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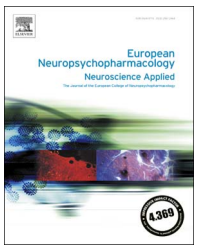

Efficacy and safety of agomelatine (10 or 25 mg/day) in non-depressed out-patients with generalized anxiety disorder: A 12-week, double-blind, placebo-controlled study

Dan J. Stein[a,*], Antti Ahokas[b], Marek Jarema[c], Alla S. Avedisova[d], Livia Vavrusova[e], Oleg Chaban[f], Céline Gruget[g], Valérie Olivier[g], Françoise Picarel-Blanchot[g], Christian de Bodinat[g]

[a]*University of Cape Town Department of Psychiatry & MRC Unit on Anxiety & Stress Disorders, Groote Schuur Hospital, J-Block, Anzio Road, Cape Town 7925, South Africa*
[b]*Mehilainen Clinic, Runeberginkatu 47 A, 00260 Helsinki, Finland*
[c]*Institute of Psychiatry and Neurology, 3rd Department of Psychiatry, Warszawa, Poland*
[d]*Serbsky National Research Centre for Social and Forensic Psychiatry, Moscow, Russia*
[e]*Private Psychiatric Practice – VAVRUŠOVÁ CONSULTING s.r.o., Záporožská 12, 851 01 Bratislava, Slovakia*
[f]*Psychosomatic Medicine and Psychotherapy, National Medical University Named After O.O. Bogomolets, M. Kotsyubynskogo 8A str., 01030 Kiev, Ukraine*
[g]*Institut de Recherches Internationales Servier (IRIS), 50 rue Carnot, 92284 Suresnes Cedex, France*

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Abstract
Agomelatine is efficacious in reducing symptoms and preventing relapse in placebo-controlled trials in generalised anxiety disorder (GAD). Nevertheless, fixed dose studies of agomelatine in GAD have not been undertaken. To determine the minimally effective optimal dose of agomelatine in GAD, the efficacy of two doses of agomelatine (10 and 25 mg/day) was investigated in a 12-week, placebo-controlled, double-blind, international study in patients with a primary diagnosis of GAD. The primary outcome measure was the Hamilton Anxiety scale (HAM-A). The study was undertaken in 35 clinical centers in Finland, Russia, Poland, Slovakia and Ukraine from August 2013 to January 2015. 131 out-patients were included in the agomelatine 10 mg group, 139 in the agomelatine 25 mg group, and 142 in the placebo group. Both doses of agomelatine were associated with significant decreases in the HAM-A at week 12 (difference *versus* placebo of 7.16 ± 1.00 at 10 mg and 11.08 ± 0.98 at 25 mg, $p < 0.0001$). Significant effects on all secondary measures were found for both doses at week 12; including

*Correspondence to: University of Cape Town Department of Psychiatry, Groote Schuur Hospital, J-Block, Anzio Road, Observatory, Cape Town 7925, South Africa. Fax: +27 21 448 8158.
E-mail address: dan.stein@uct.ac.za (D.J. Stein).

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psychic and somatic HAM-A subscales, response rate, remission on the HAM-A, and functional impairment. Findings were confirmed in subsets of more severely ill patients on all endpoints. The low placebo response rate observed in this study was consistent with an increase in the quality of data collected. Agomelatine was well-tolerated by patients, with minimal distinctions from placebo. There was a dose effect of agomelatine, with a greater placebo-agomelatine difference in the agomelatine 25 mg group, compared to the agomelatine 10 mg group.The present data support early work indicating the efficacy and tolerability of agomelatine in the treatment of GAD.

1. Introduction

Generalized anxiety disorder (GAD) is a chronic condition characterized by excessive anxiety, worry and somatic symptoms. Symptoms may fluctuate during the course of the illness, with baseline anxiety traits being compounded by GAD symptoms (so-called "double anxiety") (Rickels and Schweizer, 1998). GAD is the most common anxiety disorder in primary care practice (Hoffman et al., 2008; Wittchen et al., 2011), and is often associated with both comorbidity (including comorbidity of major depression and other anxiety disorders) and morbidity (including psychosocial impairment and economic costs) (Hoffman et al., 2008). While a number of different medication classes have demonstrated efficacy in the management of GAD (Bandelow et al., 2014), many patients fail to respond to, cannot tolerate, or develop discontinuation symptoms after use of such medications (Kapczinski et al., 2003).

The mechanism of action of agomelatine suggests that it may be useful in both major depressive disorder (MDD) and GAD (de Bodinat et al., 2010; Guardiola-Lemaitre et al., 2014). Anxiety symptoms are common in major depression (Fava et al., 2006; Stein and Hollander, 2002) and a range of work has demonstrated that in patients with MDD agomelatine is significantly more efficacious than both placebo and several comparator antidepressants in reducing anxiety symptoms (Hale et al., 2010; Kasper et al., 2010; Kennedy and Emsley, 2006; Lemoine et al., 2007; Loo et al., 2002; Olié and Kasper, 2007; Stein et al., 2013). In these studies, the favourable effects of agomelatine were seen on both the HAMA psychic and somatic sub-scores and were also observed in MDD patients with higher baseline anxiety.

Several agomelatine trials have focused on GAD. The efficacy and tolerability of agomelatine in treating GAD has been demonstrated using doses of 25–50 mg daily in a placebo-controlled phase II study (Stein et al., 2008), in a phase III study with escitalopram as active control (Stein et al., 2014), and in a relapse prevention study (Stein et al., 2012). In a recent study in MDD, symptom reduction in response to a dose of agomelatine 10 mg daily versus placebo reached statistical significance (Kennedy et al., 2014). In accordance with the requirement of EMA to ascertain the lowest effective dose of a medication, additional data on the efficacy of agomelatine 10 mg versus 25 mg daily in GAD would further optimize recommendations regarding dosage in this patient population.

The primary objective of this study was therefore to investigate the short-term (12-week) efficacy of 2 doses of agomelatine (10 and 25 mg/day) compared to placebo in reducing symptoms of GAD, as assessed by the Hamilton Anxiety Scale (HAM-A) in non-depressed out-patients. The secondary objectives were to assess the potential clinical benefit of agomelatine on a broad array of clinical measures including response and remission rates as well as functional impairment, and to provide additional data on the tolerability and safety of agomelatine.

2. Experimental procedures

2.1. Patients

A total of 412 physically healthy male and female outpatients, aged 18 (or legal age of majority in the relevant country) and over, with a primary diagnosis of GAD according to DSM-IV-TR criteria (American Psychiatric Association, 2000) and having provided signed informed consent, were recruited between August 2013 and January 2015 in Finland (6 centres), Russia (6 centres), Poland (9 centres), Slovakia (6 centres), and Ukraine (8 centres). The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.

The Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) was used to diagnose GAD (DSM-IV-TR criteria) and potential comorbid disorders. Patients were required to have a HAM-A (Hamilton, 1959) total score $\geq$ 22, a score $\geq$ 2 on both HAM-A items 1 and 2, HAM-A items 1+2 $>$ 5, a Hospital Anxiety and Depression (HAD) (Zigmond and Snaith, 1983) Anxiety score $>$ Depression score at selection and inclusion, and a Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) score $\leq$ 16 at selection. Patients with a decrease greater than 20% on the HAM-A total score between selection and inclusion were excluded.

