002). A qualitative study has subsequently described patients' experiences of such emotional side-effects in much more detail (Price et al., 2009). If such effects are in fact a SSRI side-effect, it is likely that an antidepressant with a different mode of action, such as agomelatine, would affect emotional processing in a different way. Indeed, agomelatine has been shown to have more selective effects on the processing of social cues of facial expression than conventional antidepressants in healthy volunteers (Harmer et al., 2011). Thus, we reasoned that agomelatine may provoke less blunting of emotional experience in the treatment of major depression.

The objectives of the present study, which compares agomelatine with escitalopram head to head, are 3-fold. First, it compares the short- and long-term efficacy and improvement of subjective sleep in depressed out-patients. Second, as an exploratory exercise, it compares the emotional experience of patients treated double-blind with the two antidepressants with distinct mechanisms of action. Third, additional safety and acceptability data were collected.

Method

Study design

This was an international, double-blind, randomized study using flexible dosages of agomelatine and escitalopram, conducted in 51 centres in Australia, Brazil, Canada, France, Russia, South Africa and UK from July 2007 to September 2008. The study was run in accordance with the principles of Good Clinical Practice E6 of the International Conference of Harmonisation (CPMP/ICH/135/95) and the Declaration of Helsinki, Finland. The study included only patients suffering from moderate to severe MDE in a context of MDD and having given their written informed consent.

A double-blind treatment period of 24 wk [a 12-wk mandatory double-blind treatment period followed by a 12-wk extension period (for patients having a Clinical Global Impression-Improvement of illness (CGI-I) score $\leqslant 2$ at week 12)] preceded by a 3–7-d run-in selection period between selection and inclusion (week 0) visits. At week 0, patients were randomized to one of the two treatment groups: agomelatine or escitalopram. From week 0, patients received 25 mg/d agomelatine or 10 mg/d escitalopram. In case of insufficient improvement (criteria blind for the investigator and patient), the dosage of agomelatine was increased to 50 mg/d and that of escitalopram to 20 mg/d from 2 wk onwards.

Between week 24 and week 25, patients who received 10 mg escitalopram received 5 mg for 7 d and patients who received 20 mg received 10 mg for the first 3 d, then 5 mg for the 4 following days. Patients previously on agomelatine were given placebo.

During the whole study duration, all patients took one capsule orally once per day in the evening

(around 20:00 hours). Treatments were identically labelled.

Allocation to treatment

Eligible patients were assigned to agomelatine or escitalopram treatment according to a balanced (non-adaptive) randomization with stratification on the clinical centre. The treatment allocation and the dose increase were done centrally using an Interactive Response System, in a blinded condition manner for patients and investigators.

Study population

Eligible out-patients were aged 18–70 yr, with a MDE of moderate to severe intensity (DSM-IV-TR criteria) and had to fulfil the following criteria: single or recurrent episode (at least 4 wk), with or without melancholic features, without seasonal pattern, without psychotic features and without catatonic features; Hamilton Depression Rating Scale (HAMD) 17 items ($HAMD_{17}$) total score $\geqslant 22$; Clinical Global Impression-Severity of illness (CGI-S) score $\geqslant 4$; Hospital Anxiety Depression Scale depression score $\geqslant 11$. $HAMD_{17}$ total score had to be stable between selection and inclusion (decrease <20%).

The patients were required to be physically healthy or to have stabilized significant illnesses on the basis of medical history, physical examination, 12-lead electrocardiogram (ECG) and clinical laboratory tests.

Patients with any of the following disorders were excluded: chronic MDE (>2 yr); bipolar I or II disorder; MDD superimposed on dysthymic disorder; current panic disorder; obsessive compulsive disorder; post-traumatic stress disorder; acute stress disorder; schizoaffective or any other psychotic disorder; neurological disorders or severe or uncontrolled organic disorders, Exclusion criteria also included transaminases values >2 times the upper normal limit (ULN), alkaline phosphatize >3 ULN and/or total bilirubin >34 μmol/l and/or positive plasma β-HCG; alcohol or drug abuse or dependence within the past 12 months and any personality disorder; risk of suicide.

Patients were excluded if they had not responded to an appropriate dose of two different previous antidepressant treatments ($\geqslant 4$ wk), if they had received insight-oriented and structured psychotherapy (within 3 months), light-therapy started (within 2 wk), oral antipsychotic drugs (within 4 wk), neuroleptics at low dose (within 2 wk), depot neuroleptics (within 6 months), electroconvulsive therapy (within 3 months). The wash-out periods for antidepressants were 1 wk, but non-selective monoamine oxidase inhibitors and tricyclics (2 wk) and fluoxetine (5 wk). Hypnotics, anxiolytics and neuroleptic agents were prohibited during the study and before inclusion depending on their half-life. Treatments likely to interfere with escitalopram were forbidden.

Efficacy measurements

Efficacy on depressive symptoms. The antidepressant efficacy of study medications was assessed by investigators at each visit, using the $HAMD_{17}$, the CGI-S and the CGI-I scale (Guy, 1976). The efficacy criterion was $HAMD_{17}$ total score expressed as change from baseline to last post-baseline value (over the 12- and 24-wk treatment periods). Response to treatment was established by $HAMD_{17}$ and CGI-I scales. By $HAMD_{17}$, response was defined as a total score decrease from baseline $\geqslant 50\%$ over the 24-wk period; by CGI-I, response was defined as a score of 1 or 2. Remission was respectively defined over both the 12- and 24-wk treatment periods either as a $HAMD_{17}$ total score $\leqslant 7$ or as a CGI-I score of 1.

Efficacy on subjective sleep. Efficacy criteria included patient subjective sleep improvement, using self-rating sleep visual analogue scales (VAS): six items rated at each visit between inclusion (week 0) and week 24 (i.e. weeks 0, 1, 2, 3, 4, 6, 8, 12, 16, 20, 24). The Sleep Visual Analogue Scale explores different patterns of sleep. Three items of this scale have been chosen with reference to the Leeds Sleep Evaluation Questionnaire (Hindmarch, 1975) (Supplementary material). The main efficacy criterion was the 'global satisfaction on sleep score'. The other items were 'getting off to sleep', 'quality of sleep', 'early awakening', 'feeling on waking' and 'sense of balance and coordination'.

