

# Efficacy of agomelatine in major depressive disorder: meta-analysis and appraisal



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## Abstract

Agomelatine is the first approved antidepressant that mediates its activity through the melatonergic pathway rather than the monoaminergic system. This meta-analysis aims to summarize an up-to-date report on the efficacy of agomelatine in major depressive disorder. Archives of published results in PubMed, CINAHL, Cochrane Library, EMBASE and PsycINFO databases were searched for randomized double-blind trials comparing agomelatine against placebo or antidepressant in major depressive disorder. Change in severity of depression as a result of intervention was the main outcome measure. Data necessary to compute the standardized mean difference (SMD) of this outcome and additional sample parameters that were likely to influence the main outcome were extracted for each selected studies. Summary effect sizes of various groups and subgroups were computed from SMDs between agomelatine and control (placebo or antidepressants) arms. There were nine trials involving 3943 severe cases of depression on agomelatine ( $n=2390$ ) and either placebo ( $n=689$ ) or antidepressants ( $n=864$ ). Agomelatine ( $n=1274$ ) stood superior to placebo ( $n=689$ ) by a small margin (SMD  $-0.26$ ,  $p=3.48 \times 10^{-11}$ ) and the superiority of agomelatine ( $n=834$ , dose  $\geq 25$  mg/d) over antidepressants (paroxetine, fluoxetine, sertraline, venlafaxine;  $n=864$ ) was even smaller (SMD  $-0.11$ ,  $p=0.02$ ). Although there is evidence of the superiority of agomelatine over placebo and selected antidepressants, it is questionable whether the magnitude of effect size is clinically significant and sample characteristics are relevant to the general patient population with major depressive disorder.

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## Introduction

In February 2009 the European Medicines Agency (EMA) approved agomelatine, a sleep modulating antidepressant, for the treatment of major depressive disorder (MDD) in adults (EMA, 2009); and it is awaiting approval from the Federal Drug Administration in the USA. Agomelatine became the first approved drug to mediate its effect through the melatonergic system rather than the monoaminergic system (de Bodinat *et al.* 2010). In addition, there are data to suggest that agomelatine also possesses anti-anxiety property and has a role in the treatment of

generalized anxiety disorder (Green, 2011; Stein *et al.* 2008). Due to its melatonergic mode of action, it is envisaged that it may also have a place in the treatment of seasonal affective disorder (Pjrek *et al.* 2007).

## Animal studies

Agomelatine has shown antidepressant-like activity in a number of animal models of depression, such as the learned helplessness model, the chronic mild stress model, the forced swim test model and the chronic psychosocial stress model (Popoli, 2009). Agomelatine improves the behaviour of helplessness associated with abnormality in feedback from the hypothalamic-pituitary-adrenal axis in the transgenic model of affective disorder in mice (Paizanis *et al.* 2010). Agomelatine has also been found to restore normal circadian rhythms in animal models of a disrupted circadian system, and has proved beneficial in delayed sleep

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phase syndrome (Popoli, 2009). The antidepressant-like activity of agomelatine was reported to be independent of the time of drug administration; and its efficacy was comparable to that of imipramine and fluoxetine, but greater than that of melatonin (Papp *et al.* 2003).

### Pharmacology

Agomelatine [*N*(2-(7-methoxy-1-naphthyl)ethyl)acetamide] is an agonist at both melatonergic MT<sub>1</sub> and MT<sub>2</sub> receptors (Fornaro *et al.* 2010; Masson-Pévet *et al.* 1998; San & Arranz, 2008). It also has affinity for 5-HT<sub>1A</sub> and 5-HT<sub>2B</sub> receptors, but it is unlikely that antidepressant effects are mediated via these receptors (Millan *et al.* 2003). In addition, agomelatine is an antagonist to 5-HT<sub>2C</sub> receptors (Millan *et al.* 2010) that increases slow-wave sleep (Landolt *et al.* 1999) and reduces treatment-emergent sexual dysfunction (Rosen *et al.* 1999). Agomelatine-associated suppression of 5-HT<sub>2C</sub> activity leads to release of inhibitory control on noradrenaline and dopaminergic neurotransmission (Stahl, 2007) that may contribute to improvement in anxiety symptoms (Kasper & Hamon, 2009). The influence of agomelatine on M<sub>1</sub>, M<sub>2</sub>, noradrenaline and dopamine systems is likely to contribute to the overall improvement seen in depressive symptoms.

Eighty percent of agomelatine is rapidly absorbed after oral administration and attains peak plasma level after 1–2 h. Ninety five percent of agomelatine is bound to plasma protein and there is substantial inter-individual variation in bioavailability which is more pronounced in women compared to men. This has half-life of 1–2 h; kinetics are not affected by repeated dosing, and there is no cumulative effect. Agomelatine is primarily metabolized by CYP450, CYP1A2 and CYP2C9 isoenzymes, 80% of which is excreted in urine in the form of various metabolites with very little in unchanged form (EMEA, 2009).