Patients with current (within 6 months prior to the selection visit) anxiety disorders other than GAD, including panic disorder, posttraumatic stress disorder, agoraphobia, social phobia, obsessive-compulsive disorder according to DSM-IV-TR criteria and confirmed by the MINI, were excluded. Regarding specific phobia, only patients with symptoms present almost daily or which could interfere with study evaluation were excluded. Patients with anxiety symptoms due to a general medical condition or substance use were also excluded. Patients with other psychiatric disorders including major depressive disorder, drug or alcohol abuse dependence, severe personality disorders, a history of psychotic disorder, neurological disorders, and suicide risk (as judged by the clinician, a score $>$ 3 on item 10 of the MADRS, or who had made a suicide attempt within the past year), were excluded. Women of childbearing potential without effective contraception, pregnant women, and patients with severe or uncontrolled organic disease, likely to interfere with the conduct of the study were also

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excluded. Patients receiving psychotropic agents or other treatments likely to impact on the central nervous system or on study evaluations, or having recently begun psychotherapy, were excluded. However, menopause hormone replacement therapy, and treatment with thyroid hormones or beta-blockers were allowed when used at a stable dosage (start, stop or modification within the 3 months [4 weeks for beta-blockers] prior to inclusion).

2.2. Design and measures

Patients were randomized to receive agomelatine 10 mg, agomelatine 25 mg or placebo in the evening for 12 weeks. The treatments were assigned at the inclusion visit by a balanced (non-adaptive and non-centralized) randomization with stratification by centre. Treatments were identically labeled. After the 12-week treatment period (or in case of premature withdrawal and in accordance with the investigator's opinion), patients were followed up for one week without taking any study treatment. During the 12-week period, visits were scheduled at weeks 0 (inclusion visit), 2, 4, 8 and 12 (last visit).

The primary outcome measure was the HAM-A, which was rated at the selection and inclusion visits and at weeks 2, 4, 8 and 12. Secondary outcome measures included the HAM-A psychic and somatic anxiety subscores rated at each visit, the HAD Anxiety and Depression sub-scores rated at selection and inclusion visits and at weeks 8 and 12, and the Sheehan Disability Scale (SDS) (Sheehan et al., 1996) rated at the selection visit and at weeks 8 and 12. Scores on the Clinical Global Impression (CGI) scale (Guy, 1976): the CGI-Severity of illness (CGI-S) assessed at each visit from selection, and the CGI-Improvement (CGI-I) assessed at each visit from week 2 were also secondary outcome measures. All efficacy measures were performed at the end of the study or at the last day of treatment in the case of premature withdrawal.

Safety measures included adverse events reporting at each visit, vital signs (heart rate, blood pressure) at selection and inclusion visits and at week 12, 12-lead electrocardiograms (ECGs) at selection and week 12, weight and body-mass index (BMI) at the selection visit and weeks 0 and 12; and standard laboratory tests (biochemistry, hematology) at the selection visit and week 12 (or in the case of premature withdrawal). Standard biochemistry and haematology tests, as well as liver function tests including ALAT, ASAT, γGT, ALP, and total bilirubin were undertaken at weeks 4 and 8. All safety measures were performed at the end of the study or at the last day of treatment in the case of premature withdrawal.

2.3. Training

All sites were trained in administering the diagnostic instruments and the outcome measures. Presentations were done at an International investigator's meeting on DSM-IV-TR criteria for GAD and on the MINI. Videos of clinical cases were used to establish inter-rater reliability on symptom measures. Training sessions on symptom severity measures were repeated once during the one year recruitment period.

2.4. Statistical analyses

The efficacy analyses were performed in the full analysis set (FAS) (all included and randomized patients having taken at least one dose of study medication, and having a value at baseline and at least one post-baseline visit for the primary efficacy measure). The primary analysis assessed the superiority of at least one agomelatine dose as compared to placebo on anxiety symptoms on the change from baseline to week 12 of the HAM-A total score, using a single two-way analysis of covariance model on treatment and center (random effect) with baseline HAM-A total score as covariate. Missing data at week 12 were imputed using the last observation carried forward (LOCF) approach. The Hochberg procedure was used to take into account the multiplicity of comparisons. To assess the robustness of the results of the primary analysis, each agomelatine dose was compared to placebo on the change from baseline to week 12 of HAM-A total score, using a mixed-effects model for repeated measures (MMRM) including the fixed, categorical effects of treatment, visit and treatment-by-visit interaction, the random categorical effect of centre, as well as the continuous fixed covariate of baseline score on the HAM-A.

As pre-specified in the statistical plan, this analysis was repeated in the subsets of patients greater GAD symptom severity, as defined by having 1) a HAM-A total score $\geq$ 25, and 2) a HAM-A total score $\geq$ 25 and CGI-S $\geq$ 5 at baseline.

Secondary analyses in the FAS assessed the agomelatine-placebo difference in response rate to treatment (at least 50% decrease from baseline HAM-A total score) and remission (HAM-A total score $\leq$ 7), at week 12 using a LOCF approach with a Chi-square test (*post-hoc* analysis for remission). These analyses were repeated in the two subsets of more severely ill patients.

Agomelatine-placebo differences were also evaluated in the FAS over the 12-week period using HAM-A psychic and somatic anxiety scores (post-hoc analyses), CGI-S and CGI-I scores, HAD anxiety and depression scores (post-hoc analyses), SDS total score, work, social life and family life scores (post-hoc analyses), on the value at week 12 (using the LOCF approach), and using a Student's t-test for independent samples. Additional analyses using a Chi-square test assessed agomelatine-placebo differences on percentages of patients with functional response (SDS total score of 12 or less) and/or remission (SDS total score of 6 or less) (Sheehan and Sheehan, 2008) at week 12 (using the LOCF approach) (*post-hoc* analysis). *Post-hoc* analyses using a two-way analysis of covariance model on treatment and center (random effect) with baseline HAM-A total score as covariate assessed agomelatine 10 mg-agomelatine 25 mg differences on HAM-A total score in the FAS and the subsets of severely ill patients at baseline.

For every safety measurement, 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 using SAS® software, version 9.2 (SAS Institute, Cary, NC). The type I error was set at 5% (two-tailed test).

3. Results

3.1. Patients

Four hundred and twelve patients were randomly assigned to receive agomelatine 10 mg (131 patients), agomelatine 25 mg (139 patients) or placebo (142 patients). A total of 61 patients did not complete the trial (85.2% completer rate). Reasons for withdrawal were mainly lack of efficacy and non-medical; while rates of withdrawal for non-medical reasons were the same same across treatment arms, it is noteworthy that only 1 patient on agomelatine 25 mg withdrew due to lack of efficacy *versus* 8 patients on agomelatine 10 mg daily and 20 patients on placebo (Table 1).

The patients' age was 43.9 ± 13.9 years (mean ± SD) with a greater proportion of females (67.7%). There were no clinically relevant differences between the treatment groups for demographic criteria and clinical characteristics (Table 2).

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Table 1 Disposition of patients (*n*).