The secondary efficacy parameter was a global satisfaction on sleep score decrease from baseline $\geqslant 50\%$ (after having transformed the score as 100 minus the score).

The Pittsburg Sleep Quality Index (PSQI) questionnaire was completed by the patient at inclusion and at weeks 2, 6, 12 and 24, or in case of premature withdrawal. The PSQI is most related to nocturnal sleep quality and reports patients' judgement on sleep and sleep quantity.

Using daytime sleepiness VAS: two items ('daytime sleepiness', and 'feeling good') were rated at inclusion, at each visit of the mandatory period, and at week 24 visit or in case of premature withdrawal (Supplementary material).

Effect on patient's global functioning. The patient's global functioning was assessed using the Global Assessment

of Functioning (GAF) scale rated by investigators at inclusion, week 12 and week 24 or in case of premature withdrawal.

Effect on emotional experiences. An ancillary study was conducted in four countries (Australia, Canada, South Africa and the UK) to investigate emotional side-effects of antidepressants in English-speaking patients with MDD using the first version of a questionnaire now to be called the Oxford Questionnaire on the Emotional Side-Effects of Antidepressants (OQESA; Price et al., 2009). The patient is asked to self-report the extent to which they have experienced a series of emotional experience (previously interpreted as side-effects of SSRI antidepressants); it has high construct validity – four of the seven themes identified in the qualitative study (Price et al., 2009) are represented in the OQESA as dimensions (PR – reduction in positive emotions, GR – general reduction in emotions, NC – not caring and ED – emotional detachment). The questionnaire was filled in by the patients at selection, inclusion, weeks 2, 12 and 24 or at the withdrawal visit in case of premature withdrawal.

Safety measurements

The tolerability and safety evaluations were based on adverse events spontaneously reported by patients at each visit (from week 0 to follow-up), 12-lead ECG abnormalities, biological samplings (at weeks 0, 12 and 24), physical examination (at selection, inclusion and week 24).

Vital signs (supine systolic and diastolic blood pressure, supine heart rate and weight) were assessed at selection, inclusion and weeks 12, 24 and 25 or in case of premature withdrawal.

In case of withdrawal of the patient for any reason between weeks 0 and 24, a physical examination, blood sampling and ECG were assessed.

Statistical analysis

All efficacy analyses (except OQESA) were performed in the full analysis set (FAS; intention to treat principle), defined as patients of the randomized set having taken at least one dose of study medication and having at least a value at week 0 and at least one post-baseline value over the 12-wk period for the $HAMD_{17}$ total score (last observation carried forward method). Efficacy analyses were also performed in the subset of patients with $HAMD_{17}$ total score $\geqslant 25$ at week 0 and in the subset of patients with high levels of sleep complaints (as defined by a PSQI total score $\geqslant 13$; *post hoc* analyses).

Descriptive statistics were provided by treatment group over the 12- and 24-wk periods.

Regarding the $HAMD_{17}$ total score over the 12- and 24-wk periods, the non-inferiority of agomelatine relative to escitalopram was investigated on the change from baseline to last post-baseline value, taking into account the fixed pre-defined, non-inferiority margin of -1.5. The analysis was carried in the FAS and in the subset of patients with $HAMD_{17}$ scores $\geqslant 25$ at baseline using a two-way analysis of covariance with 'treatment' and 'centre' (as random effect) factors and baseline total score as covariate.

For items of the Sleep Visual Analogue Scale, differences between agomelatine and escitalopram were studied using a two-way analysis of covariance on factors treatment and centre (random effect) with baseline as covariate. Scores from the daytime sleepiness scale were compared using Student's *t* test (*post hoc* analyses).

Emotional side-effects were described by treatment groups, at each time-point in patients of the ancillary study, and a χ^2 test was performed at week 24 to compare the treatment groups.

For safety data, descriptive statistics were provided by treatment group in the safety set, defined as all included patients having taken at least one dose of study medication.

Statistical analysis was performed on SAS® software, version 8.2. The type I error was set at 5% (two-sided tests), except for the non-inferiority test, performed at 2.5% (one-sided test). The *p* values were provided with no adjustment for multiplicity.

Results

Patients

Of the 363 patients selected, 324 (89.3%) were randomly allocated to receive agomelatine (164 patients) or escitalopram (160 patients; Fig. 1). There were no significantly different demographic characteristics between patients treated with agomelatine or escitalopram (Table 1). The average age of the randomized patients was 43.2±12.4 yr and 71.0% of them were female.

No clinically relevant differences between groups were observed for disease characteristics at baseline. The majority of MDE was recurrent (mean number of 2.8±2.3 previous episodes) and of moderate intensity. The median duration of the current episode was 3.3 months. Regarding depression and sleep criteria at baseline, no relevant differences between groups were observed (Table 1). No clinically relevant

