Online supplements to Koesters *et al*. Agomalatine efficacy and acceptability revisited…*Br J Psychiatry* doi: 10.1192/bjp.bp.112.120196

Online supplement DS1 Protocol for a systematic review, Ulm, Jan 17, 2011

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OBJECTIVES

(1) To determine the acute and long term efficacy of agomelatine in the treatment of unipolar major depression compared to placebo.

(2) To review the acceptability of agomelatine in comparison to placebo.

METHODS

Types of studies

This systematic review will include only published and unpublished double-blind parallel-group randomised controlled trials. For trials with a crossover design only results from the first randomisation period will be considered.

Types of participants

Studies in adult patients (>18 years) with a primary diagnosis of unipolar major depression according to DSM-III (1), DSM- III-R (2), DSM-IV (3), DSM- IV-TR (4), ICD- 10 (5), Feighner (6) or Research Diagnostic Criteria (7) will be included. Studies including patients with a concurrent primary diagnosis of Axis I or II disorders and antidepressant trials in depressive participants with a serious concomitant medical illness will be excluded.

Types of interventions

Trials comparing agomelatine with placebo as monotherapy in the acute and long term treatment of depression will be included. Only treatment arms within the therapeutic dose range of agomelatine (25-50mg/d) will be included. No restriction in pharmaceutical form or dose regimen (fixed or flexible) will be applied.

Types of outcome measures

Primary outcome

Acute-phase studies: The primary outcome measure for acute phase studies will be the group mean scores at the end of the trial, or group mean change from baseline to endpoint, on Hamilton Depression Rating Scale (HDRS).

Long-term studies: The primary outcome for long term studies will be the proportion of patients who relapsed during the follow-up treatment period. Any definition of depression relapse will be included.

Secondary outcomes

¬ Group mean scores at the end of the trial, or group mean change from baseline to endpoint, on HDRS, Montgomery-Asberg Depression Scale (MADRS) or Clinical Global Impression Rating scale (CGI), or on any other depression rating scale. When trials reported results from more than one rating scale, we used the HDRS results or, if not available, the MADRS results or, if not available, the results at any other depression rating scale.

¬ Treatment responders, that is the proportion of patients showing a reduction of at least 50% at the HDRS or MADRS or at any other depression scale (e.g. the Beck Depression Inventory or the CES-D scale; or were 'much or very much improved' (score 1 or 2) at the Clinical Global Impression-Improvement (CGI-I), or proportion of patients who improved using any other pre-specified criterion.

¬ Treatment remitters, that is the proportion of patients showing remission as defined by: a score of 7 or less at the 17-item HDRS, or 8 or less at longer versions of HDRS; 10 or less at the MADRS; 'not ill or borderline mentally ill' on the CGI-S; or any other equivalent value on a depression scale defined by the authors. Preference will be given to remission rates defined by HDRS or MADRS scores.

Acceptability will be evaluated using the following outcome measures:

¬ Total number of participants who dropped out during the trial as a proportion of the total number of randomised participants: total dropout rate.

¬ Number of participants who dropped out due to inefficacy during the trial as a proportion of the total number of randomised participants.

¬ Number of participants who dropped out due to side effects during the trial as a proportion of the total number of randomised participants.

¬ Total number of participants experiencing at least some side effects.

Search methods for identification of studies

Literatures searches will be performed in the following databases and article indexes: MEDLINE, CINAHL, EMBASE, PsycInfo, Cochrane Central Register of Controlled Trials (CENTRAL). Controlled vocabulary was utilized where appropriate terms were available, supplemented with keyword searches to ensure accurate and exhaustive results. Language or publication year limits were not applied to any search (Appendix for details).

To supplement the searches of published research, the internet will also be utilized to locate additional clinical trials, unpublished research and/or grey literature. Websites of pharmaceutical companies, clinical trials registers and regulatory agencies will be searched.

Data collection

Selection of studies

Included and excluded studies will be collected following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA, 8). We will examine all titles and abstracts first, and then obtain full texts of potentially relevant papers. Working independently and in duplicate, two reviewers will read the papers and determined whether they met inclusion criteria. Considerable care will be taken to exclude duplicate publications.

Data extraction and management

Two review authors will use an electronic data extraction form (EPIDATA) to independently extract the data concerning participant characteristics, intervention details and outcome measures. Disagreements will be resolved by discussion and consensus with a third member of the team.

For continuous outcomes, the mean change from baseline to endpoint, the mean scores at endpoint, the SD or standard error (SE) of these values, and the number of patients included in these analyses, will be extracted (9). Data will be extracted preferring the 17-item HDRS over any other version of the HDRS over the MADRS and over the CGI.

For dichotomous outcomes, the number of patients undergoing the randomization procedure, the number of patients rated as responders, remitters, relapsed and the number of patients leaving the study early will be recorded.

Assessment of risk of bias in included studies

The Cochrane risk-of-bias tool will be used (10). This instrument consists of six items. Two of the items assess the strength of the randomization process in preventing selection bias in the assignment of participants to interventions: adequacy of sequence generation and allocation concealment. The third item (blinding) assesses the influence of performance bias on the study results. The fourth item assesses the likelihood of incomplete outcome data, which raise the possibility of bias in effect estimates. The fifth item assesses selective reporting, the tendency to preferentially report statistically significant outcomes. This item requires a comparison of published data with trial protocols, when such are available. The final item refers to other sources of bias that are relevant in certain circumstances, such as, for example, sponsorship bias.

Summary statistics

A double-entry procedure will be employed. Data will be initially entered and analyzed using the Cochrane Collaboration's Review Manager software version 5 (Oxford, England, Cochrane Collaboration), and subsequently entered into a spreadsheet and re-analyzed using the 'metafor' package (11). Outputs were cross-checked for internal consistency.

Continuous data

Despite some critics (12), the HDRS is still the 'gold standard' for assessing antidepressant efficacy in clinical trials. Furthermore, clinical interpretation of results from metaanalysis is greatly simplified if effect sizes are calculated as (raw) mean differences (MD). Consequently, the primary outcome (acute treatment studies) data will be analysed using a mean difference and only scores from the HDRS will be pooled together. As secondary outcome, data will further be analysed using standardised mean differences (SMD), as scores from different depression scales will be pooled. If endpoint data are unavailable, change score data will be used. Where intention-to-treat (ITT) data is available it will be preferred to 'per-protocol analysis'. When only P or standard error (SE) values are reported, standard deviations will be calculated (13).

Dichotomous outcomes

For the primary outcome (long term studies) and for all secondary binary outcomes we will calculate a Mantel-Haenszel risk ratio (RR). Response, remission and relapse on treatment will be calculated using an ITT analysis. Where participants left the study before the intended endpoint, it will be assumed that they have experienced the negative outcome. When outcome data are not reported, trial authors will be asked to supply the data; in case of no response from study authors, we will estimate the number of patients responding to treatment using a validated imputation method (14;15). The robustness of this approach will be checked by sensitivity analysis.

Confidence intervals

A 99% confidence interval (CI) will be calculated for all efficacy estimates according to Barbui and colleagues (16). This approach, instead of a 95% CI approach, will be adopted to have the widest estimate of likely true effect. We set the level of significance at 0.01 as we will make multiple comparisons and we reasoned that only robust differences between treatments should inform clinical practice. In fact, it is more important to avoid the possibility of showing a difference in the absence of a true difference, than to avoid the possibility of not showing a difference in the presence of a true difference. In other words, we give priority to avoid a type I than a type II error (17). Conversely, a 95% CI will be calculated for all tolerability estimates. In terms of tolerability it is more important to avoid the possibility of not showing a difference in the presence of a true difference than to avoid the possibility of showing a difference in the absence of a true difference. In other words, we give priority to avoid a type II than a type I error.

Studies with multiple treatment groups

For dichotomous outcomes, trials comparing different doses of agomelatine with placebo were converted into two-arm trials by summing samples and averaging doses. For continuous outcomes,

means and standard deviations of different dosage arms are combined into a single arm according to the methods described in the Cochrane handbook (10, Chapter 7.7.3.8).