### Efficacy studies

In clinical trials, superior efficacy compared to placebo (Kennedy & Emsley, 2006; Lôo *et al.* 2002; Olié & Kasper 2007; Stahl *et al.* 2010; Zajecka *et al.* 2010) and equivalent efficacy compared to standard antidepressants have been reported for agomelatine in treating acute phase of major depression (Eser *et al.* 2010). Discontinuation of agomelatine from maintenance phase is linked with increased probability of relapse (Goodwin *et al.* 2009). There are indications that use of agomelatine is associated with early onset of antidepressant action compared to selective serotonin

re-uptake inhibitors and serotonin-noradrenaline re-uptake inhibitors (Lam, 2010).

Most research data on agomelatine are restricted to patients with moderate to severe (Goodwin, 2009; Kennedy & Emsley, 2006) depression on 25–50 mg/d agomelatine. Antidepressant response increases with an increase in baseline severity of depression (Kasper & Hamon, 2009), although there are reports that do not support this view (Lôo *et al.* 2002; Stahl *et al.* 2010).

There is lack of published data regarding agomelatine's efficacy in treatment of mildly depressed patients. Most randomized control trials (RCTs) lasted 6–8 wk and reported agomelatine having better efficacy than placebo (Kennedy & Emsley, 2006; Olié & Kasper, 2007; Stahl *et al.* 2010) and fluoxetine (Hale *et al.* 2010), and comparable efficacy to sertraline (Kasper *et al.* 2010) and venlafaxine (Lemoine *et al.* 2007). Agomelatine has also demonstrated sustained antidepressant efficacy for up to 6 months relative to placebo (Kennedy & Rizvi, 2010) and relapse prevention during a 10-month follow-up treatment continuation phase (Kennedy, 2009).

### Sleep, circadian rhythm and melatonergic compounds

The sleep-inducing effect of melatonin was discovered as early as 1958 (Lerner *et al.* 1958) when given in a large dose (Nordlund & Lerner, 1977). A meta-analysis in 2005 (Brzezinski *et al.* 2005) confirmed that melatonin helps in reducing time to fall asleep and sleep efficiency. This can be attributed to improvement in regulation of circadian rhythm through the melatonergic pathway and thereby has implications for the treatment of seasonal affective disorder (Pjrek *et al.* 2007).

Since melatonin has very short half-life of 20–30 min (Claustrat *et al.* 2005), attempts have been made to develop melatonin analogues with longer half-lives like LY-156735, ramelteon, tasimelteon, agomelatine and slow-release formulation circadin (Srinivasan *et al.* 2011). The latter was approved for sleep by the European drug regulatory authority in 2007 (EMEA, 2007).

As agomelatine mediates its action through MT<sub>1</sub> and MT<sub>2</sub> receptors involved in the regulation of circadian rhythm, it promotes and maintains sleep during the night, and helps in maintaining alertness during day time. Improvement in all aspects of sleep were observed as early as the first week of a randomized trial with agomelatine in contrast to treatment with venlafaxine and sertraline (Kasper *et al.* 2010).

### Side-effects

It has been suggested that agomelatine has side-effect and safety profiles better or similar to other antidepressants, including neutral effects on sexual function, bodyweight and the absence of discontinuation symptoms (De Berardis *et al.* 2011; Kennedy & Rizvi, 2010; Lam, 2008; Montgomery *et al.* 2004). However, more frequent and more severe treatment-related adverse events have been reported with higher dose of agomelatine (Lôo *et al.* 2003). Documentation of 3-fold elevations of transaminase enzymes were more common in the agomelatine group compared to placebo group (EMA, 2009) during a phase III trial and this has raised concerns for regulatory authorities. Agomelatine requires monitoring of liver function tests during the first 24 wk of initiation and then as clinically indicated, and is contraindicated in patients with impaired liver function (Green, 2011).

### Objectives

A PubMed literature search for meta-analyses on agomelatine retrieved two publications, the first (Montgomery & Kasper, 2007) focused on pooled results from three trials and the second (Serretti & Chiesa, 2009) on sexual dysfunction. Most of the quality published reports included in this analysis have emerged since the publication of the above papers. Accordingly, the main objective of this analysis is to evaluate evidence of the efficacy of agomelatine in the treatment of MDD compared to placebo and established antidepressant medications and ascertain its clinical relevance.

### Data source

The PubMed database was searched on 6 April 2011 and updated on 28 June 2011 for all RCTs in depressive disorder on agomelatine and melatonin to date. Checks were also made if there were additional publications available from other databases that included CINAHL, Cochrane Library, EMBASE and PsycINFO. English key words were used for search without language restriction.