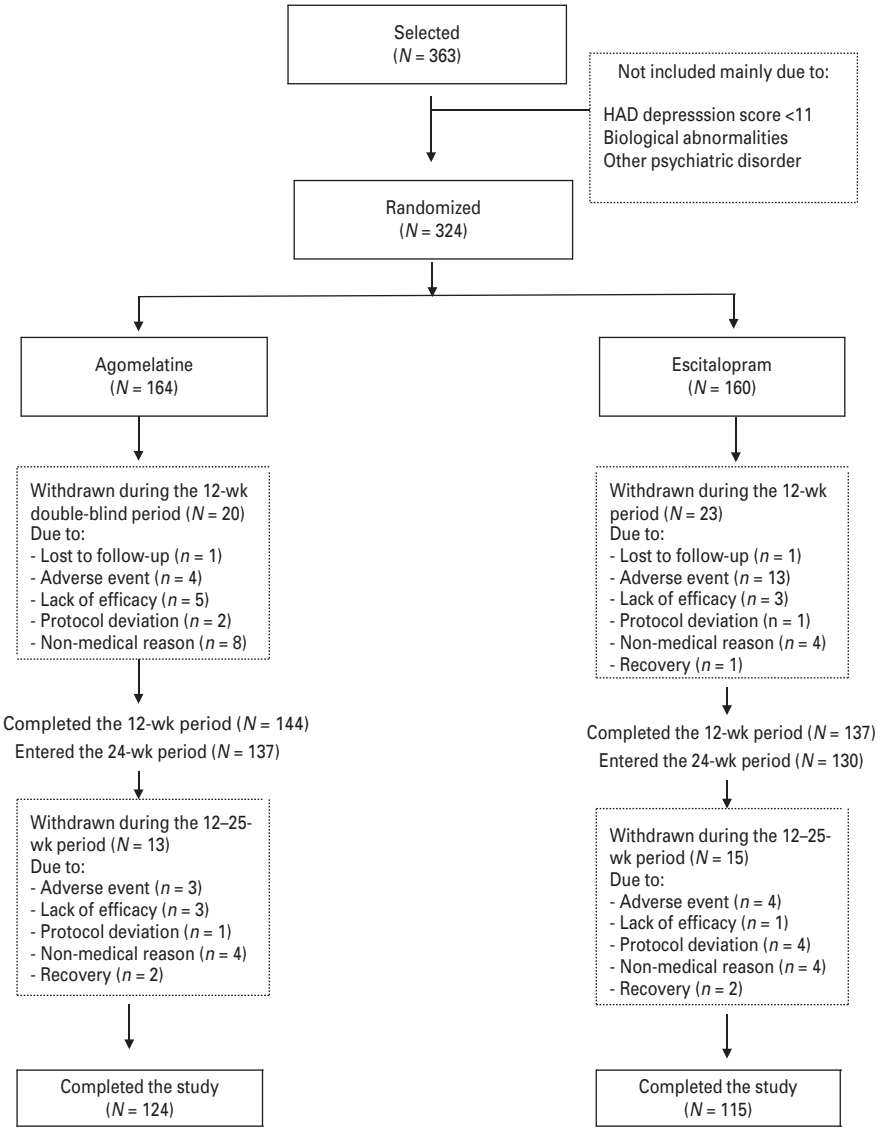

Fig. 1. Disposition of included and randomized patients.

difference between groups was observed regarding physical examination, ECG and other baseline characteristics.

A total of 83 patients had a dose increase: 41 out of the 164 randomized patients in the agomelatine group (24%) and 42 out of the 160 randomized patients in the escitalopram group (26%).

The subset of 187 patients with high levels of sleep complaints (i.e. with a PSQI total score $\geqslant$13 at baseline) represented 57.7% of the randomized patients. The demographic and baseline characteristics of this subgroup were not different from those observed in the set of randomized patients. Of the 281 patients who completed the 12-wk mandatory period, only seven in each treatment arm did not continue on the 12-wk extension period (Fig. 1).

Antidepressant efficacy(Table 2a)

$HAMD_{17}$ scale

Mean change from baseline to last post-baseline $HAMD_{17}$ total score was clinically relevant and statistically significantly non-inferior in the agomelatine group compared to the escitalopram group, over 12 and 24 wk, with a between-group difference (escitalopram minus agomelatine) of 0.36±0.67 [95% confidence intervals (CI) −0.96 to 1.68, p=0.003] over 12 wk, and a between-group difference of 0.69±0.76

Table 1. Baseline characteristics of the randomized patients

		Agomelatine (*N*=164)	Escitalopram (*N*=160)
Age (mean±S.D.) (yr)		43.6±12.9	42.8±11.8
Male/female (%)		26.8/73.2	31.3/68.7
DSM-IV Diagnosis (%)	Recurrent episode	75.0	73.1
DSM-IV Severity (%)	Moderate	76.2	73.8
	Severe without psychotic feature	23.8	26.3
Melancholic features (%)		75.0	77.5
Number of depressive episodes (mean±S.D.)		2.7±1.9	2.8±2.6
Duration of current MDE (mean±S.D.) (months)		5.54±10.70	4.62±4.23
Previous psychotropic treatments (%)		50.0	53.8
HAMD 17-item total score (mean±S.D.)		26.8±3.1	26.6±2.5
CGI Severity of illness score (mean±S.D.)		4.7±0.6	4.7±0.6
HAMD sleep sub-score (mean±S.D.)		4.9±1.3	5.0±1.2
PSQI sleep sub-score (mean±S.D.)		13.1±2.9	13.1±3.0
GAF score (mean±S.D.)		53.0±7.4	53.1±7.2
VAS Feeling good (mm)		21.5±15.9	19.4±13.9
VAS Daytime sleepiness (mm)		65.0±24.0	66.7±24.2
Sleep VAS-			
Global satisfaction on sleep (mm)		19.9±13.3	21.5±15.4
Getting off to sleep (mm)		29.8±25.6	32.3±25.6
Quality of sleep (mm)		21.8±15.1	22.6±15.4
Early awakening (mm)		31.5±24.4	33.1±24.8
Feeling on waking (mm)		18.6±15.4	20.7±17.3
Sense of balance and coordination (mm)		50.5±27.6	53.1±27.9

MDE, Major depressive episode; HAMD, Hamilton Depression Rating Scale; CGI, Global Impression-Improvement; PSQI, Pittsburgh Sleep Quality Index; GAF, Global Assessment of Functioning; VAS, visual analogue scale.

(95% CI −0.81 to 2.19, p=0.002) over 24 wk. The percentage of responders on the $HAMD_{17}$ scale at the last post-baseline assessment was similar in both groups over both treatment periods (at week 12: 83.2 and 80.0%; at week 24: 82.6 and 81.3%, in the agomelatine and escitalopram groups, respectively). The percentage of remitters ($HAMD_{17}$ total score $\leqslant$7) over both the 12- and 24-wk treatment periods was 60.9 and 69.6% in the agomelatine group *vs.* 54.4 and 63.1% in the escitalopram group.