Assessment of heterogeneity

Visual inspection of graphs will be used to investigate the possibility of statistical heterogeneity. This will be supplemented using the I-squared statistic. This provides an estimate of the percentage of variability due to heterogeneity rather than chance alone. Where the I-squared estimate is greater than or equal to 50% we interpreted this as indicating the presence of high levels of heterogeneity (18). Statistical significance of heterogeneity will additionally be tested with chi-square tests, using a threshold of $p<0.20$ as threshold of statistical significance.

Assessment of publication bias

Funnel plots will be used to investigate publication bias.

Data synthesis and presentation

Continuous and dichotomous outcomes will be analysed using a random-effects-model, as this takes into account any differences between studies even if there is no statistically significant heterogeneity (10). A fixed-effects model will be routinely applied to check for material differences.

A summary of findings (SoF) table will be produced according the methodology described by the GRADE working group (19;20).

Subgroup and sensitivity analysis

The following pre-planned subgroup and sensitivity analyses will be carried out: (a)

Agomelatine dosing (low dosage: 25 mg/d vs. flexible doses and 50mg/d)
(b) Publication status (published vs unpublished studies)
(c) Exclusion of trials with imputed data from responder analyses

Funding

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References

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11. Viechtbauer W. (2010) Conducting Meta-Analyses in R with the metafor Package. Journal of Statistical Software 36:1-48.

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Appendix

Search strategy

1 exp Neurotic Disorders/
2 exp Depressive Disorder/
3 exp Depression/
4 depress$.ab,hw,ot,sh,ti.
5 neurotic disorder$.ab,hw,ot,sh,ti.
6 seasonal affective disorder$.ab,hw,ot,sh,ti.
7 dysthymi$.ab,hw,ot,sh,ti.
8 melancholl$.ab,hw,ot,sh,ti.
9 or/1-8
10 randomized controlled trial.pt.
11 controlled clinical trial.pt.
12 exp Randomized Controlled Trials/
13 random allocation.ab,hw,ot,sh,ti.
14 exp Random Allocation/
15 random$.ti.
16 exp Double-Blind Method/
17 exp Single-Blind Method/
18 ((singl$ or doubl$ or tripl$ or trebl$) and (blind$ or mask$ or dummy$)).ab,hw,ot,sh,ti.
19 (random$ and (trial or study)).ab,hw,ot,sh,ti.
20 or/10-19
21 (agomelatin$ or valdoxan or thymanax or melitor).mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, sh, kw, tn, dm, mf, dv, tc, id, tm]
22 9 and 20 and 21

Online supplement DS2

Search strategy

Last updated: *February 2012*

Search strategy

1 exp Neurotic Disorders/
2 exp Depressive Disorder/
3 exp Depression/
4 depress$.ab,hw,ot,sh,ti.
5 neurotic disorder$.ab,hw,ot,sh,ti.
6 seasonal affective disorder$.ab,hw,ot,sh,ti.
7 dysthymi$.ab,hw,ot,sh,ti.
8 melancholl$.ab,hw,ot,sh,ti.
9 or/1-8
10 randomized controlled trial.pt.
11 controlled clinical trial.pt.
12 exp Randomized Controlled Trials/
13 random allocation.ab,hw,ot,sh,ti.
14 exp Random Allocation/
15 random$.ti.
16 exp Double-Blind Method/
17 exp Single-Blind Method/
18 ((singl$ or doubl$ or tripl$ or trebl$) and (blind$ or mask$ or dummy$)).ab,hw,ot,sh,ti.
19 (random$ and (trial or study)).ab,hw,ot,sh,ti.
20 or/10-19
21 (agomelatin$ or valdoxan or thymanax or melitor).mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, sh, kw, tn, dm, mf, dv, tc, id, tm]
22 9 and 20 and 21

Search strategy for grey and unpublished literature

Public trial registers (clinicaltrials.com, http://www.controlled-trials.com/) and the Novartis Clinical Trial Results Database (http://www.novctrd.com) were searched for relevant trials. Reviews and the public assessment reports for agomelatine from the European Medical Agency (EMA) (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000656/WC500070527.pdf; http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000915/WC500046226.pd) and the Australian Therapeutic Goods Administration (http://www.tga.gov.au/pdf/auspar/auspar-valdoxan.pdf) were screened for further published and unpublished trials.

Online supplement DS3

References for excluded studies

No placebo control group

(1) Hale A, Corral RM, Mencacci C, Ruiz JS, Severo CA, Gentil V. Superior antidepressant efficacy results of agomelatine versus fluoxetine in severe MDD patients: a randomized, double-blind study. International Clinical Psychopharmacology 2010 Nov;25:305-14.

(2) Kasper S, Hajak G, Wulff K, Hoogendijk WJ, Montejo AL, Smeraldi E, et al. Efficacy of the novel antidepressant agomelatine on the circadian rest-activity cycle and depressive and anxiety symptoms in patients with major depressive disorder: a randomized, double-blind comparison with sertraline. Journal of Clinical Psychiatry 2010 Feb;71:109-20.

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(4) 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. Journal of Clinical Psychiatry 2007 Nov;68:1723-32.

(5) Quera-Salva M-A, Hajak G, Gall SKL, Nutt D. Efficacy and safety of agomelatine in patients with major depressive disorder compared to escitalopram: A randomized, double-blind study. International Journal of Neuropsychopharmacology 2010;13:June.

(6) Vasile D, Vasiliu O, Vasile ML, Terpan M, Ojog DG. Agomelatine versus selective serotoninergic reuptake inhibitors in major depressive disorder and comorbid diabetes mellitus. European Neuropsychopharmacology 2011;21:September-S384.

Double publication

(1) Goodwin GM, Rouillon F, Emsley R. Long-term treatment with agomelatine: Prevention of relapse in patients with Major Depressive Disorder over 10 months. European Neuropsychopharmacology 2008;18:August-S339.

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(3) Loo H, Dalery J, Macher JP, Payen A. Pilot study comparing in blind the therapeutic effect of two doses of agomelatine, melatoninergic agonist and selective 5HT2C receptors antagonist, in the treatment of major depressive disorders. [French]. [References]. L'Encephale: Revue de psychiatrie clinique biologique et therapeutique 2003 Mar;Vol.29:165-71.

(4) Quera-Salva M-A, Hajak G, Philip P, Montplaisir J, Keufer-Le GS, Laredo J, et al. Comparison of agomelatine and escitalopram on nighttime sleep and daytime condition and efficacy in major depressive disorder patients. International Clinical Psychopharmacology 2011;26:September-262.

Not within the dose range

(1) Loo H, Dalery J, Macher J-P, Payen A. Pilot study comparing in blind the therapeutic effect of two doses of agomelatine, melatoninergic agonist and selective 5HT_{2C} receptors antagonist, in the treatment of major depressive disorders. [French]. Encephale 2002;28:2002-362.

(2) Serfaty MA, Osborne D, Buszewicz MJ, Blizard R, Raven PW. A randomized double-blind placebo-controlled trial of treatment as usual plus exogenous slow-release melatonin (6 mg) or placebo for sleep disturbance and depressed mood. International Clinical Psychopharmacology 2010 May;25:132-42.

Ongoing

(1) Vahia V. Efficacy and safety of agomelatine with flexible dose (25 mg/day with blinded adjustment at 50 mg) given orally for 8 weeks in Indian outpatients with Major Depressive Disorder A randomised double-blind national multicentric study with parallel groups, versus sertraline (50 mg/day with blinded potential adjustment at 100 mg). EU Clinical Trials Register [www 2011;2010.

Withdrawl study

(1) Montgomery SA, Kennedy SH, Burrows GD, Lejoyeux M, Hindmarch I. Absence of discontinuation symptoms with agomelatine and occurrence of discontinuation symptoms with paroxetine: a randomized, double-blind, placebo-controlled discontinuation study. International Clinical Psychopharmacology 2004 Sep;19:271-80.