### Study selection

Selection criteria included (i) primary research trials involving (ii) head-to-head comparison of agomelatine with placebo or other antidepressants in (iii) a randomized sample of (iv) cases with criteria-based diagnosis of MDD (v) applying a double-blind method of

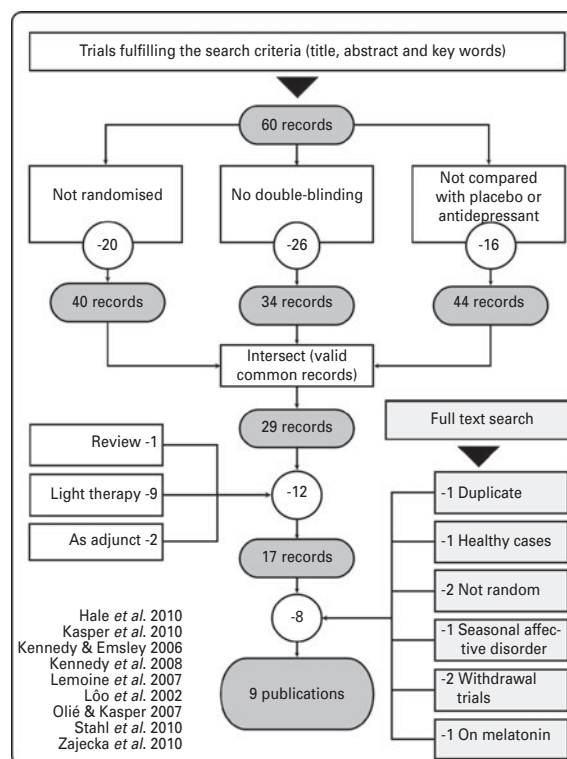


Fig. 1. Study selection process.

assessment to (vi) measure change in depressive symptoms using standardized scales (Fig. 1). Two of the authors (S. P. S., V. S.) separately applied inclusion and exclusion criteria, and decisions on acceptance or rejection of discordant selections were reached through consensus agreement involving the third author (N. K.). The electronic search retrieved 60 records which were verified for randomization, blinding and placebo or active drug comparison that generated a list of 29 trials (Fig. 1). Further screening of the list found a review paper (Howland, 2007), two publications on agomelatine as adjunct medication (Dolberg *et al.* 1998; Grunhaus *et al.* 2001) and nine papers on light therapy (Danilenko & Putilov, 2005; Epperson *et al.* 2004; Goel *et al.* 2005; Jacobsen *et al.* 1987; Koorengel *et al.* 2001; Lieverse *et al.* 2011; Loving *et al.* 2005; Lu *et al.* 2005; Wirz-Justice *et al.* 1996) and they were deemed unsuitable and therefore excluded. A full text search resulted in removal of one duplicate article (Lôo *et al.* 2003), one trial (Kellner *et al.* 1997) on healthy volunteers and two non-randomized trials (Lewy *et al.* 1998; Lieverse *et al.* 2011). There were two trials (Goodwin *et al.* 2009; Montgomery *et al.* 2004) assessing the effects of withdrawal from agomelatine in patients who had previously responded to agomelatine. These studies were

also excluded as this approach was considered biased for the purpose of measuring treatment efficacy after initiation. To conform with the diagnostic category of MDD and specific therapeutic intervention with agomelatine, one trial on seasonal affective disorder (Leppämäki *et al.* 2003) and one on melatonin (Serfaty *et al.* 2010) were excluded (Fig. 1) from the final list.

Search for completed or partially completed clinical trials on agomelatine for depression on the web retrieved three trials from the USA (<http://www.clinicaltrials.gov/ct2>), six from Europe (<http://www.clinicaltrialsregister.eu>), two from India (<http://www.ctri.nic.in/Clinicaltrials>) and eight from the WHO site (<http://apps.who.int/trialsearch/>). All records from the USA site were included in the WHO search results. Details provided on the sites were inadequate to contact the investigators, except those from the USA. Results of one of the trials (NCT00411242) from the USA Clinical Trial Register have already been published and are included in this study (Stahl *et al.* 2010). We requested results of two other trials from the investigators without success.

#### Data extraction

All of nine primary publications (Hale *et al.* 2010; Kasper *et al.* 2010; Kennedy & Emsley, 2006; Kennedy *et al.* 2008; Lemoine *et al.* 2007; Lôo *et al.* 2002; Olié & Kasper, 2007; Stahl *et al.* 2010; Zajecka *et al.* 2010) in the final list had an optimum dataset for determination of effect size as standardized mean difference (SMD). Information about relevant sample parameters that were likely to influence the main outcome measure of change in depression scores on rating scales was also extracted. The retrieved set of parameters consisted of the average number depressive episodes, proportion of cases with first episode, mean duration of index episodes, proportion of male patients, mean age of sample, and mean duration of illness. Difference between post- and pre-trial symptom mean scores and their pooled standard deviation for agomelatine and control groups were extracted for all individual trials. The SMD between agomelatine and control groups represents the effect size for that trial, and an effect of negative magnitude represents response in favour of agomelatine. A default correlation coefficient of  $r=0.5$  was used if needed as association between pre- and post-trial scores to compute the standard deviation for repeated measures (Singh *et al.* 2010; Winkley *et al.* 2006). Defined daily dose (DDD) of agomelatine and drug in control groups was determined using WHO criteria (WHO, 2010).