Similar results were observed in the subset of patients with severe depression (HAMD total score $\geqslant$25 at inclusion). The mean decrease from baseline to last post-baseline HAMD total score was statistically significantly non-inferior in the agomelatine group compared to the escitalopram group with a between-group difference of 0.15±0.80 (−1.42 to 1.72, p=0.02) after the first 12-wk treatment period and a between-group difference of 0.69±0.90 (−1.08 to 2.46, p=0.008) over 24 wk. The percentage of responders on the $HAMD_{17}$ scale was similar in both groups over both treatment periods (at week 12: 83.6 and 79.7%; at week 24: 82.0 and 79.7%, in the agomelatine and escitalopram groups, respectively). The percentage of remitters over both the 12- and 24-wk treatment periods was 55.7 and 65.6% in the agomelatine group *vs.* 52.3 and 62.5% in the escitalopram group.

In the subset of patients with a PSQI total score $\geqslant$13 at inclusion, a clinically relevant decrease on $HAMD_{17}$ scale from baseline was observed in both treatment groups after the first 12- and 24-wk treatment periods. The percentage of responders on the $HAMD_{17}$ scale was similar in both groups over both treatment periods (at week 12: 80.6 and 80.9%; at week 24: 83.7 and 82.0%, in the agomelatine and escitalopram groups, respectively). The percentage of remitters over both the 12- and 24-wk treatment periods was 58.2 and 68.4% in the agomelatine group *vs.* 57.3 and 68.5% in the escitalopram group.

CGI scale (Table 2b)

The mean CGI-S and CGI-I scores decreased between week 0 and the last post-baseline assessment in both

Table 2. Antidepressant efficacy of agomelatine and escitalopram (*a*) $HAMD_{17}$ scores (expressed as mean change from baseline in the FAS) and subsets of patients with $HAMD_{17} \geqslant 25$ at baseline or with PSQI $\geqslant 13$ at baseline and (*b*) CGI-S and CGI-I scores (expressed as mean score±S.D.) at baseline and weeks 12 and 24 in the FAS

	Baseline	Change at week 12	Change at week 24
(*a*) $HAMD_{17}$ total score			
FAS			
Agomelatine (25–50 mg)	26.8±3.1	−18.7±6.9	−19.9±7.6
Escitalopram (10–20 mg)	26.6±2.5	−18.3±6.8	−19.2±7.2
Subset $HAMD_{17} \geqslant 25$			
Agomelatine (25–50 mg)	28.0±2.6	−19.4±7.0	−20.5±7.5
Escitalopram (10–20 mg)	27.4±2.1	−18.8±7.1	−19.4±7.7
Subset PSQI $\geqslant 13$			
Agomelatine (25–50 mg)	27.3±3.2	−18.9±6.9	−20.3±7.6
Escitalopram (10–20 mg)	27.1±2.5	−19.2±6.7	−20.1±7.0
(*b*) CGI-S score			
Agomelatine (25–50 mg)	4.7±0.6	2.1±1.1	1.8±1.2
Escitalopram (10–20 mg)	4.7±0.6	2.1±1.1	1.9±1.2
CGI-I score			
Agomelatine (25–50 mg)	–	1.5±0.9	1.5±1.0
Escitalopram (10–20 mg)	–	1.5±0.9	1.6±1.1

HAMD17, Hamilton Depression Rating Scale 17 item; FAS, full analysis set; PSQI, Pittsburgh Sleep Quality Index; CGI-S, Clinical Global Impression-Severity of illness; CGI-I, Clinical Global Impression-Improvement of illness.

groups. Results were clinically relevant in both groups and there was no between-group difference at last post-baseline value over 12 or 24 wk. Over the 24-wk period, the percentage of responders to treatment on the CGI-I scale for the last value was 86.3 and 85.0% in the agomelatine and escitalopram groups, respectively; the percentage of remitters (global improvement score=1) was 75.8% in the agomelatine group and 70.6% in the escitalopram group.

In the subset of patients with severe sleep symptoms, the mean CGI-S and CGI-I scores similarly decreased in both groups over 12 or 24 wk. Over the 24-wk period, the percentage of responders to treatment on the CGI-I scale for the last value was 88.7 and 85.4% in the agomelatine and escitalopram groups, respectively; the percentage of remitters was 76.5% in the agomelatine group and 73.0% in the escitalopram group.

Subjective sleep (Table 3)

Global satisfaction score

Over the first 12-wk treatment period, the mean change for 'global satisfaction on sleep' score from baseline at the last post-baseline assessment was not different in the agomelatine and escitalopram groups. The percentage of responders was not different in the agomelatine and escitalopram groups at the last post-baseline assessment (61.3 *vs.* 60.6%, respectively). Over the 24-wk period, the 'global satisfaction on sleep' score increased in both treatment groups. The percentage of responders at the last post-baseline assessment was 66.3% in the agomelatine group *vs.* 59.4% in the escitalopram group.

Similar results were observed in the subset of patients with severe depression (HAMD total score $\geqslant 25$ at inclusion) and the subset of patients with severe sleep symptoms (PSQI total score $\geqslant 13$). In the latter subset, a trend for a higher response in favour of agomelatine was found at the last post-baseline assessment over the 24-wk period with a between-group difference of 11.88±6.92 ($p=0.09$).

'Getting off to sleep' score, 'quality of sleep' score, 'early awakening' score

There was no significantly relevant difference between groups for getting off to sleep, quality of sleep and early awakening scores over the 12- and 24-wk treatment periods.