Excluded unpublished studies indentified by other sources:

Ongoing:

C2301 (NCT01110889)

C2302 (NCT01110902)

CL3-069 (ISRCTN10845256)

CL3-070 (ISRCTN57507360)

CL3-073 (ISRCTN97599615)

No placebo control group:

CL3-048 (ISRCTN 68222771)

CL3-056 (ISRCTN 44737909)

CL3-062 (ISRCTN 96725312)

CL3-063 (ISRCTN 55250367)

Not Major Depression:

CL3-029 (bipolar patients, no further information available)

Not in the specified dose range:

CL2-005 (ISRCTN 38378163)

Insufficient information:

CL3-027 - no further information available
CL3- 037 (Seasonal Affective Disorder, no further information available)

Online supplement DS4

Characteristics of included studies

CAGO2303[50]

Other Identifiers:	-
Trial registration number:	NCT00411099
Methods:	8-week, multicenter, randomized, double-blind placebo and paroxetine-controlled trial
Participants:	18 to 70 years with diagnosis of major depression according to DSM-IV, Baseline HRDS ≥22, without comorbid illnesses
Interventions:	Agomelatine (25-50mg/day), paroxetine (20-40mg/day) and placebo
Setting:	Not reported
Primary Outcome:	Change in HRDS from baseline to week 8

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not reported, but probably done
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind trial". Probably done
Blinding of outcome assessment (detection bias)	Low risk	Quote: "double-blind trial". Probably done
Incomplete outcome data (attrition bias)	Low risk	Attrition balanced between groups
Selective reporting (reporting bias)	Low risk	Trial registered, all mentioned outcomes listet in the report, no protocol available
Other bias	Unclear risk	Sponsorship bias cannot be ruled out

CAGO2304[51]

Other Identifiers:	-
Trial registration number:	NCT00411242
Methods:	52-week, multicenter, randomized, double-blind placebo controlled relapse prevention study following 16-24 weeks of open-label treatment (Agomelatine-50mg/day)
Participants:	18 to 70 years with diagnosis of major depression according to DSM-IV, Baseline HRDS ≥22, without comorbid illnesses
Interventions:	Agomelatine (25-50mg/day), placebo
Setting:	Not reported
Primary Outcome:	Time to relapse

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not reported, but probably done
Allocation concealment (selection bias)	Unclear risk	No details reported

Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blind trial". Probably done
Blinding of outcome assessment (detection bias)	Low risk	Quote: "double-blind trial". Probably done
Incomplete outcome data (attrition bias)	Unclear risk	Not fully reported
Selective reporting (reporting bias)	Low risk	Trial registered, all listed outcomes reported, no protocol available
Other bias	Unclear risk	Sponsorship bias cannot be ruled out

CL3-021[42]

Other Identifier:	-
Trial registration number:	-
Methods:	34 week multicenter, randomized, double-blind placebo controlled relapse prevention trial following 8 weeks of open-label treatment (Agomelatine 25mg/day)
Participants:	Patients with recurrent major depression with recurrent episode according to DSM-IV, other criteria unclear (“similar to those in short-term studies”)
Interventions:	Agomelatine (25mg/day), placebo
Setting:	Not reported
Primary Outcome:	Time to relapse

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Procedure described on page 32 of EMEA 2008
Allocation concealment (selection bias)	Low risk	Done. Quote: "Each centre was given entire permutaion blocks"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "identical apperance and taste" (page 33, EMEA 2008)
Blinding of outcome assessment (detection bias)	Low risk	No information available, but probably done
Incomplete outcome data (attrition bias)	Low risk	Attrition balanced between groups
Selective reporting (reporting bias)	Unclear risk	Incomplete data from EMEA report only
Other bias	Unclear risk	Sponsorship bias cannot be ruled out

CL3-022[43]

Other Identifier:	-
Trial registration number:	-
Methods	6-week, multicenter, randomized, double-blind placebo and fluoxetine-controlled trial
Participants	18 to 59 years with diagnosis of major depression according to DSM-IV without atypical features and without psychotic features, Baseline HRDS≥22 and CGI-S≥4 and not more than 20% HRDS reduction during placebo run-in phase, other criteria unclear
Interventions:	Agomelatine (25 mg/day), paroxetine (25mg/day), placebo
Setting:	In- and outpatients
Primary Outcome:	Last post baseline HRDS score

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not reported, but probably done
Allocation concealment (selection bias)	Unclear risk	Quote: "non centralised"
Blinding of participants and personnel (performance bias)	Low risk	"tablet masked at capsule", identical apperance and taste
Blinding of outcome assessment (detection bias)	Low risk	Not reported, but probably done
Incomplete outcome data (attrition bias)	Low risk	Attrition balanced between groups
Selective reporting (reporting bias)	Unclear risk	Incomplete data from EMEA report only
Other bias	Unclear risk	Sponsorship bias cannot be ruled out

CL3-023[46]

Other Identifier:	-
Trial registration number:	-
Methods	6-week, multicenter, randomized, double-blind placebo and paroxetine-controlled trial
Participants	18 to 59 years with diagnosis of major depression according to DSM-IV; with or without seasonal patterns, without atypical features and without psychotic features, Baseline HRDS≥22, other criteria unclear
Interventions:	Agomelatine (25 mg/day), fluoxetine (25mg/day), placebo
Setting:	In- and outpatients
Primary Outcome:	Last post baseline HRDS score

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not reported, but probably done
Allocation concealment (selection bias)	Unclear risk	Quote: "non centralised"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "tablet masked at capsule". Identical apperance and taste
Blinding of outcome assessment (detection bias)	Low risk	Not reported, but probably done
Incomplete outcome data (attrition bias)	Low risk	Attrition balanced between groups
Selective reporting (reporting bias)	Unclear risk	Incomplete data from EMEA report only
Other bias	Unclear risk	Sponsorship bias cannot be ruled out

CL3-024[44]

Other Identifier:	-
Trial registration number:	-
Methods	6-week, multicenter, randomized, double-blind placebo and fluoxetine-controlled trial
Participants	18 to 59 years with diagnosis of major depression according to DSM-IV; with or without seasonal patterns, without atypical features and without psychotic

	features, Baseline HRDS≥22, other criteria unclear
Interventions:	Agomelatine (25 or 50mg/day), fluoxetine (25mg/day), placebo
Setting:	In- and outpatients
Primary Outcome:	Last post baseline HRDS score

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not reported, but probably done
Allocation concealment (selection bias)	Unclear risk	Quote: "non centralised"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "tablet masked at capsule". Identical apperance and taste
Blinding of outcome assessment (detection bias)	Low risk	Quote: "double blind"
Incomplete outcome data (attrition bias)	Low risk	Attrition balanced between groups
Selective reporting (reporting bias)	Unclear risk	Incomplete data from EMEA report only
Other bias	Unclear risk	Sponsorship bias cannot be ruled out

***CL3-026*[45]**

Other Identifier:	-
Trial registration number:	-
Methods	6-week, multicenter, randomized, double-blind placebo-controlled trial
Participants	Elderly (>60 years) patients with major depression according to DSM-IV, Baseline MADRS≥24
Interventions	Agomelatine (25 mg/day), placebo
Setting:	In- and outpatients
Outcomes	Last post baseline MADRS score

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not reported, but probably done
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double blind". Probably done
Blinding of outcome assessment (detection bias)	Low risk	Quote: "double blind". Probably done
Incomplete outcome data (attrition bias)	Unclear risk	No information available
Selective reporting (reporting bias)	Unclear risk	Incomplete data from EMEA report only
Other bias	Unclear risk	Sponsorship bias cannot be ruled out

***Goodwin et al., 2009*[47]**

Other Identifier:	CL3-041
Trial registration number:	ISRCTN53193024
Methods:	24 week multicenter, randomized, double-blind placebo controlled relapse

	prevention trial following 8-10 weeks of open-label treatment (Agomelatine 25 or 50mg/day)
Participants:	Patients with recurrent major depression according to DSM-IV, Baseline HRDS≥22 and sum of items 1+2+5+6+7+8+10+13 constituting 55% of the total score and CGI-S≥4, Hosptal Anxiety Depression sub-score ≥11, without comorbid illnesses
Interventions:	Agomelatine (25 or 50mg/day), placebo
Setting:	Outpatients
Primary Outcome:	Time to relapse

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The computer generated randomization list was drawn up blind by the Biometrie Department of the Instutut de Recherches Internationals Serverie, France"
Allocation concealment (selection bias)	Low risk	Quote: "The computer generated randomization list was drawn up blind by the Biometrie Department of the Instutut de Recherches Internationals Serverie, France"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "All study personnel and participants were blinded to treatment assignement for the duration of the study."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "All study personnel and participants were blinded to treatment assignement for the duration of the study."; "All cases depressive relapse judged by investigators were reviewed in blind condition by an independent expert committee..."
Incomplete outcome data (attrition bias)	Low risk	Attrition balanced between groups
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	Sponsorship bias cannot be ruled out