#### Statistical analysis

The Linux (Ubuntu 10.04-LTS) based statistical software packages available with R-programming language (R Development Core Team, 2011) were used for analysis. These included meta-analysis package METAFOR (Viechtbauer, 2010) and MICE (multi-variate imputation by chained equations) (van Buuren & Groothuis-Oudshoorn, 2010) for predictive-mean-matching imputation of missing values. Publication bias (fail-safe  $N$ ) was calculated using Stouffer's method (inverse square) (Rosenthal, 1991) for combined significance level set to fail at a  $p$  value of 0.05. Lack of residual heterogeneity (QE) was a prerequisite for application of a fixed-effects (FE) model, and restricted maximum-likelihood (REML) estimation model with iterations (Cooper, 2009; Viechtbauer, 2005) was applied if the QE test failed at a level of  $p < 0.05$ . Baseline severity of depression was measured as the ratio between mean score on depression rating scale with standard deviation for individual trials.

Intent-to-treat (ITT) analysis was performed on a full analysis set (FAS) of all selected trials with last observation carried forward (LOCF) from all randomized patients who received at least one study medication and one post-baseline assessment. In one study (Stahl *et al.* 2010), three patients were excluded as they were subsequently randomized to another agomelatine trial; and LOCF was used only for any further dropouts. Analyses were performed for each individual dose of agomelatine (DDD: 0.04, 0.02, 1.0, 1.5, 2) in the placebo group, and studies with agomelatine dose  $\geq 1$  DDD were grouped together in the antidepressant group to manage bias arising from multiple comparisons with common placebo control arm in three studies (Lôo *et al.* 2002; Stahl *et al.* 2010; Zajecka *et al.* 2010).

#### Data synthesis

All trials in the final list fulfilled DSM-IV diagnostic criteria of MDD (APA, 2000) except for one intervention (Lôo *et al.* 2002) which included depression from bipolar disorder. The Hamilton Depression Rating Scale (HAMD) was used to measure change in severity of depression in all trials except for one (Kennedy *et al.* 2008) that used the Montgomery-Asberg Depression Rating Scale (MADRS). Patients entering all trials had a minimum score of  $\geq 19$  on HAMD and MADRS fulfilling the criterion for severe depression in accord with the standard adopted by the *Handbook of Psychiatric Measures* (APA, 2008). Information on the proportion of cases with first

**Table 1.** General characteristics of included studies

Cites	Authors (year)	Rating scale	Entry score	Ago (n)	Control (n)	Depression score (Ago)	Depression score (control)	Severity*	Ago DDD	Control	Control DDD	Trial weeks	No. of episodes	Illness duration (yr)	Mean age (yr)	Males proportion
1	Lôo <i>et al.</i> (2002)	HAMD <sub>17</sub>	>21	136	136	27.90	27.40	9.05	0.04	Placebo		8	2.70	4.80	42.30	0.34
2	Lôo <i>et al.</i> (2002)	HAMD <sub>17</sub>	>21	146	136	27.30	27.40	9.60	0.20	Placebo		8	2.70	4.80	42.30	0.34
3	Lôo <i>et al.</i> (2002)	HAMD <sub>17</sub>	>21	135	136	27.40	27.40	9.44	1.00	Placebo		8	2.70	4.80	42.30	0.34
4	Kennedy & Emsley (2006)	HAMD <sub>17</sub>	>21	106	105	26.50	26.70	9.18	1.50	Placebo		6	2.60	5.00	42.20	0.40
5	Olié & Kasper (2007)	HAMD <sub>17</sub>	>21	116	119	27.40	27.20	10.13	1.50	Placebo		6	2.65	2.51	45.00	0.35
6	Stahl <i>et al.</i> (2010)	HAMD <sub>17</sub>	>21	158	163	26.80	26.40	8.57	1.00	Placebo		8	5.24	4.80	43.10	0.34
7	Stahl <i>et al.</i> (2010)	HAMD <sub>17</sub>	>21	161	163	26.80	26.40	8.46	2.00	Placebo		8	5.30	4.80	43.40	0.36
8	Zajacka <i>et al.</i> (2010)	HAMD <sub>17</sub>	>21	156	166	26.10	26.40	4.90	1.00	Placebo		8	6.08	4.80	43.80	0.33
9	Zajacka <i>et al.</i> (2010)	HAMD <sub>17</sub>	>21	160	166	26.60	26.40	4.52	2.00	Placebo		8	6.04	4.80	43.80	0.33
10	Hale <i>et al.</i> (2010)	HAMD <sub>17</sub>	>24	247	257	28.50	28.70	11.00	1.28	Fluoxetine	1.23	8	2.50	4.90	42.30	0.33
11	Lôo <i>et al.</i> (2002)	HAMD <sub>17</sub>	>21	136	144	27.90	27.30	8.57	0.04	Paroxetine	1.00	8	2.70	4.80	42.30	0.34
12	Lôo <i>et al.</i> (2002)	HAMD <sub>17</sub>	>21	146	144	27.30	27.30	9.04	0.20	Paroxetine	1.00	8	2.70	4.80	42.30	0.34
13	Lôo <i>et al.</i> (2002)	HAMD <sub>17</sub>	>21	135	144	27.40	27.30	8.89	1.00	Paroxetine	1.00	8	2.70	4.80	42.30	0.34
14	Kasper <i>et al.</i> (2010)	HAMD <sub>17</sub>	>21	150	157	26.10	26.50	9.05	1.50	Sertraline	1.50	6	2.90	4.70	43.90	0.29
15	Lemoine <i>et al.</i> (2007)	HAMD <sub>17</sub>	>19	165	167	25.90	26.00	7.99	1.50	Venlafaxine	1.38	6	2.20	4.80	40.10	0.29
16	Kennedy <i>et al.</i> (2008)	MADRS	>19	137	139	27.90	27.90	6.41	2.00	Venlafaxine	1.50	12	2.35	2.95	40.90	0.28