	Agomelatine 10 mg	Agomelatine 25 mg	Placebo
Included (randomised)	**131**	**139**	**142**
With a protocol deviation ≤ week 0	**1**	**4**	**3**
Lost to Follow-up	-	-	-
Withdrawn	**18**	**13**	**30**
due to adverse event	1	3	1
due to non-medical reason	8	8	8
due to lack of efficacy	8	1	20
due to protocol deviation	1	1	1
due to remission	-	-	-
Completed (%)	**113 (86.3)**	**126 (90.6)**	**112 (78.9)**
Full analysis Set (FAS)	130	138	140
Sub-FAS with HAM-A total score ≥ 25 at week 0	115	122	128
Sub-FAS with HAM-A total score ≥ 25 and CGI-S ≥ 5 at week 0	65	72	65
Safety Set	131	139	140

Table 2 Baseline patient demographic and clinical characteristics - Randomised set.

	Agomelatine 10 mg (*N*=131)	Agomelatine 25 mg (*N*=139)	Placebo (*N*=142)
Age (mean±SD) (years)	43.6±13.4	44.1±15.2	44.1±13.1
% female	67.9	71.9	63.4
Duration of GAD (Median) (years)	3.7	4.2	3.6
Previous anxiolytic treatment (n(%))	25 (19.1)	21 (15.1)	27 (19.0)
Previous antidepressant treatment (n(%))	33 (25.2)	37 (26.6)	31 (21.8)
HAM-A total score (mean±SD)	28.6 ± 3.5	29.0 ± 3.7	28.8 ± 3.6
HAM-A psychic anxiety score (mean±SD)	15.8± 2.3	16.1 ± 2.5	16.0 ± 2.3
HAM-A somatic anxiety score (mean±SD)	12.8 ± 2.6	12.9 ± 2.5	12.8 ± 2.7
CGI severity of illness score (mean±SD)	4.5 ± 0.5	4.5 ± 0.6	4.5 ± 0.6
HAD anxiety score (mean±SD)	14.8 ± 2.6	14.6 ± 2.4	14.2 ± 2.5
HAD depression score (mean±SD)	5.7±2.8	6.5±2.9	6.0±3.1
MADRS total score (mean±SD)	11.4 ± 2.4	11.8 ± 2.4	11.5 ± 2.6
SDS total score (mean±SD)	***n*=104**	***n*=104**	***n*=114**
	19.1 ± 4.4	18.8 ± 3.9	18.8 ± 4.2
SDS work (mean±SD)	***n*=104**	***n*=104**	***n*=114**
	6.4±1.7	6.2±1.7	6.5±1.7
SDS social life (mean±SD)	6.5±1.7	6.5±1.7	6.3±1.9
SDS family life (mean±SD)	6.3±1.9	6.3±1.5	6.3±1.6

3.2. Primary efficacy measure

3.2.1. In the FAS

The mean HAM-A total score decreased from baseline to week 12 in all groups (Figure 1). The treatment with both doses of agomelatine was associated with a statistically significant and clinically relevant diminution of GAD symptoms as indicated by the decrease in HAM-A total score at week 12 (LOCF) with a change from baseline of −13.7±8.7 on agomelatine 10 mg and −18.7±7.7 on agomelatine 25 mg as compared to placebo (−6.9±9.2) (difference *versus* placebo of 7.16±1.00 for agomelatine 10 mg and 11.08±0.98 for agomelatine 25 mg, $p<0.0001$) (Table 3). This result was confirmed by the MMRM sensitivity analysis, with a statistically significant difference *versus* placebo in favor of both agomelatine 10 mg (6.97±1.02 $p<0.0001$) and 25 mg (11.26±1.01; $p<0.0001$). The decrease in HAM-A total score at week 12 (LOCF) was significantly more robust in the group of patients receiving 25 mg than 10 mg of agomelatine (adjusted difference between doses of 3.71±0.84, $p<0.0001$).

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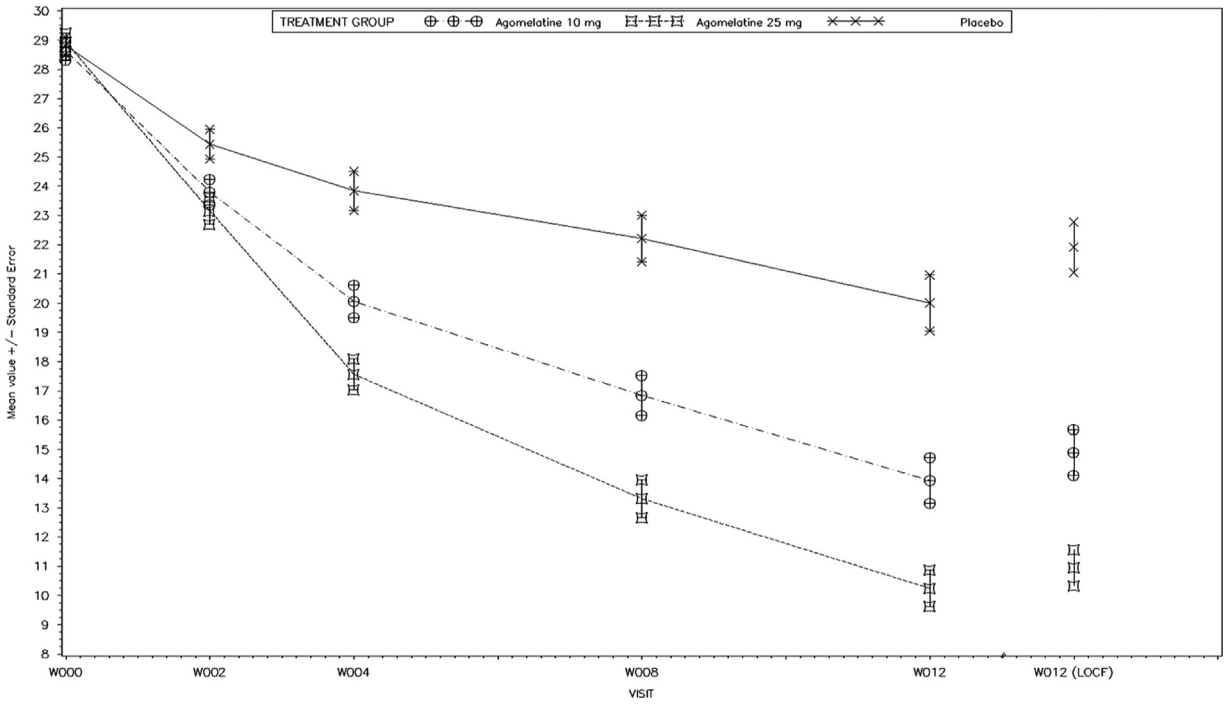

Figure 1 HAM-A total scores by visit (mean ± SEM) over 12 weeks in the FAS.
The mean HAM-A total score decreased from baseline to week 12 in all groups. Both doses of agomelatine were associated with a statistically significant and clinically relevant decrease in HAM-A total score at week 12 (LOCF).

Table 3 HAM-A total score (expressed as change from baseline to week 12 - LOCF approach), response to treatment and remission rates (week 12 (LOCF)) - FAS (n=408).