***Kennedy et al., 2006*[48]**

Other Identifier:	CL3-043
Trial registration number:	-
Methods	6-week, multicenter, randomized, double-blind placebo-controlled trial
Participants	18 to 65 years with diagnosis of major depression according to DSM-IV, Baseline HRDS ≥22, without comorbid illnesses
Interventions	Agomelatine (25-50mg/day), placebo
Setting:	In- and outpatients
Primary Outcome:	Last post baseline HRDS score

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not reported, but probably done
Allocation concealment (selection bias)	Unclear risk	No information reported
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Patients and investigators were double blind"
Blinding of outcome assessment (detection bias)	Low risk	Not reported, but probably done
Incomplete outcome data (attrition bias)	Low risk	Attrition balanced between groups

Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	Sponsorship bias cannot be ruled out

Loo et al., 2002[49]

Other Identifier:	CL3-014
Trial registration number:	-
Methods	8-week, multicenter, randomized, double-blind placebo and paroxetine-controlled trial
Participants	18 to 65 years with diagnosis of major depression or bipolar disorder (depressed) according to DSM-IV, Baseline HRDS≥22 and CGI-S≥4 and not more than 20% reduction in HRDS score during placebo run-in phase
Interventions	Agomelatine (1, 5 and 25mg/day), placebo, paroxetine (40mg/day)
Primary Outcome:	Last post baseline HRDS score

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not reported, but probably done
Allocation concealment (selection bias)	Low risk	No information reported
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double blind". Probably done
Blinding of outcome assessment (detection bias)	Low risk	Quote: "double blind". Probably done
Incomplete outcome data (attrition bias)	Low risk	Attrition balanced between groups
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	Sponsorship bias cannot be ruled out

Olie et al., 2007[52]

Other Identifier:	CL3-042
Trial registration number:	-
Methods	6-week, multicenter, randomized, double-blind placebo-controlled trial
Participants	18 to 65 years with diagnosis of major depression according to DSM-IV, Baseline HRDS ≥22, without comorbid illnesses
Interventions	Agomelatine (25-50mg/day), placebo
Setting:	In- and outpatients
Primary Outcome:	Last post baseline HRDS score

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Done
Allocation concealment (selection bias)	Low risk	Quote: "double dummy technique and the use of an interactive voice response system...."
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double blind". Probably done
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "double blind".

Incomplete outcome data (attrition bias)	Low risk	Attrition balanced between groups
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	Sponsorship bias cannot be ruled out

Stahl[53]

Other Identifier:	CAGO2302
Trial registration number:	NCT00411242
Methods:	8-week, multicenter, randomized, double-blind placebo-controlled trial
Participants:	18 to 70 years with diagnosis of major depression according to DSM-IV, Baseline HRDS≥22 and CGI-S≥4, without comorbid illnesses
Interventions:	Agomelatine (25 or 50 mg/day), placebo
Setting:	Not reported
Outcomes:	Change in HRDS from baseline to week 8

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not reported, but probably done
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	Unclear risk	Quote: "double blind".
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "double blind".
Incomplete outcome data (attrition bias)	Unclear risk	Slighly more agomelatine patients not included in ITT (25mg: 10/168, 50mg: 8/169, PLB: 3/166)
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	Sponsorship bias cannot be ruled out

Zajecka et al. 2010[54]

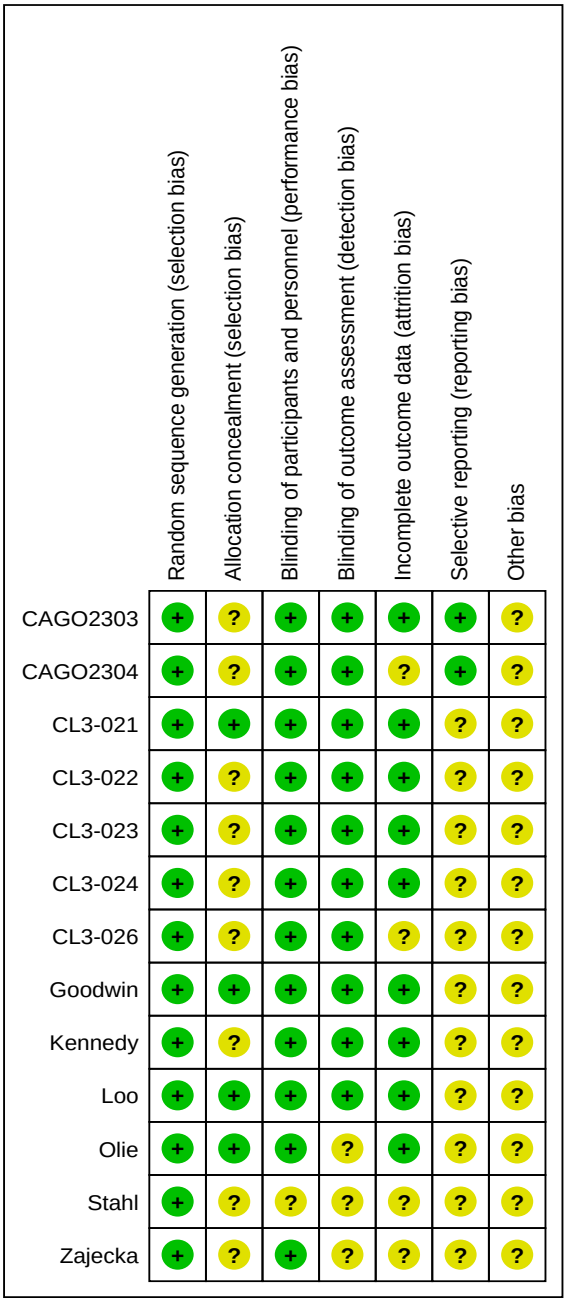
Other Identifier:	CAGO2301
Trial registration number:	NCT00411242
Methods:	8-week, multicenter, randomized, double-blind placebo-controlled trial
Participants:	18 to 70 years with diagnosis of major depression according to DSM-IV, Baseline HRDS≥22 and CGI-S≥4, without comorbid illnesses
Interventions:	Agomelatine (25 or 50 mg/day), placebo
Setting:	Not reported
Outcomes:	Change in HRDS from baseline to week 8

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not reported, but probably done
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double blind". Probably done

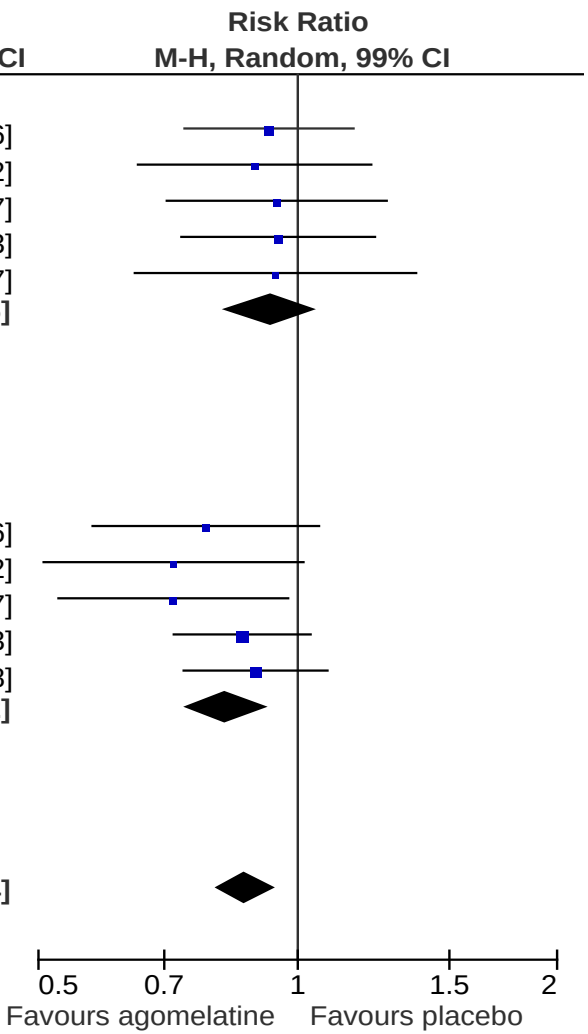
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Unclear risk	More agomelatine patients not included in ITT (25mg: 14/170, 50mg: 7/168, PLB: 6/173)
Selective reporting (reporting bias)	Unclear risk	No protocol available
Other bias	Unclear risk	Sponsorship bias cannot be ruled out