Ago, Agomelatine; HAMD<sub>17</sub>, 17-item Hamilton Depression Rating Scale; MADRS, Montgomery–Asberg Depression Rating Scale; DDD, defined daily dose; Duration (yr), total duration of illness; Severity, severity of depression.

Empty cells represent missing values that required imputation for meta-regression.

Cite numbers match Id numbers in Figs 1–3.

Total sample size: agomelatine group ( $n=2390$ ), control group ( $n=1553$ ), after excluding multiple treatment comparisons.

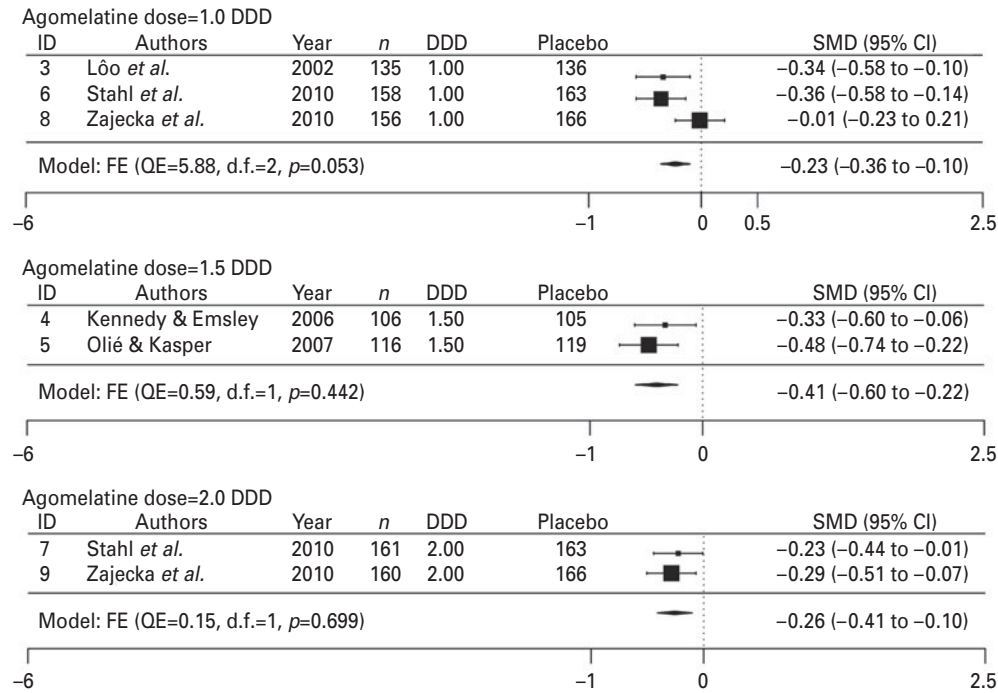


Fig. 2. Efficacy of agomelatine compared to placebo. Negative standardized mean difference (SMD) favours agomelatine. DDD, Defined daily dose.

episode and duration of index episode were lacking in many studies and hence excluded from regression analysis.

One of the trials (Lôo et al. 2002) compared three different dose of agomelatine with paroxetine and placebo, and another two (Stahl et al. 2010; Zajecka et al. 2010) compared two different doses of agomelatine with placebo. Accordingly, there were 16 comparisons from nine primary publications involving 2390 patients on agomelatine and 1553 patients in control groups mostly undergoing trial for a period of 6–8 wk. Mean age of the samples varied between 40 yr and 45 yr, with a predominance of female patients, and with illness severity between 4.5 and 11 (Table 1).