		Difference *vs.* placebo			
		Estimate	**SE**	**95% CI**	***p*-Value**
HAM-A total score	**(mean ± SD)**				
Placebo (n=140)	−6.9±9.2				
Agomelatine 10 mg (n=130)	−13.7±8.7	7.16	1.00	[5.19; 9.13]	<0.0001[a]
Agomelatine 25 mg (n=138)	−18.0±7.7	11.08	0.98	[9.14;13.01]	<0.0001[a]
HAM-A response rate	**(%)**				
Placebo (n=140)	22.9				
Agomelatine 10 mg (n=130)	51.5	28.68	5.64	[17.63; 39.74]	<0.0001[b]
Agomelatine 25 mg (n=138)	70.3	47.43	5.27	[37.11; 57.75]	<0.0001[b]
HAM-A remission rate [c]	**(%)**				
Placebo (n=140)	12.9				
Agomelatine 10 mg (n=130)	25.4	12.53	4.75	[3.22; 21.84]	0.009[a]
Agomelatine 25 mg (n=138)	39.9	27.00	5.04	[17.13; 36.87]	<0.0001[a]

E (SE): Estimate (Standard Error) of the difference between treatment group - 95% CI: Two-sided 95% Confidence Interval of the estimate - p value: p-value of treatment effect
[a]ANCOVA model - adjustment for center (random effect) and HAM-A total score at week 0.
[b]Chi-Square test: two-sided p-value.
[c]Post-hoc analysis.

A clinically relevant difference in active treatment efficacy *versus* placebo was seen for both doses of agomelatine, with a delta (agomelatine-placebo) response rate of 28.7%±5.64% for agomelatine 10 mg (p<0.0001) and 47.4% ±5.27% for agomelatine 25 mg (p<0.0001). Remission rates were 25.4% on agomelatine 10 mg, 39.9% on agomelatine

Table 4 HAM-A total score (expressed as change from baseline to week 12 - LOCF approach), response to treatment and remission rates (week 12 (LOCF)) - Subsets of more severely anxious patients at baseline.

Sub-FAS HAM-A total score ≥ 25 ($n=365$)		**Difference *vs.* placebo**			
		Estimate	**SE**	**95% CI**	***p*-value**
HAM-A total score	**(mean ± SD)**				
Placebo ($n=128$)	−6.9 ± 9.3				
Agomelatine 10 mg ($n=115$)	−13.8 ± 8.8	7.20	1.06	[5.11; 9.29]	<0.0001[a]
Agomelatine 25 mg ($n=122$)	−18.7 ± 7.5	11.72	1.05	[9.67;13.78]	<0.0001[a]
HAM-A response rate	**(%)**				
Placebo ($n=128$)	21.1				
Agomelatine 10 mg ($n=115$)	49.6	28.47	5.89	[16.92; 40.02]	<0.0001[b]
Agomelatine 25 mg ($n=122$)	71.3	50.22	5.46	[39.52; 60.91]	<0.0001[b]
HAM-A remission rate [c]	**(%)**				
Placebo ($n=128$)	12.5				
Agomelatine 10 mg ($n=115$)	22.6	10.11	4.87	[0.56; 19.66]	0.037[b]
Agomelatine 25 mg ($n=122$)	40.2	27.66	5.31	[17.25; 38.08]	<0.0001[b]
Sub-FAS HAM-A total score ≥ 25 & CGI-S ≥ 5 ($n=202$)		**Difference *vs.* placebo**			
		Estimate	**SE**	**95% CI**	***p*-value**
HAM-A total score	**(mean ± SD)**				
Placebo ($n=65$)	−6.4 ± 8.5				
Agomelatine 10 mg ($n=65$)	−14.5 ± 8.5	8.11	1.39	[5.37; 10.84]	<0.0001[a]
Agomelatine 25 mg ($n=72$)	-19.2 ± 7.6	12.86	1.35	[10.20.15.52]	<0.0001[a]
HAM-A response rate	**(%)**				
Placebo ($n=65$)	15.4				
Agomelatine 10 mg ($n=65$)	50.8	35.38	7.65	[20.40; 50.37]	<0.0001[b]
Agomelatine 25 mg ($n=72$)	70.8	55.45	6.98	[41.77; 69.13]	<0.0001[b]
HAM-A remission rate [c]	**(%)**				
Placebo ($n=65$)	7.7				
Agomelatine 10 mg ($n=65$)	20.0	12.31	5.96	[0.62; 23.99]	0.042[b]
Agomelatine 25 mg ($n=72$)	45.8	38.14	6.74	[24.93; 51.35]	<0.0001[b]

E (SE): Estimate (Standard Error) of the difference between treatment group - 95% CI: Two-sided 95% Confidence Interval of the estimate - *p* value: *p*-value of treatment effect

[a]ANCOVA model - adjustment for center (random effect) and HAM-A total score at week 0.

[b]Chi-Square test: two-sided *p*-value.

[c]Post-hoc analysis.

25 mg and 12.9% on placebo; statistical significance was reached when comparing the agomelatine and placebo groups ($p=0.009$ and $p<0.0001$, respectively, Table 3).

3.2.2. More severely anxious patients

For patients with HAM-A total score at baseline ≥ 25 ($N=365$; 88.6% of the whole population), the superiority of both doses of agomelatine *versus* placebo was established with an adjusted difference on change in HAM-A total score of 7.20 ± 1.06 points ($p<0.0001$) for agomelatine 10 mg and 11.72 ± 1.05 points ($p<0.0001$) for agomelatine 25 mg (Table 4). The decrease in HAM-A total score at week 12 (LOCF) was significantly higher at 25 mg than at 10 mg (difference between doses of 4.31 ± 0.89, $p<0.0001$).

Response rates were 49.6% for agomelatine 10 mg and 71.3% for agomelatine 25 mg, both significantly higher than for placebo (21.1%) ($p<0.0001$, Table 4). Remission rates were 22.6% on agomelatine 10 mg, 40.2% on agomelatine 25 mg and 12.5% on placebo ($p=0.037$ and $p<0.0001$ for the comparisons with placebo, Table 4).

For patients with HAM-A total score ≥ 25 and CGI-S ≥ 5 at baseline ($N=202$, 49% of the whole population), the

Table 5 Secondary efficacy measures - expressed as scores at week 12 (LOCF) (Mean ± SD).