Online Fig. DS1 Risk of bias summary: review authors' judgements about each risk of bias item for each included study

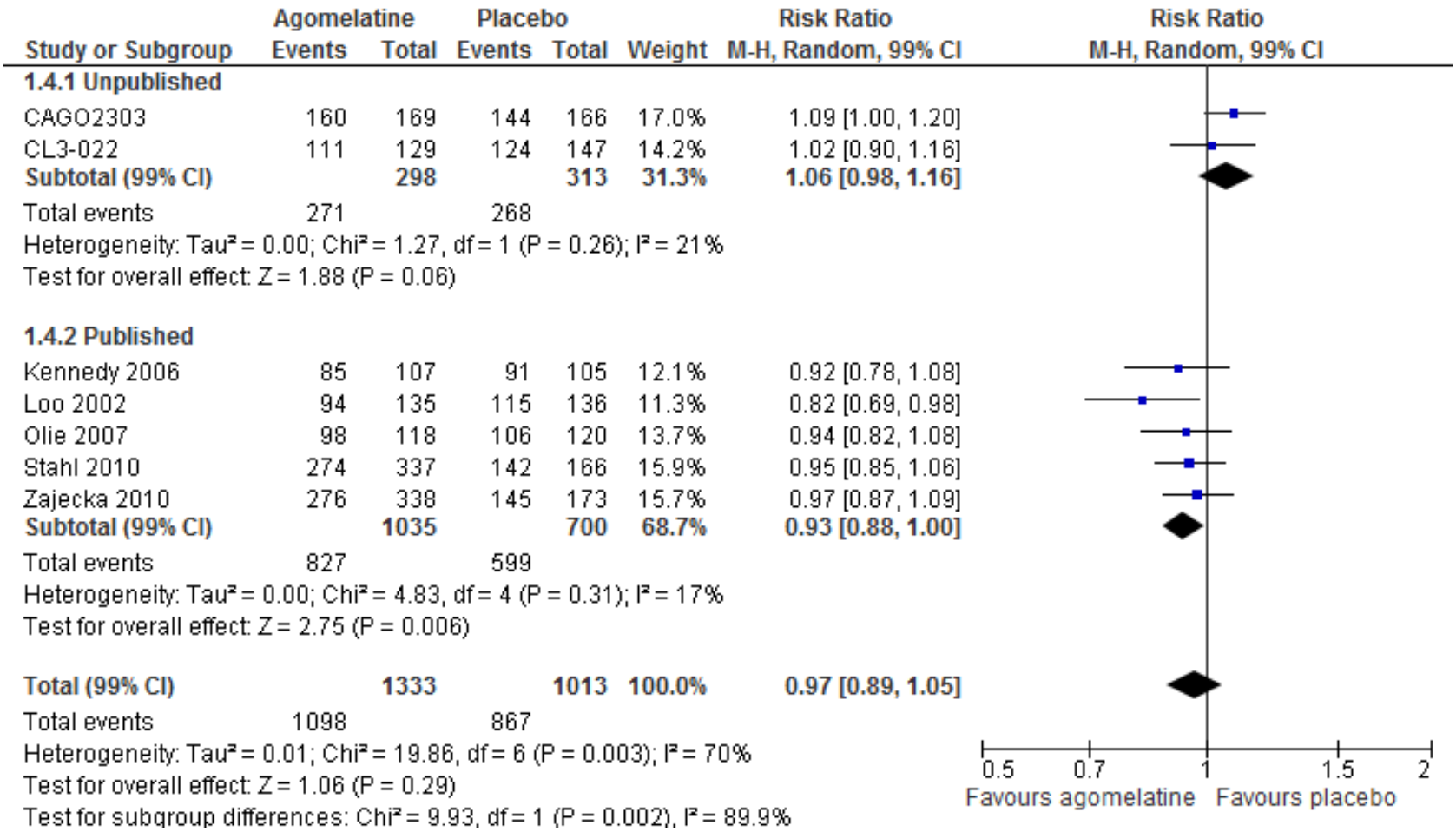


Online Fig. DS2 Random effects meta-analysis of the effect of agomelatine versus placebo on the proportion of patients failing to respond

Study or Subgroup	Agomelatine Events	Agomelatine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 99% CI
1.3.1 Unpublished						
CAGO2303	99	169	105	166	13.0%	0.93 [0.74, 1.16]
CL3-022	61	129	78	147	6.8%	0.89 [0.65, 1.22]
CL3-023	72	141	74	137	7.7%	0.95 [0.70, 1.27]
CL3-024	140	295	79	158	9.9%	0.95 [0.73, 1.23]
CL3-026	49	109	52	109	4.7%	0.94 [0.65, 1.37]
Subtotal (99% CI)		**843**		**717**	**42.2%**	**0.93 [0.82, 1.06]**
Total events	421		388			
Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 4 (P = 1.00); I² = 0%						
Test for overall effect: Z = 1.47 (P = 0.14)						
1.3.2 Published						
Kennedy 2006	55	107	69	105	7.3%	0.78 [0.58, 1.06]
Loo 2002	52	135	73	136	5.5%	0.72 [0.51, 1.02]
Olie 2007	55	118	78	120	7.1%	0.72 [0.53, 0.97]
Stahl 2010	196	337	112	166	19.9%	0.86 [0.72, 1.03]
Zajecka 2010	192	338	110	173	18.0%	0.89 [0.74, 1.08]
Subtotal (99% CI)		**1035**		**700**	**57.8%**	**0.83 [0.74, 0.92]**
Total events	550		442			
Heterogeneity: Tau² = 0.00; Chi² = 4.25, df = 4 (P = 0.37); I² = 6%						
Test for overall effect: Z = 4.43 (P < 0.00001)						
Total (99% CI)		**1878**		**1417**	**100.0%**	**0.87 [0.80, 0.94]**
Total events	971		830			
Heterogeneity: Tau² = 0.00; Chi² = 7.77, df = 9 (P = 0.56); I² = 0%						
Test for overall effect: Z = 4.41 (P < 0.0001)						
Test for subgroup differences: Chi² = 3.42, df = 1 (P = 0.06), I² = 70.7%						

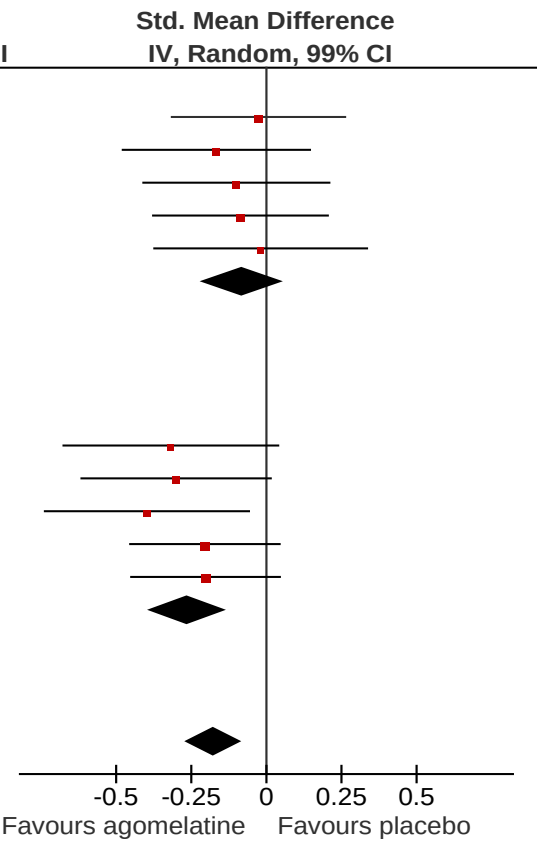


Online Fig. DS3 Random effects meta-analysis of the effect of agomelatine versus placebo on the proportion of patients failing to show remission



Online Fig. DS4 Random effects meta-analysis of the effect of agomelatine versus placebo on standardised depression outcomes