#### Agomelatine vs. placebo

There were five trials in this category with 1274 patients in the agomelatine group and 689 in the placebo group. Subgroup analyses performed for each dose of agomelatine demonstrated lack of heterogeneity and superiority of agomelatine over placebo (Fig. 2, Table 3). This superiority ranged between SMD  $-0.23$  for 1 DDD agomelatine to SMD  $-0.41$  for 1.5 DDD agomelatine. These results were statistically significant, in particular the 1.5 DDD agomelatine was

significant at  $p < 1.92 \times 10^{-5}$ . After exclusion of the trial (Lôo et al. 2002) that also included cases of bipolar depression type II, the reduced effect size for the recommended dose of agomelatine (1.0 DDD) became non-significant (QE = 4.73, d.f. = 1, QE $p$  = 0.03, REML model, SMD  $-0.18$ ,  $p$  = 0.28). Grouping of all trials on agomelatine ( $n$  = 1274) and comparing to placebo ( $n$  = 689) also produced a small but statistically significant size (SMD  $-0.26$ ,  $p$  =  $3.48 \times 10^{-11}$ ). Interpretation of this result requires caution because of multiple comparisons with the same placebo groups (Lôo et al. 2002; Stahl et al. 2010; Zajecka et al. 2010).

#### Agomelatine vs. antidepressants

Analysis of data from five trials on 834 patients in the agomelatine ( $\geq 1.0$  DDD) group and 864 patients on antidepressants in the control group (fluoxetine, paroxetine, sertraline, venlafaxine) demonstrated marginal superiority of agomelatine over the antidepressant group (SMD  $-0.11$ ,  $p$  = 0.02) (Fig. 3, Table 3). There was very little difference in the result (QE = 2.47, d.f. = 3, QE $p$  = 0.48, FE model, SMD  $-0.13$ ,  $p$  = 0.02) after exclusion of the trial (Lôo et al. 2002) that comprised in part of bipolar depression type II cases. Summarized effect size from venlafaxine trials were also non-significant (SMD  $-0.07$ ,  $p$  = 0.39).

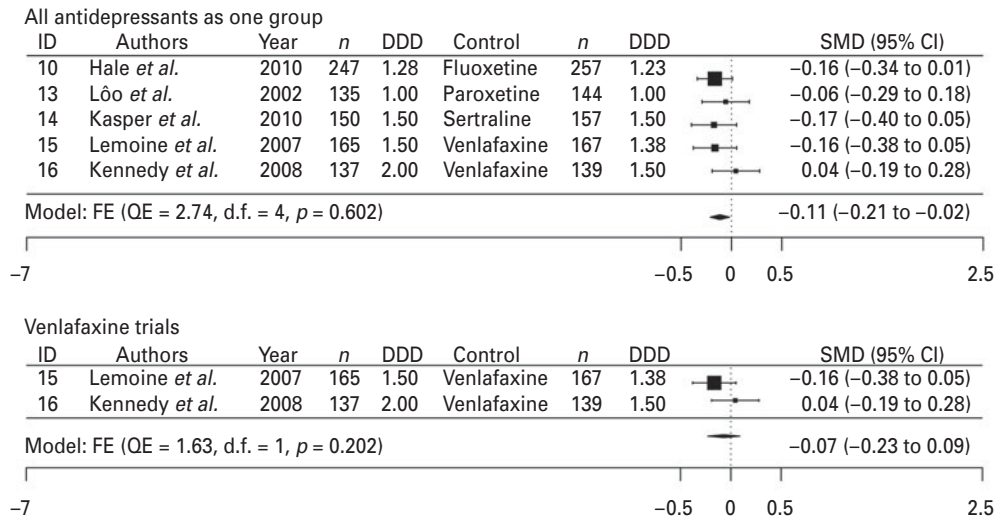


Fig. 3. Efficacy of agomelatine compared to antidepressants. Negative standardized mean difference (SMD) favours agomelatine. DDD, Defined daily dose.

**Influence of moderators on effect size**

Moderators used for meta-regression consisted of mean dose of agomelatine, trial period, number of episodes, duration of illness, age, proportion of males in sample, and severity of depression at entry into trial (Table 2). The dataset from comparison of agomelatine with placebo, revealed some statistically significant estimates of appreciable magnitude indicating that younger patients (estimate 4.11) with more frequent episodes (estimate -1.08) and shorter duration of illness (estimate 5.59) were likely to respond favourably to agomelatine. No such trend was apparent in the group comparing agomelatine with antidepressants.