In the subset of patients with severe sleep symptoms, the difference in favour of agomelatine was statistically significant over the 24-wk period for the 'quality of sleep' score with a between-group

Table 3 Mean change from baseline (mm±S.D.) after agomelatine and escitalopram treatments on global satisfaction on sleep score and getting off to sleep, quality of sleep and awakening, feeling on waking, sense of coordination, daytime sleepiness and feeling good scores – FAS (over the 12 and 24-wk periods) and subset of patients with PSQI ⩾13 at baseline (over the 24-wk period)

Criterion	FAS		Subset PSQI⩾13
Treatment	Week 12	Week 24	Week 24
Global satisfaction on sleep			
Agomelatine (25–50 mg)	43.5±29.1	47.7±30.2	52.6±27.7
Escitalopram (10–20 mg)	42.7±30.6	43.5±32.0	45.7±30.9
Getting off to sleep			
Agomelatine (25–50 mg)	41.7±32.9	43.8±33.3	48.2±34.2
Escitalopram (10–20 mg)	34.6±36.4	39.1±36.9	39.9±37.8
Quality of sleep			
Agomelatine (25–50 mg)	38.3±27.2	44..2±28.8	50.5±26.6
Escitalopram (10–20 mg)	39.1±26.9	40.4±28.2	40.8±29.7
Early awakening			
Agomelatine (25–50 mg)	35.6±37.3	38.9±37.1	46.4±34.3
Escitalopram (10–20 mg)	38.2±32.4	40.6±32.8	44.1±30.9
Feeling on waking			
Agomelatine (25–50 mg)	38.4±29.1	42.3±29.2	46.8±29.7
Escitalopram (10–20 mg)	32.7±31.4	34.7±34.9	33.1±33.1
Sense of coordination			
Agomelatine (25–50 mg)	27.5±28.4	28.6±28.6	33.5±28.3
Escitalopram (10–20 mg)	25.1±31.5	25.0±33.3	28.7±34.3
PSQI			
Agomelatine (25–50 mg)	−6.5±4.5	−6.8±4.9	6.3±4.4*
Escitalopram (10–20 mg)	−6.3±4.4	−6.4±4.7	7.4±4.6*
Daytime sleepiness			
Agomelatine (25–50 mg)	−28.9±31.5	−32.3±32.5	34.1±29.1
Escitalopram (10–20 mg)	−26.1±33.6	−29.5±34.2	40.6±30.0
Feeling good			
Agomelatine (25–50 mg)	35.5±31.1	40.7±31.9	64.0±28.1
Escitalopram (10–20 mg)	37.2±30.1	38.0±34.0	55.0±28.9

FAS, Full analysis set.

* Pittsburgh Sleep Quality Index (PSQI) total score at the last post-baseline assessment.

difference of −8.72±3.60 mm (p=0.016). No significant advantage of agomelatine over escitalopram was found in this subset of patients, either for 'getting off to sleep' or for 'early awakening'.

'Feeling on waking' score

A higher 'feeling on waking' score (mean change from baseline) was recorded over both study periods in the agomelatine group than in the escitalopram group with a between-group difference of −6.64±2.95 mm (p=0.02) over the 24-wk period.

In the subset of patients with severe sleep symptoms, the difference in favour of agomelatine was statistically significant over the 24-wk period with a between-group difference of −10.77±4.05 mm (p=0.009).

'Sense of coordination' score

Sense of coordination was not different between groups over both study periods.

In the subset of patients with severe sleep symptoms, no significant advantage of agomelatine over escitalopram was found over the 24-wk period.

PSQI

The decrease in PSQI total score between the baseline and the last post-baseline assessment differed between

groups neither in the FAS (for both study periods) nor in the subset of patients with severe sleep symptoms over the 24-wk period.

Daytime sleepiness

The 'decrease in daytime sleepiness' score did not differ between groups over the 12 and the 24 wk of the study nor in the subset of patients with severe sleep symptoms over the 24-wk period.

Feeling good score

The 'decrease in daytime sleepiness' score and the increase in 'feeling good' score did not differ between groups over the 12 and 24 wk of the study. In the subgroup of patients with severe sleep complaints, the 'feeling good' score was significantly higher in the agomelatine group than in the escitalopram group over the 24-wk period, with a between-group difference of −9.06±4.17 mm (p=0.03).

GAF

The treatments were equally effective on the GAF scale (mean score changes in agomelatine and escitalopram groups respectively: 23.7±13.1 and 24.7±12.4 at week 12 and 27.0±15.6 and 27.0±15.0 at week 24).

Similar changes from baseline were obtained in the subset of patients with severe sleep symptoms over both treatment periods (agomelatine: 24.0±12.6, escitalopram: 24.5±12.6 at week 12; agomelatine: 27.6±16.2, escitalopram: 26.1±15.9 at week 24).

OQESA

The total study sample of this ancillary study comprised 69 English-speaking patients (37 receiving agomelatine and 32 receiving escitalopram). Of these, 66 provided data at week 0. The OQESA was completed by 62 participants at week 2, 54 participants at week 12 and 45 participants at week 24.

Table 4 describes the possible emotional side-effects reported by a subset of patients in four countries. At baseline, the emotional experiences probed were extremely common and the same in both treatment groups. Thus, of 20 items, eight were more common in the escitalopram group and 12 in the agomelatine group. The occurrence of blunting items was associated with the depressed state measured by the HAMD and CGI.

Twenty-four weeks after the initiation of the treatment, all items had reduced in frequency but on every single one of 20 items the frequency of complaint was less on agomelatine than on escitalopram. This part of the study was not designed and powered for a definitive analysis but our hypothesis remains that emotional experience was globally less blunted in the patients successfully treated with agomelatine compared with escitalopram.

The largest effects were seen in the percentage of patients on agomelatine who 'felt that things that they cared about before illness did not seem important any more' (16%) compared with the group of escitalopram-treated patients (53%). The item 'other people being upset affects me less than I think it should do' was also much less frequently reported in the agomelatine group (12% of patients) than in the escitalopram (50% of patients); a finding that was also found at 2 wk (32 *vs.* 65%). In addition, a 2-fold lower percentage of patients felt that their emotions lacked intensity in the agomelatine group (28%) than in the escitalopram group (60%).