Study or Subgroup	Std. Mean Difference	SE	Agomelatine Total	Placebo Total	Weight	Std. Mean Difference IV, Random, 99% CI
1.6.1 Unpublished						
CAGO2303	-0.02613912	0.11181691	162	158	10.8%	-0.03 [-0.31, 0.26]
CL3-022	-0.16635959	0.1208503	129	147	9.3%	-0.17 [-0.48, 0.14]
CL3-023	-0.1	0.12003939	141	137	9.4%	-0.10 [-0.41, 0.21]
CL3-024	-0.08613	0.11274355	232	59	10.6%	-0.09 [-0.38, 0.20]
CL3-026	-0.019	0.13736367	106	106	7.2%	-0.02 [-0.37, 0.33]
Subtotal (99% CI)			**770**	**607**	**47.2%**	**-0.08 [-0.22, 0.06]**
Heterogeneity: Tau² = 0.00; Chi² = 0.97, df = 4 (P = 0.91); I² = 0%						
Test for overall effect: Z = 1.51 (P = 0.13)						
1.6.2 Published						
Kennedy 2006	-0.31778788	0.13855354	106	105	7.1%	-0.32 [-0.67, 0.04]
Loo 2002	-0.30033277	0.12217516	135	136	9.1%	-0.30 [-0.62, 0.01]
Olie 2007	-0.39733767	0.1317572	116	119	7.8%	-0.40 [-0.74, -0.06]
Stahl 2010	-0.20442	0.0964246	319	82	14.4%	-0.20 [-0.45, 0.04]
Zajecka 2010	-0.20248	0.09596922	317	84	14.5%	-0.20 [-0.45, 0.04]
Subtotal (99% CI)			**993**	**526**	**52.8%**	**-0.26 [-0.39, -0.13]**
Heterogeneity: Tau² = 0.00; Chi² = 2.06, df = 4 (P = 0.73); I² = 0%						
Test for overall effect: Z = 5.22 (P < 0.00001)						
Total (99% CI)			**1763**	**1133**	**100.0%**	**-0.18 [-0.27, -0.08]**
Heterogeneity: Tau² = 0.00; Chi² = 9.21, df = 9 (P = 0.42); I² = 2%						
Test for overall effect: Z = 4.78 (P < 0.00001)						
Test for subgroup differences: Chi² = 6.19, df = 1 (P = 0.01), I² = 83.8%						

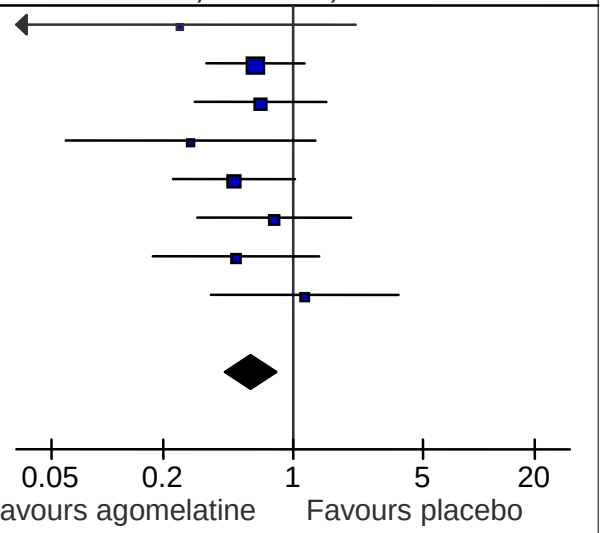


Online Fig. DS5 Random effects meta-analysis of the effect of agomelatine versus placebo on treatment discontinuation due to inefficacy

Study or Subgroup	Agomelatine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CAGO2303	1	169	4	166	2.3%	0.25 [0.03, 2.17]
CL3-022	14	133	25	149	28.7%	0.63 [0.34, 1.16]
CL3-023	9	142	13	137	16.1%	0.67 [0.30, 1.51]
Kennedy 2006	2	107	7	105	4.5%	0.28 [0.06, 1.32]
Loo 2002	9	137	19	139	18.7%	0.48 [0.23, 1.02]
Olie 2007	7	118	9	120	11.8%	0.79 [0.30, 2.05]
Stahl 2010	7	337	7	166	10.1%	0.49 [0.18, 1.38]
Zajecka 2010	9	338	4	173	7.9%	1.15 [0.36, 3.69]
Total (95% CI)		**1481**		**1155**	**100.0%**	**0.60 [0.43, 0.83]**
Total events	58		88			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.66$, df = 7 (P = 0.82); $I^2 = 0\%$

Test for overall effect: Z = 3.07 (P = 0.002)

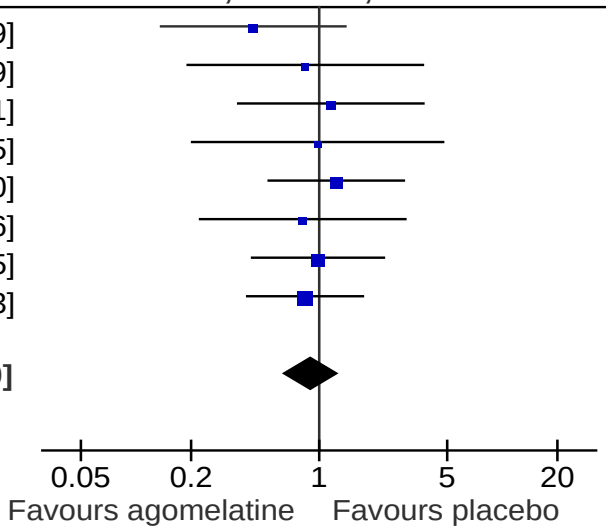


Online Fig. DS6 Random effects meta-analysis of the effect of agomelatine versus placebo on treatment discontinuation due to adverse events

Study or Subgroup	Agomelatine Events	Agomelatine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
CAGO2303	4	169	9	166	9.7%	0.44 [0.14, 1.39]
CL3-022	3	133	4	149	6.0%	0.84 [0.19, 3.69]
CL3-023	6	142	5	137	9.6%	1.16 [0.36, 3.71]
Kennedy 2006	3	107	3	105	5.2%	0.98 [0.20, 4.75]
Loo 2002	11	137	9	139	18.1%	1.24 [0.53, 2.90]
Olie 2007	4	118	5	120	7.8%	0.81 [0.22, 2.96]
Stahl 2010	16	337	8	166	19.0%	0.99 [0.43, 2.25]
Zajecka 2010	18	338	11	173	24.6%	0.84 [0.40, 1.73]
Total (95% CI)		**1481**		**1155**	**100.0%**	**0.90 [0.63, 1.30]**
Total events	65		54			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.36$, df = 7 (P = 0.94); $I^2 = 0\%$

Test for overall effect: Z = 0.55 (P = 0.58)

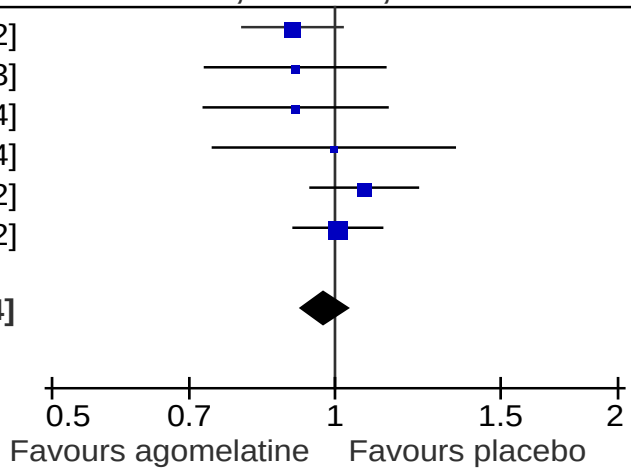


Online Fig. DS7 Random effects meta-analysis of the effect of agomelatine versus placebo on the proportion of patients with adverse events