**Sensitivity analysis**

Effects sizes of comparisons between the agomelatine and placebo groups did not require trim-filling and their respective fail-safe N scores (11, 12, 6) were considerably larger than number of trials (3, 2, 2) included in the analysis (Table 3). This rules out any significant publication bias and the results appear to be stable as evident from statistically significant boot-strapped confidence intervals. In contrast, results from comparison with antidepressants had a fail-safe N score (FSN 5) equal to the number of trials (n = 5) included in the analysis, and required trim-filling; and therefore publication bias cannot be ruled out. However, the boot-strapped confidence intervals still confirm marginal superiority of agomelatine over antidepressants. Taking these various factors into account, this marginal superiority over antidepressants seems to be of suspect value. Non-parametric randomized

Table 2. Meta-regression: influence of moderators

	Estimate	p
<b>Agomelatine vs. placebo</b>		
Intercept	-180.82	0.02
Agomelatine dose in DDD	-0.16	0.16
Duration of trials (wk)	-1.00	0.12
Number of episodes	-1.08	0.02
Duration of illness (yr)	5.59	0.03
Sample mean age (yr)	4.11	0.02
Proportion of males	-41.42	0.10
Severity of depression	0.50	0.06
<b>Agomelatine vs. antidepressants</b>		
Intercept	2.93	0.50
Agomelatine dose in DDD	-0.10	0.53
Duration of trials (wk)	0.02	0.72
Number of episodes	0.50	0.61
Duration of illness (yr)	-0.07	0.77
Sample mean age (yr)	-0.10	0.60

DDD, Defined daily dose.

confidence intervals reported in this analysis are derived from 25 000 resamples with replacement (Table 3). There was definite evidence of pharmaceutical sponsorship for all trials with the exception of one publication (Lôo *et al.* 2002) for which no sponsorship disclosure was made.

**Dropouts and adverse effects**

The effect size in terms of risk difference (RD) from meta-analysis of drug-related dropouts as a function

**Table 3.** Sensitivity analysis

Cluster	Agomelatine	Comparator	Trials	<i>n</i>	QE	QEp	Method	SMD	<i>p</i>	FSN	Trim-fill	95% BCI
1	DDD=0.04	Placebo	1	272				-0.36	0.00			
2	DDD=0.2	Placebo	1	282				-0.07	0.56			
3	DDD=1.0	Placebo	3	914	5.88	0.05	FE	-0.23	0.00	11	0	-0.35 to -0.01
4	DDD=1.5	Placebo	2	446	0.59	0.44	FE	-0.41	0.00	12		-0.48 to -0.41
5	DDD=2.0	Placebo	2	650	0.15	0.70	FE	-0.26	0.00	6		-0.29 to -0.26
6	All doses	<b>Placebo</b>	9	2564	12.39	0.13	FE	-0.26	0.00	142	0	-0.34 to -0.15
7	DDD=0.04	Paroxetine	1	280				-0.07	0.55			
8	DDD=0.2	Paroxetine	1	290				0.22	0.07			
9	≥1 DDD	Antidepressants	5	1698	2.74	0.60	FE	-0.11	0.02	5	0	-0.17 to -0.02
10	≥1 DDD	Venlafaxine	2	608	1.63	0.20	FE	-0.07	0.39	0		-0.16 to -0.07
11	All doses	<b>Antidepressants</b>	7	2268	9.47	0.15	FE	-0.07	0.11	0	1	-0.14 to 0.07
12	All doses	<b>Placebo + antidepressants</b>	16	4832	33.34	0.00	REML	-0.17	0.00	196	0	-0.24 to -0.08

DDD, Defined daily dose; *n*, sample size; QE, test of residual heterogeneity; QEp, *p* value of QE; SMD, standardized mean difference; FSN, fail-safe *N* score; FE, fixed-effects model; REML, restricted maximum-likelihood estimation model – a type of random-effects model.

Trim-fill, After trim-filling, effect size and statistical significance remained very close to results without trim-filling.

BCI, 95% non-parametric bootstrapped confidence interval from 25 000 resamples with replacement.

All *p* values are greater than 0.

Antidepressants, Non-placebo comparison group consists of trials using fluoxetine, paroxetine, sertraline and venlafaxine.

Cluster 6: All trials comparing agomelatine with placebo. Total sample size = 1963 (1274 + 689) after exclusion of multiple treatment comparisons.

Cluster 11: All trials comparing agomelatine with with antidepressants. Total sample size = 1980 (1116 + 864) after exclusion of multiple treatment comparisons.

Cluster 12: Includes all trials from clusters 6 and 7. Total sample size = 3943 (2390 + 1533) after excluding multiple treatment comparisons.

of sample size in each arm was significantly small with agomelatine (4%) compared to antidepressants (9%) (RD -0.044, *p* = 0.005) and non-significant compared to placebo (agomelatine 5%, placebo 5%; RD -0.002, *p* = 0.888). Drug-related dropouts as a function of total dropouts in each arm were not significant for either group (agomelatine 25%, placebo 27%; RD -0.003, *p* = 0.948; and agomelatine 30%, antidepressants 42%; RD -0.122, *p* = 0.072). Difference in prevalence of adverse events of 66% and 62%, respectively in agomelatine and placebo groups (RD 0.004, *p* = 0.873), and 48% and 54% in agomelatine and antidepressant groups, respectively (RD -0.74, *p* = 0.056) were statistically non-significant. The total numbers of dropouts in agomelatine and control arms were missing in one trial (Kennedy *et al.* 2008) and this required imputation with mean value. All studies included in these analyses were homogeneous and meta-analytical results are based on fixed-effects model.