		Difference *vs.* placebo			
	(mean ± SD)	Estimate	SE	95% CI	*p*-Value
HAMA *psychic anxiety score*					
Placebo (*n*=140)	12.1 ± 5.7				
Agomelatine 10 mg (*n*=130)	8.0 ± 4.8	4.04	0.64	[2.77; 5.31]	<0.0001[a]
Agomelatine 25 mg (*n*=138)	5.8 ± 4.2	6.26	0.60	[5.08; 7.44]	<0.0001[a]
HAMA *somatic anxiety score*					
Placebo (*n*=140)	9.8 ± 5.0				
Agomelatine 10 mg (*n*=130)	6.9 ± 4.7	2.98	0.59	[1.82; 4.14]	<0.0001[a]
Agomelatine 25 mg (*n*=138)	5.1 ± 3.6	4.71	0.52	[3.67; 5.74]	<0.0001[a]
CGI *severity of illness score*					
Placebo (*n*=140)	3.8 ± 1.3				
Agomelatine 10 mg (*n*=130)	2.9 ± 1.3	0.82	1.16	[0.51; 1.13]	<0.0001[a]
Agomelatine 25 mg (*n*=138)	2.3 ± 1.0	1.42	0.14	[1.14; 1.70]	<0.0001[a]
CGI *global improvement score*					
Placebo (*n*=140)	3.2 ± 1.3				
Agomelatine 10 mg (*n*=130)	2.2 ± 1.1	1.00	0.15	[0.71; 1.30]	<0.0001[a]
Agomelatine 25 mg (*n*=138)	1.7 ± 0.8	1.56	0.13	[1.30; 1.82]	<0.0001[a]
HAD *depression score*					
Placebo (*n*=140)	5.6 ± 3.8				
Agomelatine 10 mg (*n*=130)	3.4 ± 3.5	2.22	0.45	[1.33; 3.11]	<0.0001[a]
Agomelatine 25 mg (*n*=138)	2.7 ± 2.9	2.92	0.41	[2.11; 3.73]	<0.0001[a]
HAD *anxiety score*					
Placebo (*n*=140)	11.0 ± 4.8				
Agomelatine 10 mg (*n*=130)	7.5 ± 4.6	3.48	0.58	[2.35; 4.62]	<0.0001[a]
Agomelatine 25 mg (*n*=138)	5.3 ± 4.0	5.73	0.53	[4.69; 6.78]	<0.0001[a]
SDS- total score					
Placebo (*n*=117)	14.7 ± 7.7				
Agomelatine 10 mg (*n*=103)	10.1 ± 7.3	4.63	1.01	[2.63; 3.63]	<0.0001[a]
Agomelatine 25 mg (*n*=106)	6.3 ± 6.0	8.35	0.93	[6.51;10.19]	<0.0001[a]
Work					
Placebo (*n*=117)	5.0 ± 2.6				
Agomelatine 10 mg (*n*=103)	3.5 ± 2.5	1.51	0.35	[0.82; 2.20]	<0.0001[a]
Agomelatine 25 mg (*n*=106)	2.2 ± 2.2	2.76	0.32	[2.12; 3.40]	<0.0001[a]
Social life					
Placebo (*n*=140)	5.1 ± 2.8				
Agomelatine 10 mg (*n*=128)	3.4 ± 2.5	1.67	0.33	[1.03; 2.31]	<0.0001[a]
Agomelatine 25 mg (*n*=136)	2.2 ± 2.1	2.90	0.30	[2.32; 3.48]	<0.0001[a]
Family life					
Placebo (*n*=140)	4.9 ± 2.6				
Agomelatine 10 mg (*n*=128)	3.2 ± 2.4	1.70	0.31	[1.10; 2.31]	<0.0001[a]
Agomelatine 25 mg (*n*=136)	2.1 ± 2.0	2.86	0.28	[2.30; 3.41]	<0.0001[a]

E (SE): Estimate (Standard Error) of the difference between treatment group - 95% CI: Two-sided 95% Confidence Interval of the estimate - *p* value: *p*-value of treatment effect

[a]Student's *t*-test: two-sided *p*-value.

adjusted difference *vs.* placebo on HAM-A total score was 8.11±1.39 points ($p<0.0001$) for agomelatine 10 mg, and 12.86±1.35 ($p<0.0001$) for agomelatine 25 mg (Table 4). The decrease in HAM-A total score at week 12 (LOCF) was significantly higher when the patients were treated with 25 mg of agomelatine than with 10 mg (difference between doses of 4.65±1.15, $p<0.0001$).

Response rates were significantly higher for both doses of agomelatine as compared to placebo (agomelatine 10 mg: 50.8%, agomelatine 25 mg: 70.8%, and placebo: 15.4%; $p<0.0001$, Table 4). Remission rates were 20.0% on agomelatine 10 mg, 45.8% on agomelatine 25 mg and 7.7% on placebo ($p=0.042$ and $p<0.0001$ for the comparisons with placebo, Table 4).

3.3. Secondary efficacy measures in the FAS

Psychic and somatic symptoms of GAD were significantly more improved on both doses of agomelatine compared with placebo at week 12 (LOCF) ($p<0.0001$ for each subscore and for both comparisons, Table 5).

The agomelatine-placebo difference on the mean CGI-S score was statistically significant at week 12 (LOCF) for both doses of agomelatine ($p<0.0001$) (Table 5).

HAD Depression and Anxiety sub-scores were significantly more improved on both doses of agomelatine compared with placebo at week 12 (LOCF) ($p<0.0001$ for each subscore and for both comparisons, Table 5).

Results of the three SDS scores showed that both doses of agomelatine significantly separated from placebo in improving patients' functionality (Table 5). Over the 12 weeks of treatment, mean decreases in the total SDS score were significantly greater in both the 10 and 25 mg agomelatine groups, than in the placebo group. The placebo-agomelatine difference was 4.63±1.01 points ($p<0.0001$) in the 10 mg group and 8.35±0.93 points ($p<0.0001$) in the 25 mg group. Decreases in all sub-scores were significantly more pronounced with the two doses of agomelatine than in the placebo group (Table 5).

The number of patients with an SDS total score of 12 or less, indicating functional response, was 64 (62.1%) in the agomelatine 10 mg arm, 91 (85.9%) in the agomelatine 25 mg arm, and 44 (37.6%) in the placebo arm. The placebo-agomelatine difference was 24.5±6.6% ($p<0.001$) at 10 mg, and 48.2±5.6% ($p<0.0001$) at 25 mg.

The number of patients with an SDS total score of 6 or less, indicating functional remission was 41 (39.8%) in the agomelatine 10 mg arm, 62 (58.5%) in the agomelatine 25 mg, and 24 (20.5%) in the placebo arm. The placebo-agomelatine difference was 19.3±6.1% ($p=0.002$) at 10 mg, and 38.0±6.1% ($p<0.0001$) at 25 mg.

3.4. Tolerability

In the safety set ($N=410$), similar percentages of patients reported at least one emergent adverse event (EAE) during the 12-week treatment period in agomelatine 10 mg (29.8%), agomelatine 25 mg (34.5%) and placebo (25.7%) groups (Table 6). The most frequent EAEs on agomelatine were headache, nasopharyngitis and back pain. Compared to the placebo, the frequency of headache was lower in the agomelatine 10 mg group (4.6% vs. 6.4%), while the frequency of nasopharyngitis was higher (5.3% vs. 0.7%); no patient reported back pain in the agomelatine 10 mg group. The relevant percentages of patients in the agomelatine 25 mg and placebo groups were comparable for headache (6.5% vs. 6.4%) and nasopharyngitis (0.7%), and higher in the agomelatine 25 mg group for back pain (4.3% vs. 0.7%). Compared to placebo, nasopharyngitis, somnolence, fatigue and influenza were more frequently reported by patients in the agomelatine 10 mg group; while back pain, somnolence, nausea, dry mouth and arthralgia were more frequently reported by patients in the agomelatine 25 mg group (Table 6). The majority of EAEs were rated as mild or moderate.