	Agomelatine		Placebo			Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**
CAGO2303	120	167	130	163	25.4%	0.90 [0.80, 1.02]
Kennedy 2006	61	107	66	105	7.8%	0.91 [0.73, 1.13]
Loo 2002	70	141	76	139	7.5%	0.91 [0.73, 1.14]
Olie 2007	50	118	51	120	4.4%	1.00 [0.74, 1.34]
Stahl 2010	232	330	108	165	22.2%	1.07 [0.94, 1.22]
Zajecka 2010	244	325	126	169	32.7%	1.01 [0.90, 1.12]
Total (95% CI)		**1188**		**861**	**100.0%**	**0.98 [0.92, 1.04]**
Total events	777		557			

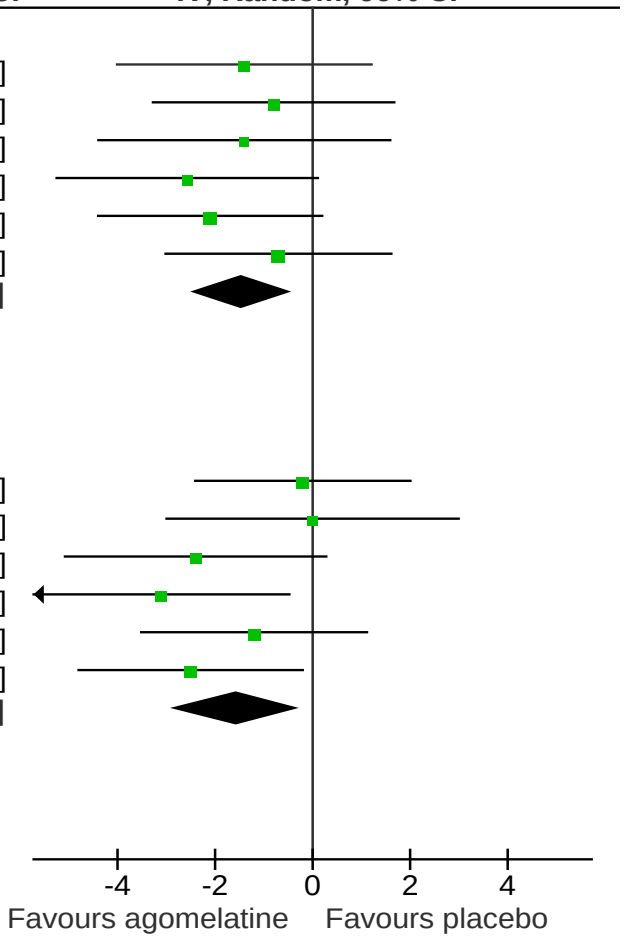
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.85$, df = 5 (P = 0.43); $I^2 = 0\%$

Test for overall effect: Z = 0.75 (P = 0.46)



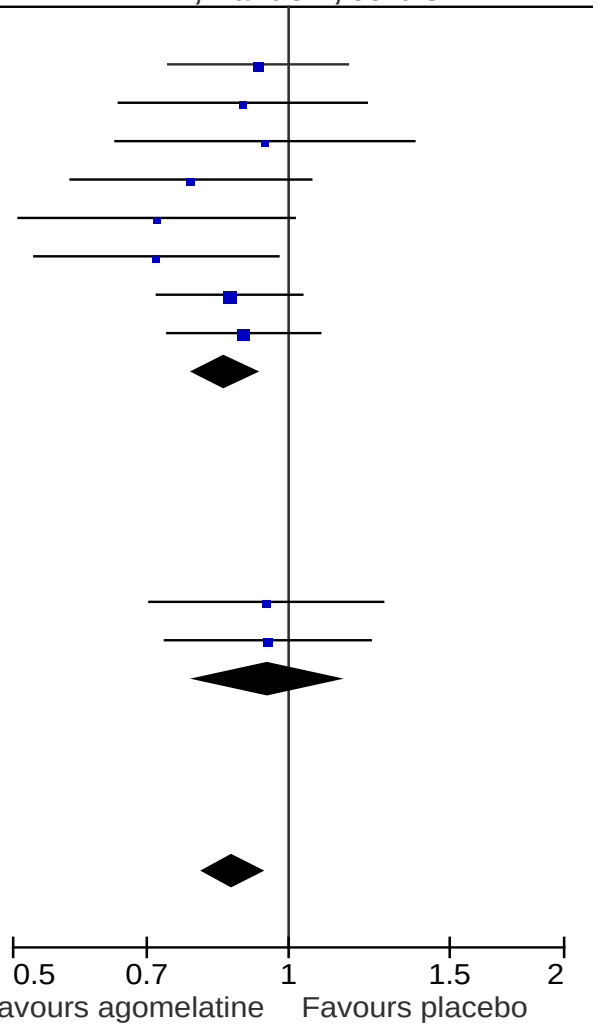
Online Fig. DS8 Efficacy of agomelatine versus placebo by agomelatine dose

Study or Subgroup	Agomelatine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 99% CI
1.11.1 25mg								
CL3-022	14.5	8.2	129	15.9	8.6	147	15.7%	-1.40 [-4.01, 1.21]
CL3-023	13	8	141	13.8	8	137	17.4%	-0.80 [-3.27, 1.67]
CL3-024	12	8.2	148	13.4	8.4	79	11.9%	-1.40 [-4.39, 1.59]
Loo 2002	12.77	8.23	135	15.34	8.87	136	14.9%	-2.57 [-5.25, 0.11]
Stahl 2010	15	8.04	158	17.1	7.92	163	20.2%	-2.10 [-4.40, 0.20]
Zajecka 2010	15.9	7.74	156	16.6	8.4	167	19.9%	-0.70 [-3.01, 1.61]
Subtotal (99% CI)			**867**			**829**	**100.0%**	**-1.47 [-2.50, -0.44]**
Heterogeneity: Tau² = 0.00; Chi² = 2.85, df = 5 (P = 0.72); I² = 0%								
Test for overall effect: Z = 3.67 (P = 0.0002)								
1.11.2 >25mg								
CAGO2303	17.1	7.38	162	17.3	7.92	158	19.2%	-0.20 [-2.41, 2.01]
CL3-024	13.4	8.2	147	13.4	8.4	79	13.3%	0.00 [-2.99, 2.99]
Kennedy 2006	14.1	7.7	106	16.5	7.4	105	15.3%	-2.40 [-5.08, 0.28]
Olie 2007	13.9	7.7	116	17	7.9	119	15.7%	-3.10 [-5.72, -0.48]
Stahl 2010	15.9	8.25	161	17.1	7.92	163	18.2%	-1.20 [-3.51, 1.11]
Zajecka 2010	14.1	7.74	161	16.6	8.4	167	18.3%	-2.50 [-4.80, -0.20]
Subtotal (99% CI)			**853**			**791**	**100.0%**	**-1.57 [-2.90, -0.24]**
Heterogeneity: Tau² = 0.66; Chi² = 8.54, df = 5 (P = 0.13); I² = 41%								
Test for overall effect: Z = 3.04 (P = 0.002)								
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%								