During trial periods of included studies there were three suicides: one in a participant on agomelatine

(total sample 1745), one on antidepressants (total sample 875) and one on placebo (total sample 703). There were 21 incidents of parasuicide: ten in patients on placebo, eight on agomelatine and three on antidepressants.

## Conclusions

Based on a pooled sample of 1963 (agomelatine 1274, placebo 689) patients from five large randomized placebo-controlled trials in MDD, agomelatine in all three dosages demonstrated significantly better efficacy than placebo (DDD 1.0, SMD -0.23; DDD 1.5, SMD -0.41; DDD 2.0, SMD -0.26). Two of these three results from agomelatine (DDD 1.5 and 2.0) remained consistent even after exclusion of the trial that also included cases of bipolar depression type II. The effect sizes of trials with placebo in the control arm were symmetrically distributed, fail-safe *N* scores of summary effect size was relatively high, and their statistical significance was maintained on bootstrapping.



The effect size from 1.5 DDD agomelatine was more pronounced than the other dosages and its statistical significance was high ( $p = 1.92 \times 10^{-5}$ ).

Agomelatine had marginal superiority (SMD  $-0.11$ ) over the group of antidepressants (fluoxetine, paroxetine, sertraline, venlafaxine). The results were not statistically significant for any individual antidepressant in this analysis. However, using alternative criteria and techniques, authors of four (Hale *et al.* 2010; Kasper *et al.* 2010; Lemoine *et al.* 2007; L o *et al.* 2002) of five included research papers on antidepressants concluded that their trials demonstrated improved efficacy with agomelatine. As described in the Results section, the effect size observed for this group is not only fragile but also lacks clinical relevance SMD  $-0.11$ .

Loss of statistical significance after exclusion of the trial with the sample partially comprised of bipolar depression type II cases in the placebo comparison group with agomelatine (DDD 1.0) raises the possibility that agomelatine may be more effective in bipolar disorder depression. However, this observation requires confirmation through more direct research-based evidence.

Findings of this analysis match reports of a previous review (Montgomery & Kasper, 2007) published in 2007 from three trials on over 300 cases of severe depression in both agomelatine and control groups. However, SMDs achieved in both of these analyses fall well below the acceptable level of clinical significance (0.50) for efficacy (NICE, 2004). Two recent meta-analyses concluded that efficacy of antidepressants reaches clinical relevance (SMD  $\geq 0.50$ ) only for patients with a depression rating score of  $>24$  (Fournier *et al.* 2010) or  $>28$  (Kirsch *et al.* 2008) on HAMD. In contrast, although all trials included in this analysis had mean baseline severity scores in the range of very severe depression (HAMD  $>26$ ), their effect size reached only 50% of the expected magnitude in the placebo comparison group and only 25% in the randomized antidepressant comparison group.

Moreover, some of scales may rely more heavily on rating of sleep-related symptoms (e.g. three questions in HAMD *vs.* one question in MADRS) – symptoms that may respond better to agomelatine (Kasper *et al.* 2010; Lemoine *et al.* 2007) as a melatonergic compound. This partial response can manifest as a small improvement in depression rating score up to 6 points on HAMD and the desired level of statistical significance can be achieved by increasing the sample size.

Eight of 12 main comparisons had used agomelatine in dose range above the DDD of 25 mg and eight of nine trials had sponsorship from the pharmaceutical

industry. There are indications from meta-regression that younger patients with more frequent episodes and shorter duration of illness are more likely to respond favourably to agomelatine. However, there is uncertainty about its utilization as very little difference exists among the included trials in terms of age, number of episodes and duration of illness.

There is scope for further trials on agomelatine as adjunct in MDD, in treatment of resistant depression, and in dysthymia as evident from a recent publication (Di Giannantonio *et al.* 2011). Irrespective of the statistical fragility of efficacy of agomelatine over antidepressants and the small effect size in severe to very severe depression (APA, 2008), there is scope to consider the use of agomelatine in treatment-resistant depression. However, these assumptions require evidence-based validation.

Melatonin is a natural melatonergic substance secreted from pineal body. This is available as a food product in many countries and its slow-release formulation is now available in Europe as a licensed product for sleep in people aged  $>55$  yr (EMA, 2007). Only one (Serfaty *et al.* 2010) of three RCTs on melatonin involved 31 patients with MDD and its small effect size (SMD 0.10) was statistically non-significant ( $p = 0.78$ ). However, number of patients in this trial was too low to detect small difference and cannot be treated as conclusive. By logical extension, melatonin should have a similar effect as agomelatine and vice versa, and melatonin and its analogues may have therapeutic potential as well.

In summary, agomelatine is superior to placebo in treatment of depressive episodes of MDD. However, it is questionable if its effect size is clinically relevant for the general clinic population.

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### Statement of Interest

None.

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