A total of 6 patients (1.5%) reported at least one severe emergent adverse event without apparent difference

Table 6 Most frequently reported emergent adverse events[a] during the double-blind treatment period (at least 2% of the patients in any group) – Safety set.

Adverse events	Agomelatine 10 mg ($N=131$)	Agomelatine 25 mg ($N=139$)	Placebo ($N=140$)
All	29.8	34.5	25.7
Headache	4.6	6.5	6.4
Back pain	-	4.3	0.7
Somnolence	1.5	2.9	0.7
Nausea	0.8	2.9	1.4
Dizziness	0.8	2.2	2.1
Dry mouth	0.8	2.2	0.7
Arthralgia	-	2.2	-
Fatigue	2.3	1.4	1.4
Sinusitis	0.8	1.4	2.9
Nasopharyngitis	5.3	0.7	0.7
Influenza	2.3	-	1.4

[a]expressed as percent of affected patients among exposed patients in the considered treatment group.

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between the groups (2 patients in each group). All severe EAEs were reported once.

Adverse events leading to treatment discontinuation were similar in the three groups. One patient (0.8%) on agomelatine 10 mg had an EAE (hyperthyroidism) which led to a treatment withdrawal. Three patients (2.2%) on agomelatine 25 mg had EAEs which led to a treatment withdrawal (ASAT, ALAT and GGT increase, gastrointestinal disorders, headache). Two patients (1.4%) on placebo had treatment-related EAEs which led to a treatment withdrawal (psychiatric disorders, neck pain).

Five serious EAEs (SEAEs) were reported by 4 patients (3.1%) in the agomelatine 10 mg, 11 SEAEs were reported by 3 patients (2.2%) in the agomelatine 25 mg, and 5 SEAEs were reported by 2 patients (1.4%) in the placebo group.

The most frequent SEAEs in any agomelatine group were somnolence (2 patients on agomelatine 10 mg), AST and ALT increased (2 patients on agomelatine 25 mg). Three SEAEs were considered treatment-related: somnolence in one patient on agomelatine 10 mg group, one AST and one ALT increase in one patient on agomelatine 25 mg. These 3 SEAEs did not lead to the study drug withdrawal, and resolved.

There were no clinically relevant between group differences, nor changes from baseline to the last value on treatment, in the biochemical and haematological parameters during the study.

Two patients had emergent potentially clinically significant abnormal (PCSA) transaminases at week 12. One patient on agomelatine 10 mg: PCSA values of ALT and AST were 1.9 ULN and 4.1 ULN respectively; one patient on agomelatine 25 mg with PCSA values of ALT 11.4 ULN and AST 8.3 ULN. The latter case was related to treatment. All values normalized after study drug discontinuation.

There were neither clinically relevant between group differences nor changes from baseline to the last post-baseline value during treatment for supine blood pressure, heart rate, weight and BMI. No clinically relevant ECG abnormalities were recorded in the two agomelatine groups; one patient in the placebo group presented with one emergent ECG abnormality, considered as clinically significant by the investigator.

4. Discussion

This placebo-controlled study demonstrates the efficacy of both agomelatine 10 mg and 25 mg daily in the short-term treatment of GAD. The clear efficacy of agomelatine was demonstrated on the primary outcome measure (HAM-A total score), with both agomelatine arms separating significantly from placebo, and with clinically relevant differences of 7 and 11 points for agomelatine 10 mg and 25 mg, respectively. This efficacy was supported by consistent findings on secondary measures of clinical response (51% to 70%) and remission (25% to 40%) on HAMA, CGI and HAD scores, and a decrease in associated functional impairment.

The study also provided evidence for a dose effect of agomelatine, with superiority of the 10 mg dose over placebo but a more marked superiority of agomelatine 25 mg over placebo. Indeed, a significantly more pronounced decrease in HAM-A in agomelatine 25 mg compared to agomelatine 10 mg was observed. There have been relatively few dose-finding studies of antidepressants in GAD. There is little evidence for differences in efficacy between paroxetine 20 mg and 40 mg (Rickels et al., 2003) or between duloxetine 60 mg and 120 mg (Koponen et al., 2007). However, escitalopram 5 mg does not differ from placebo and effect sizes are larger with escitalopram 20 mg than escitalopram 10 mg (Baldwin et al., 2006), and similarly, there appears to be a dose-response relationship with venlafaxine, with 37.5 mg the least efficacious dose and venlafaxine 150 mg the most efficacious dose (Allgulander et al., 2001). Such differences in dose-response curves may well reflect dose-related alterations in receptor binding profiles (Millan et al., 2005; Papp et al., 2006).

Whereas some agents that are efficacious in GAD act primarily on psychic rather than somatic symptoms assessed by the HAM-A, the benefits of agomelatine were significant on both psychic and somatic symptoms of GAD, in agreement with the previous GAD trials with this agent (Stein et al., 2008, 2012). The benefit of agomelatine was also apparent for both doses in subsets of more severely anxious patients. Agomelatine 25 mg was particularly efficacious in the subset of patients with HAM-A total score $\geq$ 25 and CGI-S $\geq$ 5 at baseline, with a 13 point difference *versus* placebo on the HAM-A total score, and a substantial difference *versus* placebo on rate of response to treatment (about 56%) over the 12 week period. In this group, remission on agomelatine 25 mg was achieved for about half the sample (46%). In the placebo group, only 15.4% of patient showed a response and 7.7% a remission of symptoms. As in the whole study sample, agomelatine 10 mg was significantly less efficacious than agomelatine 25 mg in the two subsets of severely ill patients, with relevant differences of at least 4 points on the final HAM-A total score between the two agomelatine doses (post-hoc analyses).

Taken together, these findings provide additional evidence for the efficacy of agomelatine in the management of GAD disorder and give further support for 25 mg as the dose of choice, as was found in previous GAD trials with agomelatine (Stein et al., 2014; Stein et al., 2008). The 11 point difference between agomelatine 25 mg and placebo is considerable larger than the 3.3 and 4.7 point differences in those earlier studies. All 3 studies had similar baseline levels of GAD severity, and roughly similar endpoint scores on the HAM-A (12.3 ± 9.5 and 13.0 ± 9.4 *versus* 10.9 ± 7.2 at 25 mg in the present study); but in the current study a lower proportion of patients responded to placebo (23%) as compared to the two previous studies (approx. 47% and 37%, respectively). This was particularly apparent in the subset of more severely depressed patients, where an even smaller proportion of patients responded to placebo (21% and 15%).

In addition to reducing anxiety symptoms, agomelatine had a range of other positive effects, including improvement of functioning. Again, SDS data corroborated findings that agomelatine 25 mg was more efficacious than agomelatine 10 mg daily. The mean change difference in the SDS total score over a 12-week period of treatment was about -9 and -13 points in 10 mg and 25 mg agomelatine doses respectively, with significant differences of about 5 and 8 points *versus* placebo at week 12. The benefits of agomelatine 25 mg on functioning have been previously reported in MDD (Kennedy et al., 2016; Kennedy et al.,

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2014; Pecenak and Novotny, 2013); these effects remain robust in GAD.