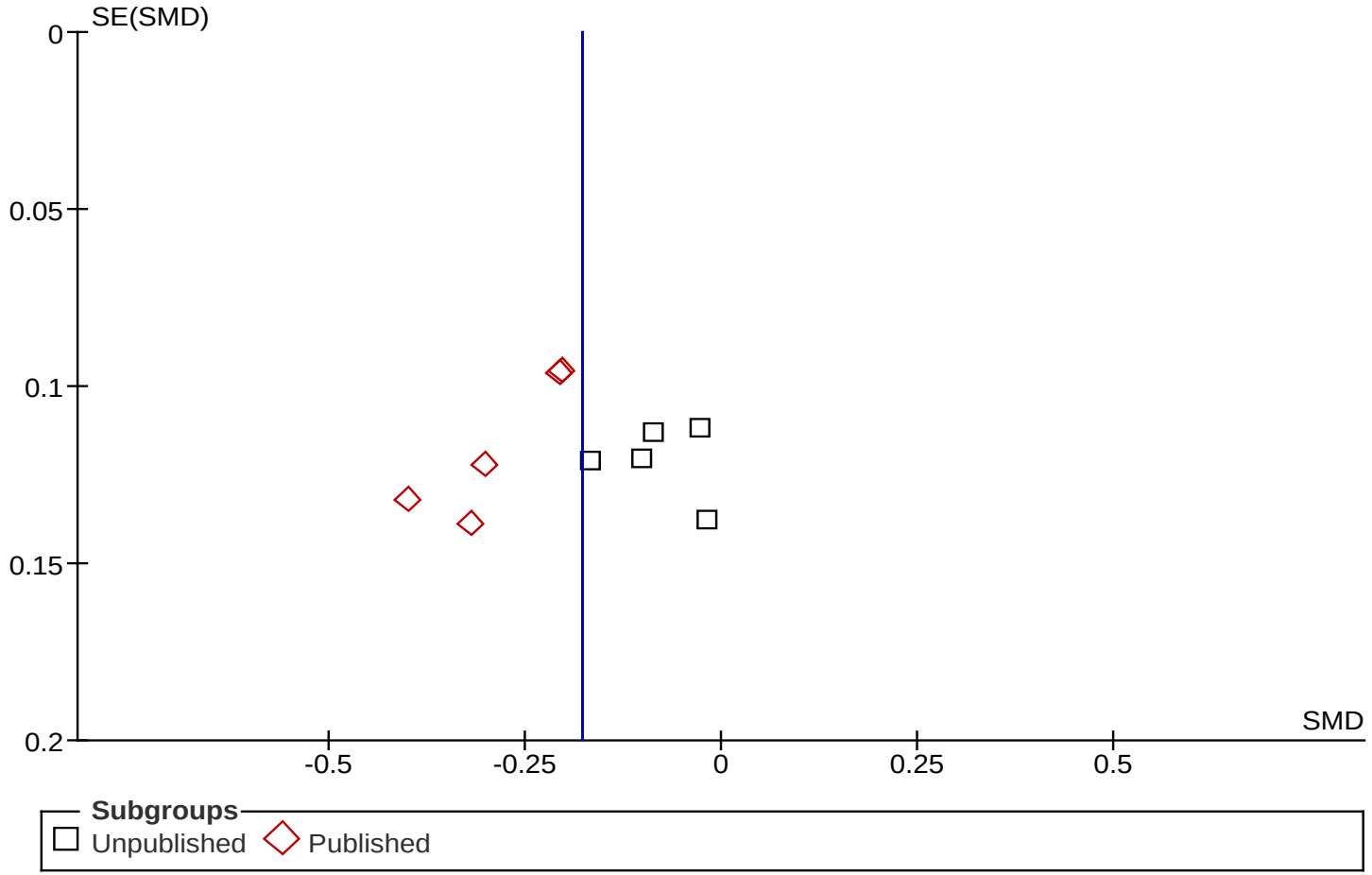


Online Fig. DS9 Proportion of patients failing to respond of agomelatine versus placebo by data source (from file *v.* imputed)

Study or Subgroup	Agomelatine Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 99% CI
1.12.1 Data from file						
CAGO2303	99	169	105	166	13.0%	0.93 [0.74, 1.16]
CL3-022	61	129	78	147	6.8%	0.89 [0.65, 1.22]
CL3-026	49	109	52	109	4.7%	0.94 [0.65, 1.37]
Kennedy 2006	55	107	69	105	7.3%	0.78 [0.58, 1.06]
Loo 2002	52	135	73	136	5.5%	0.72 [0.51, 1.02]
Olie 2007	55	118	78	120	7.1%	0.72 [0.53, 0.97]
Stahl 2010	196	337	112	166	19.9%	0.86 [0.72, 1.03]
Zajecka 2010	192	338	110	173	18.0%	0.89 [0.74, 1.08]
Subtotal (99% CI)		**1442**		**1122**	**82.4%**	**0.85 [0.78, 0.93]**
Total events	759		677			
Heterogeneity: Tau² = 0.00; Chi² = 6.22, df = 7 (P = 0.51); I² = 0%						
Test for overall effect: Z = 4.53 (P < 0.00001)						
1.12.2 Data imputed						
CL3-023	72	141	74	137	7.7%	0.95 [0.70, 1.27]
CL3-024	140	295	79	158	9.9%	0.95 [0.73, 1.23]
Subtotal (99% CI)		**436**		**295**	**17.6%**	**0.95 [0.78, 1.15]**
Total events	212		153			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.72 (P = 0.47)						
Total (99% CI)		**1878**		**1417**	**100.0%**	**0.87 [0.80, 0.94]**
Total events	971		830			
Heterogeneity: Tau² = 0.00; Chi² = 7.77, df = 9 (P = 0.56); I² = 0%						
Test for overall effect: Z = 4.41 (P < 0.0001)						
Test for subgroup differences: Chi² = 1.57, df = 1 (P = 0.21), I² = 36.4%						



Online Fig. DS10 Funnel plot of comparison: agomelatine versus placebo, outcome: all studies; Standardised Mean Difference



Online Table DS1

GRADE QUALITY ASSESSMENT AND SUMMARY OF FINDINGS TABLE

Question: Should agomelatine vs placebo be used in adults with unipolar major depression?

Bibliography: Agomelatine versus placebo

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Placebo	With Agomelatine		Risk with Placebo	Risk difference with Agomelatine (95% CI)
Depressive symptoms: HDRS score (CRITICAL OUTCOME; Better indicated by lower values)											
2947 (9 studies[b])	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected[a]	⨁⨁⨁⨁ **HIGH**[a]	1290	1657	-		The mean depressive symptoms: hdrs score in the intervention groups was **1.51 lower** (2.29 to 0.73 lower)[c]
Risk of relapse in the long-term (CRITICAL OUTCOME)											
983 (3 studies[g])	no serious risk of bias	serious[d]	no serious indirectness	serious[e]	undetected[f]	⨁⨁⨁⨀ **LOW**[d,e,f] due to inconsistency, imprecision	151/494 (30.6%)	114/489 (23.3%)	**RR 0.78** (0.41 to 1.48)[c]	**306 per 1000**	**67 fewer per 1000** (from 180 fewer to 147 more)
Treatment acceptability (CRITICAL OUTCOME)											
3095 (9 studies[j])	no serious risk of bias	no serious inconsistency	serious[h]	no serious imprecision	undetected[i]	⨁⨁⨁⨀ **MODERATE**[h,i] due to indirectness	278/1313 (21.2%)	358/1782 (20.1%)	**RR 0.92** (0.8 to 1.06)	**212 per 1000**	**17 fewer per 1000** (from 42 fewer to 13 more)

Lack of improvement (IMPORTANT OUTCOME)											
3295 (10 studies[l])	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected[k]	⊕⊕⊕⊕ **HIGH**[k]	830/1417 (58.6%)	971/1878 (51.7%)	**RR 0.87** (0.8 to 0.94)[c]	**586 per 1000**	**76 fewer per 1000** (from 35 fewer to 117 fewer)
Lack of remission (IMPORTANT OUTCOME)											
2346 (7 studies[o])	no serious risk of bias	serious[m]	no serious indirectness	serious[e]	undetected[n]	⊕⊕⊖⊖ **LOW**[e,m,n] due to inconsistency, imprecision	867/1013 (85.6%)	1098/1333 (82.4%)	**OR 0.82** (0.49 to 1.36)[c]	**856 per 1000**	**26 fewer per 1000** (from 112 fewer to 34 more)
Depressive symptoms: any scale (IMPORTANT OUTCOME; Better indicated by lower values)											
2896 (10 studies[p])	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	undetected[k]	⊕⊕⊕⊕ **HIGH**[k]	1133	1763	-		The mean depressive symptoms: any scale in the intervention groups was **0.18 standard deviations lower** (0.27 to 0.08 lower)[c]

a. Four unpublished studies were included in this analysis. Additionally, inspection of funnell plot did not suggest asymmetry.

b. From Fig. 3.

c. 99% confidence interval.

d. Visual inspection of forest plot suggested inconsistency. I-squared further suggested inconsistency (I-squared = 81%).

e. Confidence interval ranges from the possibility of appreciable benefit of agomelatine to the possibility of no benefit at all.

f.Two of the three included studies were unpublished.

g. From Fig. 4.

h.Overall dropout rates are only a proxy measure of treatment acceptability.

i. Four unpublished studies were included in this analysis.

j. From Fig. 5.

k. Five unpublished studies included in this analysis.

l. From online Fig. DS2.

m. Visual inspection of forest plot suggested inconsistency. I-squared further suggested inconsistency (I-squared = 77.5%).

n. Two unpublished studies included in this analysis.

o. From online Fig.DS3.

p. From online Fig. DS4.