Withdrawal

During both the first 12-wk treatment period and the 12-wk extension period, the rate of withdrawals was lower in the agomelatine group than in the escitalopram group (11.6 *vs.* 13.8% and 9.5 *vs.* 11.5%, respectively). The difference was mostly related to a lower rate of withdrawals due to adverse events in the agomelatine group than in the escitalopram group during both periods, and particularly during the first 12-wk treatment period (2.4 *vs.* 8.1%). Fewer withdrawals due to protocol deviations were also seen during the extension period in the agomelatine group (0.7%) than in the escitalopram group (3.1%; Fig. 1). During the acute and extension periods, rates of withdrawal for lack of efficacy were 3.1 and 2.2% in the agomelatine group and 1.9 and 0.8%, in the escitalopram group, respectively).

Safety

The percentage of patients in the safety set who reported at least one emergent adverse event on treatment over 24 wk was 70.6% in the agomelatine group and 76.3% in the escitalopram group. No death occurred during the treatment period.

The most frequently affected system organ classes were gastrointestinal disorders (33.7% for agomelatine and 35.0% for escitalopram), infections and infestations (28.8% for agomelatine and 35.6% for escitalopram) and nervous system disorders (25.8% for agomelatine and 30.0% for escitalopram). Psychiatric disorders were reported in 9.2% of the agomelatine group *vs.* 16.9% of the escitalopram group. System organ classes

Table 4. Experience of each individual OQESA item by treatment group in patients of the ancillary study, *N* (% of patients who agree with the sentence)

	Week 0		Week 2		Week 12		Week 24	
Part 1	Agomelatine *N*=36	Escitalopram *N*=30	Agomelatine *N*=31	Escitalopram *N*=31	Agomelatine *N*=28	Escitalopram *N*=26	Agomelatine *N*=25	Escitalopram *N*=20
All my emotions, both 'pleasant' and 'unpleasant', are 'toned down'	28 (77.8%)	22 (73.3%)	23 (74.2%)	25 (80.6%)	11 (39.3%)	11 (42.3%)	8 (32.0%)	10 (50.0%)
X^2 *p* value	0.896		0.761		1.000		0.358	
I don't fully enjoy things that should give me pleasure, such as beautiful places or things or music	35 (97.2%)	29 (96.7%)	20 (64.5%)	24 (77.4%)	10 (37.0%)	12 (46.2%)	8 (32.0%)	9 (45.0%)
X^2 *p* value	1.000		0.401		0.693		0.559	
When I'm talking to other people, I feel as though I'm more of a spectator than a participant	29 (80.6%)	23 (76.7%)	21 (67.7%)	19 (61.3%)	7 (25.0%)	10 (38.5%)	6 (24.0%)	9 (45.0%)
X^2 *p* value	0.934		0.791		0.441		0.243	
I just don't care about things that used to matter to me, such as my hobbies and interests	35 (97.2%)	28 (93.3%)	22 (71.0%)	23 (74.2%)	15 (53.6%)	13 (50.0%)	8 (32.0%)	7 (35.0%)
X^2 *p* value	0.871		1.000		1.000		1.000	
Other people being upset affects me less than I think it should do	20 (55.6%)	21 (70.0%)	**10 (32.3%)**	**20 (64.5%)**	7 (25.0%)	10 (38.5%)	**3 (12.0%)**	**10 (50.0%)**
X^2 *p* value	0.342		0.022		0.441		0.014	
I don't have the passion and enthusiasm for life that I should	35 (97.2%)	29 (96.7%)	21 (67.7%)	25 (80.6%)	18 (64.3%)	14 (53.8%)	10 (40.0%)	11 (55.0%)
X^2 *p* value	1.000		0.384		0.615		0.483	
Unpleasant emotions, such as sadness, disappointment, and upset, feel toned down or different in some way	24 (66.7%)	17 (56.7%)	18 (58.1%)	18 (58.1%)	10 (35.7%)	9 (34.6%)	6 (24.0%)	7 (35.0%)
X^2 *p* value	0.563		1.000		1.000		0.633	
I don't look forward to things with eager anticipation	33 (91.7%)	30 (100.0%)	22 (71.0%)	21 (67.7%)	14 (50.0%)	9 (34.6%)	9 (36.0%)	10 (50.0%)
χ^2 *p* value	0.305		1.000		0.386		0.521	
I feel emotionally detached and disconnected from things around me	31 (86.1%)	28 (93.3%)	18 (58.1%)	21 (67.7%)	8 (28.6%)	8 (30.8%)	6 (24.0%)	10 (50.0%)
X^2 *p* value	0.584		0.599		1.000		0.134	

My emotions lack intensity	23 (63.9%)	20 (66.7%)	13 (41.9%)	18 (58.1%)	**6 (21.4%)**	**13 (50.0%)**	**7 (28.0%)**	**12 (60.0%)**
X^2 p value	1.000		0.310		0.056		0.063	
I don't care about my day to day responsibilities as much as I should	31 (88.6%)	25 (83.3%)	23 (74.2%)	20 (64.5%)	14 (50.0%)	8 (30.8%)	6 (24.0%)	8 (42.1%)
X^2 p value	1.000		0.582		0.246		0.342	
I don't feel very emotionally connected with other people	27 (75.0%)	28 (93.3%)	18 (58.1%)	24 (77.4%)	10 (35.7%)	9 (34.6%)	7 (28.0%)	10 (50.0%)
X^2 p value	0.097		0.174		1.000		0.229	
I feel spaced out and distant from the world around me	31 (86.1%)	23 (76.7%)	20 (64.5%)	23 (74.2%)	11 (39.3%)	12 (46.2%)	7 (28.0%)	8 (42.1%)
X^2 p value	0.503		0.582		0.815		0.511	
	Week 0		Week 2		Week 12		Week 24	
Part 2	Agomelatine N=36	Escitalopram N=30	Agomelatine N=31	Escitalopram N=31	Agomelatine N=28	Escitalopram N=26	Agomelatine N=25	Escitalopram N=20
I don't feel things emotionally in the way that I did before I developed my illness/problem	31 (86.1%)	25 (83.3%)	21 (67.7%)	20 (64.5%)	15 (53.6%)	17 (65.4%)	11 (44.0%)	12 (60.0%)
χ^2 p value	1.000		1.000		0.545		0.443	
Day to day life just doesn't have the same emotional impact on me that it did before my illness/problem	33 (91.7%)	26 (86.7%)	21 (67.7%)	24 (77.4%)	14 (50.0%)	15 (57.7%)	8 (32.0%)	11 (55.0%)
X^2 p value	0.798		0.569		0.769		0.212	
I don't experience pleasant emotions as much as I did before I developed my illness/problem	33 (91.7%)	28 (93.3%)	20 (64.5%)	25 (80.6%)	11 (39.3%)	9 (34.6%)	7 (28.0%)	10 (50.0%)
X^2 p value	1.000		0.255		0.942		0.229	
I don't care as much about my day to day responsibilities as I did before I developed my illness/problem	29 (80.6%)	24 (80.0%)	21 (67.7%)	23 (74.2%)	14 (50.0%)	9 (34.6%)	7 (28.0%)	7 (36.8%)
X^2 p value	1.000		0.780		0.386		0.766	
I don't get as much of a 'high' from good things in my life as I did before my illness/problem	36 (100.0%)	29 (96.7%)	23 (74.2%)	24 (77.4%)	16 (57.1%)	13 (50.0%)	8 (32.0%)	9 (45.0%)
χ^2 p value	0.927		1.000		0.800		0.559	