Based on cut-offs for functional response and remission (Sheehan and Sheehan, 2008), SDS total scores in the whole study population indicate a remarkably high rate of remission (85.9%) after 12 weeks of agomelatine 25 mg. The almost three-fold higher functional remission rates in patients treated with agomelatine 25 mg *versus* placebo provide important evidence in favour of this dosage of agomelatine. It is also noteworthy that agomelatine acts on the three functional domains of work, social, and family, supporting its clinically relevant and broad-spectrum actions in reducing anxiety symptoms and improving function.

The low placebo response rate observed in this study is consistent with an increase in the quality of data collected. High response rates to placebo have negatively impacted clinical investigations of antidepressants. For that reason, a number of methodological innovations were introduced to minimize placebo response and increase assay sensitivity in MDD trials with agomelatine, and were included in the current trial. First, strict entry criteria from different sources were cross-checked at baseline. In addition to a minimum entry score on HAM-A, diagnostic criteria (DSM-IV-TR), ratings by the investigator (HAM-A) and self-evaluation by the patients (HAD) were used to exclude less suitable mildly ill patients. Second, training of clinicians was given particular emphasis in the current study; in comparison to the training used in earlier agomelatine GAD studies, the training in this study was more intensive, with a particular focus on GAD diagnosis and symptoms ratings. It is notable that placebo response decreased over time from 47% (Stein 2008), to 37% (Stein et al., 2014), and then again to 23% in the present study. The low placebo response is particularly remarkable given that low levels of adverse events on agomelatine ensure that the blind is maintained.

The profile of adverse events found here is consistent with prior work on agomelatine in GAD (Stein et al., 2008, 2012, 2014); agomelatine was well-tolerated, with only minimal distinctions from placebo. The emergent PCSA transaminases observed in two patients on agomelatine normalized after study drug discontinuation. As with a number of other antidepressants, the hepatic adverse events observed with agomelatine consist mainly of isolated and asymptomatic increases in transaminases, with rapid recovery after withdrawal of agomelatine. The incidence of reported cases is in agreement with that reported in a recent retrospective pooled analysis of changes in transaminase levels in 9234 patients treated in 49 agomelatine trials (Perlemuter et al., 2016), as well as with the description in the Summary of Product Characteristics for MDD treatment (Servier Laboratories, 2015).

4.1. Limitations

The study has the limitation that enrolled patients may not be representative of those seen in general psychiatric or medical practice, where there may be significant comorbidity with depression and other psychiatric disorders (Hoertel et al., 2012). Nevertheless, patients had severe GAD symptoms and high levels of associated disability. Following European Medicines Agency and USA Food and Drug Administration guidelines, trials in GAD exclude primary psychiatric comorbidities, so that our patient sample is comparable to many of those reported in the literature, including registration trials for other agents.

Of note, the present results were based on a cohort of participants enrolled in 35 centers from 5 close countries (Finland, Russia, Poland, Slovakia and Ukraine). A broader spectrum of geographical locations and clinical settings, and a higher number of centers may help increase generalizability of the findings (ICH E9, 1999) but it may also add to variance in the data (Dechartres et al., 2011).

5. Conclusion

In conclusion, there are several pharmacologic treatment options for GAD, but each has limitations. There is still a need in clinical practice for agents with novel mechanisms of action for patients who i) do not respond adequately, or ii) cannot tolerate existing therapies due to side-effects. The present data reinforce early work indicating the efficacy and tolerability of agomelatine 25 mg for the short and long-term treatment of GAD. Taken together, the findings of four trials with agomelatine support the view that this compound is useful for the management of GAD (Stein et al., 2008, 2012, 2014).

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Contributors

The authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Pr. Stein was the scientific advisor for this project. Dan J. Stein and Françoise Picarel-Blanchot managed the literature searches and analyses, and wrote the first draft of the manuscript. Antti Ahokas, Marek Jarema, Alla S. Avedisova, Livia Vavrusova, Oleg Chaban, Céline Gruget, Valérie Olivier, Françoise Picarel-Blanchot and Christian de Bodinat were involved in the collection and analysis of data. All authors contributed to and have approved the final manuscript.

Conflict of interest

DS STEIN has received research grants and/or consultancy honoraria from Abbott, Astrazeneca, Eli-Lilly, GlaxoSmithKline, Jazz Pharmaceuticals, Johnson & Johnson, Lundbeck, Orion, Pfizer, Pharmacia, Roche, Servier, Solvay, Sumitomo, Takeda, Tikvah, and Wyeth. A AHOKAS has received research grants and/or consultancy honoraria from AstraZeneca, Bristol-Myers Scibb, Eli Lilly, GlaxoSmithKline, Lundbeck, Orion, Otsuka, Sanofi-Aventis, Servier and Wyeth. M JAREMA has received research grants and/or consultancy honoraria from BMS, Eli-Lilly, GlaxoSmithKline, Janssen, Medagro, Roche, Servier. AS AVEDISOVA has received research grants and/or consultancy honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Lundbeck, Sanofi-Aventis, Servier. L VAVRUSOVA has no disclosures. O CHABAN has received research grants and/or consultancy honoraria from Alkermes, AstraZeneca, Eli Lilly, Janssen, Lundbeck, Novartis, MSD, Otsuka, Pfizer and Servier. C

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References

Allgulander, C., Hackett, D., Salinas, E., 2001. Venlafaxine extended release (ER) in the treatment of generalised anxiety disorder: twenty-four-week placebo-controlled dose-ranging study. Br. J. Psychiatry 179, 15–22.

Baldwin, D.S., Huusom, A.K., Maehlum, E., 2006. Escitalopram and paroxetine in the treatment of generalised anxiety disorder: randomised, placebo-controlled, double-blind study. Br. J. Psychiatry 189, 264–272.

Bandelow, B., Lichte, T., Rudolf, S., Wiltink, J., Beutel, M.E., 2014. The diagnosis of and treatment recommendations for anxiety disorders. Dtsch. Arztebl. Int. 111, 473–480.

de Bodinat, C., Guardiola-Lemaitre, B., Mocaer, E., Renard, P., Munoz, C., Millan, M.J., 2010. Agomelatine, the first melatonergic antidepressant: discovery, characterization and development. Nat. Rev. Drug Discov. 9, 628–642.

Dechartres, A., Boutron, I., Trinquart, L., Charles, P., Ravaud, P., 2011. Single-center trials show larger treatment effects than multicenter trials: evidence from a meta-epidemiologic study. Ann. Intern. Med. 155, 39–51.

Fava, M., Rush, A.J., Alpert, J.E., Carmin, C.N., Balasubramani, G. K., Wisniewski, S.R., Trivedi, M.H., Biggs, M.M., Shores-Wilson, K., 2006. What clinical and symptom features and comorbid disorders characterize outpatients with anxious major depressive disorder: a replication and extension. Can. J. Psychiatry 51, 823–835.

Guardiola-Lemaitre, B., Bodinat, C., Delagrange, P., Millan, M.J., Munoz, C., Mocaer, E., 2014. Agomelatine: mechanism of action and pharmacological profile in relation to antidepressant properties. Br. J. Pharmacol..

Guy, W., 1976. ECDEU Assessment Manual for Psychopharmacology. US Department of Health, Education and Welfare publication ADM 76-338. National Institute of Mental Health, Rockville MD, pp. 217–222.

Hale, A., Marcelo-Corral, R., Mencacci, C., Saiz Ruiz, J., Albarran Severo, C., Gentil, V., 2010. Superior antidepressant efficacy results of agomelatine versus fluoxetine in severe MDD patients: a randomized, double-blind study. Int. Clin. Psychopharmacol. 25, 305–314.

Hamilton, M., 1959. The assessment of anxiety states by rating. Br. J. Med. Psychol. 32, 50–55.

Hoertel, N., Le, S.Y., Blanco, C., Lavaud, P., Dubertret, C., 2012. Generalizability of clinical trial results for generalized anxiety disorder to community samples. Depress. Anxiety 29, 614–620.

Hoffman, D.L., Dukes, E.M., Wittchen, H.U., 2008. Human and economic burden of generalized anxiety disorder. Depress. Anxiety 25, 72–90.

ICH E9, 1999. ICH Harmonised Tripartite Guideline. Statistical principles for clinical trials. International Conference on Harmonisation E9 Expert Working Group. Stat. Med. 18, pp. 1905–1942.

Kapczinski, F., Lima, M.S., Souza, J.S., Schmitt, R., 2003. Antidepressants for generalized anxiety disorder. Cochrane. Database Syst. Rev. (CD003592).

Kasper, S., Hajak, G., Wulff, K., Hoogendijk, W.J., Montejo, A.L., Smeraldi, E., Rybakowski, J.K., Quera-Salva, M.A., Wirz-Justice, A.M., Picarel-Blanchot, F., Bayle, F.J., 2010. 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. J. Clin. Psychiatry 71, 109–120.

Kennedy, S.H., Emsley, R., 2006. Placebo-controlled trial of agomelatine in the treatment of major depressive disorder. Eur. Neuropsychopharmacol. 16, 93–100.

Kennedy, S.H., Avedisova, A., Gimenez-Montesinos, N., Belaidi, C., de Bodinat, C., 2014. A placebo-controlled study of three agomelatine dose regimens (10 mg, 25 mg, 25-50 mg) in patients with major depressive disorder. Eur. Neuropsychopharmacol. 24, 553–563.

Kennedy, S.H., Avedisova, A., Belaidi, C., Picarel-Blanchot, F., de Bodinat, C., 2016. Sustained efficacy of agomelatine 10 mg, 25 mg, and 25–50 mg on depressive symptoms and functional outcomes in patients with major depressive disorder.**A placebo-controlled study over 6 months**. Eur. Neuropsychopharmacol. 26, 378–389.

Koponen, H., Allgulander, C., Erickson, J., Dunayevich, E., Pritchett, Y., Detke, M.J., Ball, S.G., Russell, J.M., 2007. Efficacy of duloxetine for the treatment of generalized anxiety disorder: implications for primary care physicians. Prim. Care Companion. J. Clin. Psychiatry 9, 100–107.

Lemoine, P., Guilleminault, C., Alvarez, E., 2007. Improvement in subjective sleep in major depressive disorder with a novel antidepressant, agomelatine: randomized, double-blind comparison with venlafaxine. J. Clin. Psychiatry 68, 1723–1732.

Loo, H., Hale, A., D'haenen, H., 2002. Determination of the dose of agomelatine, a melatoninergic agonist and selective 5-HT2C antagonist, in the treatment of major depressive disorder: a placebo-controlled dose range study. Int. Clin. Psychopharmacol. 17, 239–247.

Millan, M.J., Brocco, M., Gobert, A., Dekeyne, A., 2005. Anxiolytic properties of agomelatine, an antidepressant with melatoninergic and serotonergic properties: role of 5-HT2C receptor blockade. Psychopharmacology (Berlin) 177, 448–458.

Montgomery, S.A., Asberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389.

Olié, J.P., Kasper, S., 2007. Efficacy of agomelatine, a MT1/MT2 receptor agonist with 5-HT2C antagonistic properties, in major depressive disorder. Int. J. Neuropsychopharmacol. 10, 661–673.

Papp, M., Litwa, E., Gruca, P., Mocaer, E., 2006. Anxiolytic-like activity of agomelatine and melatonin in three animal models of anxiety. Behav. Pharmacol. 17, 9–18.

Pecenak, J., Novotny, V., 2013. Agomelatine as monotherapy for major depression: an outpatient, open-label study. Neuropsychiatr. Dis. Treat. 9, 1595–1604.

Perlemuter, G., Cacoub, P., Valla, D., Guyader, D., Saba, B., Batailler, C., Moore, K., 2016. Characterisation of Agomelatine-Induced Increase in Liver Enzymes: frequency and Risk Factors Determined from a Pooled Analysis of 7605 Treated Patients. CNS Drugs 30, 877–888.

Rickels, K., Schweizer, E., 1998. The spectrum of generalised anxiety in clinical practice: the role of short-term, intermittent treatment. Br. J. Psychiatry Suppl., 49–54.

Servier Laboratories, 2015. Summary of product characteristics: Valdoxan.

Sheehan, D.V., Harnett-Sheehan, K., Raj, B.A., 1996. The measurement of disability. Int. Clin. Psychopharmacol. 11 (Suppl 3), S89–S95.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59 (Suppl 20), S22–S33.

Sheehan, K.H., Sheehan, D.V., 2008. Assessing treatment effects in clinical trials with the discan metric of the Sheehan Disability Scale. Int. Clin. Psychopharmacol. 23, 70–83.

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Stein, D.J., Hollander, E., 2002. Anxiety Disorders Comorbid with Depression: Social Anxiety Disorder, Post-Traumatic Stress Disorder, Generalized Anxiety Disorder and Obsessive-Compulsive Disorder. Martin Dunitz, London.

Stein, D.J., Ahokas, A.A., de Bodinat, C., 2008. Efficacy of agomelatine in generalized anxiety disorder: a randomized, double-blind, placebo-controlled study. J. Clin. Psychopharmacol. 28, 561–566.

Stein, D.J., Ahokas, A.A., Albarran Severo, C., Olivier, V., Allgulander, C., 2012. Agomelatine prevents relapse in generalised anxiety disorder: a 6-month placebo-controlled discontinuation study. J. Clin. Psychiatry 73, 1002–1008.

Stein, D.J., Ahokas, A., Marquez, M.S., Hoschl, C., Oh, K.S., Jarema, M., Avedisova, A.S., Albarran, C., Olivier, V., 2014. Agomelatine in generalized anxiety disorder: an active comparator and placebo-controlled study. J. Clin. Psychiatry 75, 362–368.

Stein, D.J., Picarel-Blanchot, F., Kennedy, S.H., 2013. Efficacy of the novel antidepressant agomelatine on anxiety symptoms in major depression.

Wittchen, H.U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jonsson, B., Olesen, J., Allgulander, C., Alonso, J., Faravelli, C., Fratiglioni, L., Jennum, P., Lieb, R., Maercker, A., van, O.J., Preisig, M., Salvador-Carulla, L., Simon, R., Steinhausen, H.C., 2011. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur. Neuropsychopharmacol. 21, 655–679.

Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. Acta Psychiatr. Scand. 67, 361–370.

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