Table 4. (*Cont.*)

Part 2	Week 0		Week 2		Week 12		Week 24	
	Agomelatine *N*=36	Escitalopram *N*=30	Agomelatine *N*=31	Escitalopram *N*=31	Agomelatine *N*=28	Escitalopram *N*=26	Agomelatine *N*=25	Escitalopram *N*=20
Things that I cared about before my illness/problem don't seem important to me any more	27 (75.0%)	21 (70.0%)	16 (51.6%)	22 (71.0%)	12 (42.9%)	13 (50.0%)	**4 (16.0%)**	**10 (52.6%)**
χ^2 *p* value	0.860		0.192		0.800		0.024	
I don't react to other people's emotions (such as their sadness, anger or upset) as much as I did before my illness/ problem	20 (55.6%)	19 (63.3%)	**12 (38.7%)**	**21 (67.7%)**	9 (32.1%)	13 (50.0%)	3 (12.0%)	8 (40.0%)
χ^2 *p* value	0.698		0.042		0.290		0.068	

Part 3	Week 2		Week 12		Week 24	
	Agomelatine *N*=27	Escitalopram *N*=31	Agomelatine *N*=28	Escitalopram *N*=25	Agomelatine *N*=25	Escitalopram *N*=19
The antidepressant changes the way that I experience my emotions in a way that is unhelpful to me at the moment	5 (18.5%)	4 (12.9%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)
χ^2 *p* value	0.821		0.954		NA	
The antidepressant is preventing me from feeling my emotions in some way	3 (11.1%)	5 (16.1%)	2 (7.1%)	5 (20.0%)	5 (20.0%)	1 (5.3%)
χ^2 *p* value	0.864		0.330		0.333	

OQESA, Oxford Questionnaire on the Emotional Side-Effects of Antidepressants.
Values shown in bold indicate $p<0.05$.

Table 5. Most frequently reported emergent adverse events* during the double-blind treatment period (at least 2% of the patients in any group)

Adverse events	Agomelatine (*N*=163)	Escitalopram (*N*=160)
Headache	11	18.1
Nausea	9.2	15.0
Diarrhoea	8.0	7.5
Constipation	5.5	1.3
Nasopharyngitis	4.3	6.9
Gastroenteritis	3.1	6.9
Back pain	3.1	4.4
Fatigue	3.1	4.4
Sinusitis	3.1	2.5
Gastritis	3.1	0
Bronchitis	2.5	4.4
Somnolence	2.5	3.8
Upper respiratory tract infection	2.5	3.8
Dyspepsia	2.5	2.5
Abnormal dreams	2.5	0.6
Suicide attempt	2.5	0.6
Sedation	1.8	3.1
Anxiety	1.2	4.4
Pharyngolaryngeal pain	1.2	3.1
Hypertension	1.2	2.5
Hyperhidrosis	0.6	4.4
Cough	0.6	3.1
Insomnia	0.6	2.5
Agitation	0	2.5
Arthralgia	0	2.5

* Expressed as per cent of number of affected patients to number of exposed patients in the considered treatment (g).

were generally less affected in the agomelatine than in the escitalopram group.

The most frequent emergent adverse events in both groups were headache, nausea and diarrhoea (Table 5). Adverse events were generally less frequently reported in the agomelatine group than in the escitalopram group (headache: 11.0 *vs.* 18.1%; nausea: 9.2 *vs.* 15.0%). Only diarrhoea and constipation were more frequently reported in the agomelatine group than in the escitalopram group (8.0 *vs.* 7.5% and 5.5 *vs.* 1.3%, respectively). The proportion of patients who experienced at least one emergent adverse event rated as severe was the same in the agomelatine and escitalopram groups (3.7 *vs.* 3.8%). The percentage of patients with at least one emergent adverse event considered to be related to treatment was lower in the agomelatine group than in the escitalopram group (39.3 *vs.* 50.0%). The incidence of patients with at least one emergent adverse event leading to treatment discontinuation was lower in the agomelatine group than in the escitalopram group (5.5 *vs.* 10.6%).

During the study, no clinically relevant changes or differences between groups over time were detected for biochemistry or haematological parameters, physical examination including vital signs except four patients (n=3 in the agomelatine group, n=1 in the escitalopram group), who had elevations in liver enzyme values more than three times the upper limit of the reference range. All enzyme levels returned to a normal range.

Discussion

Agomelatine and escitalopram had similar antidepressant efficacy. The antidepressant efficacy of both drugs was high, confirming previous findings obtained at the same 24-wk time-point with agomelatine and escitalopram in MDD patients (Colonna et al., 2005; Kennedy and Rizvi, 2010). We additionally demonstrate that both drugs exert a comparable antidepressant efficacy over this treatment period. Results also show a similar rate of response to treatment and remission for the two antidepressants (on both $HAMD_{17}$ and CGI-I scales).

Using PSQI, most related to nocturnal sleep quality and two VAS that explored different patterns of sleep and additionally addressed daytime functioning of patients, we found that agomelatine and escitalopram induced similar improvement of long-term global satisfaction about the sleep–wake profile of depressed patients. These results corroborate previous findings on subjective sleep in depressed patients (Quera-Salva et al., 2011). Yet it is interesting that subjective findings differ notably from objective ones. Thus, a previous comparative polysomnography study has shown that, unlike escitalopram, agomelatine induces a sustained reduction of sleep latency without affecting the number of sleep cycles or the duration of rapid eye movement (REM) nor the REM latency (Quera-Salva et al., 2011).

The higher scores of 'quality of sleep' and 'feeling on waking' observed in patients with pronounced sleep complaints at baseline (i.e. with a PSQI score $\geqslant$13) most likely reflect a better alertness on waking with agomelatine than with SSRIs. These observations are in line with those of previous studies, likewise pointing to superior early improvement in daytime functioning and subjective sleep with agomelatine as compared to the SSRIs escitalopram and sertraline

(Kasper et al., 2010; Quera-Salva et al., 2011) and to the *serotonin–norepinephrine reuptake inhibitor* venlafaxine (Lemoine and Guilleminault, 2007). The present study further shows that the benefit over escitalopram persisted for at least 24 wk. These maintained effects may relate to the normalization of sleep–wake rhythms by agomelatine (Kasper et al., 2010), probably through the regulation of sleep architecture and by increasing sleep efficiency (Quera Salva et al., 2007, 2010, 2011).

Interestingly, neither antidepressants exerted a stronger antidepressant effect in patients with more sleep complaints at baseline. The clinically relevant decrease on $HAMD_{17}$ and CGI scales from baseline, as well as the rates of responders and remitters, were roughly similar to that observed in the whole study population, over both treatment periods. This supports the conclusion that the antidepressant efficacy of both drugs is not driven primarily by their sleep-improving properties. On the other hand, the improvement of daytime functioning ('feeling on waking', 'feeling good') and 'quality of sleep' in this subset of patients was better with agomelatine compared with escitalopram treatment, which provides evidence for a supplementary clinical benefit of agomelatine.

We also provide additional data in confirmation of the good tolerability and safety profiles of 25–50 mg/d agomelatine reported in previous studies (de Bodinat et al., 2010). The tolerability profile of agomelatine compares favourably with that of escitalopram, since the rate of emergent adverse effects over 24 wk is lower in the agomelatine group than in the escitalopram group. Such improved tolerability, already seen previously (Quera-Salva et al., 2011), certainly represents a key advantage over SSRIs as it likely translates into fewer treatment withdrawals as a result of adverse effects. It is also noteworthy that a lower incidence of adverse events such as headache, fatigue, somnolence and insomnia may be connected to the better global satisfaction on 'feeling on waking' scores and quality of sleep reported by agomelatine-treated patients.

Finally, the most original and promising result of this study concerns emotional blunting. Indeed, emotional blunting has been studied here for the first time under double-blind conditions. We had previously developed questions that capture an experience attributed by patients to antidepressant treatment, especially SSRIs (Price et al., 2009). We show here that emotional blunting is prominent among patients with MDD at baseline, before conventional antidepressant treatment. It is significantly less prominent after 2 wk, 12 wk and 24 wk of treatment. Thus, it behaves overall like a correlate of depressive symptoms. For that reason, we believe it should be regarded henceforth as a depression scale – the OQESA.

In the subgroup of patients studied here, there was an overall difference in the rate of emotional blunting between treatment with agomelatine and escitalopram at 24 wk, reflected by the more frequent endorsement of items indicating emotional blunting in the escitalopram group at that time. This occurred despite closely similar scores on conventional ratings of depression symptoms in the two groups. The study was not designed and not powered to be definitive, so the blunting conclusion awaits confirmation in a larger sample. The simplest explanation for our present findings is that emotional blunting is a symptom of depression not measured in conventional scales, which is incompletely treated with SSRIs as compared with agomelatine. We cannot yet document whether withdrawal of the SSRI (and/or switch to agomelatine) would see relief of blunting and that this would represent the completion of normal recovery from depression, but that would be a prediction of these findings. It requires confirmation under double-blind conditions.

The limited number of emotional complaints on agomelatine after recovery confirms preliminary results obtained in healthy volunteers (Harmer et al., 2011). The report of emotional complaints with escitalopram is also obviously in line with the emotional blunting commonly described in unblinded conditions with other SSRIs (Price et al., 2009). More generally, our findings show that two antidepressants with different mechanisms of action can affect emotional processing in different ways and, therefore, may be associated with more or less risks of those residual emotional symptoms often seen following partial or full recovery from the index illness.

To conclude, the present findings point to potential new short- and long-term clinical benefits of the antidepressant agomelatine. Together with an antidepressant efficacy comparable to that of a widely used SSRI, agomelatine treatment further offers to depressed patients more favourable effects on sleep–wake conditions, a maintained range of emotions on treatment and the absence of drug-induced emotional blunting, together with better safety and tolerability profiles.

Appendix 1. Members of the agomelatine study group

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Supplementary material

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Statement of Interest

E. Corruble has received consulting fees within the last 3 yr from Servier, Lundbeck, Sanofi-Aventis, Bristol Myers Squibb, Eisai. C. de Bodinat is an employee at Servier C. Belaïdi is an employee at Servier. G. Goodwin has held grants from Sanofi-Aventis and Servier, has received honoraria for speaking from AstraZeneca, BMS, Eisai, Lundbeck, Sanofi-Aventis, Servier and for advice from AstraZeneca, BMS, Cephalon, Lilly, Lundbeck, Otsuka, P1Vital, Pfizer, Sanofi-Aventis, Servier, Takeda.

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