Agomelatine for the Treatment of Generalized Anxiety Disorder: A Meta-Analysis

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Objective: Despite multiple drugs available, a large proportion of patients with generalized anxiety disorder (GAD) do not show adequate response and remission. Thus, additional novel pharmacological agents are needed to increase treatment option for GAD. We aimed to investigate efficacy and safety of agomelatine in the treatment of GAD by conducting a meta-analysis.
Methods: An extensive search of multiple databases and clinical trial registries were conducted. Mean change in total scores on Hamilton Anxiety Rating Scale (HAM-A) from baseline to endpoint was our primary outcome measure. Secondary efficacy measures included response and remission rates, as defined by a 50% or greater reduction in HAM-A total scores and a score of 7 or less in HAM-A total scores at study endpoint respectively.
Results: Four published double blinded, randomized, placebo-controlled trials were included in this meta-analysis. Agomelatine more significantly (standardized mean difference = −0.56, p = 0.004) improved HAM-A total scores than placebo. The odds ratios (ORs) of agomelatine over placebo for response and remission rates were 3.75 (p < 0.00001) and 2.74 (p < 0.00001), respectively. Agomelatine was generally well tolerated with insignificance in dropout rate, somnolence, headache, nasopharyngitis, and dizziness compared with placebo. However, agomelatine showed significantly higher incidence of liver function increment (OR = 3.13, p = 0.01) and nausea (OR = 3.27, p = 0.02).
Conclusion: We showed that agomelatine may be another treatment option in patients with GAD. However, the results should be interpreted and translated into clinical practice with caution because the meta-analysis was based on limited numbers of clinical trials.

KEY WORDS: Agomelatine; Anxiety disorder; Clinical trial; Treatment; Meta-analysis.

INTRODUCTION

Generalized anxiety disorder (GAD) is a common and debilitating psychiatric disorder, with lifetime prevalence of 6% [1,2]. The impairment of psychosocial functioning and magnitude of economic loss caused by GAD is comparable to that of major depressive disorder (MDD) [3-5]. Various drugs including benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors, tricyclic antidepressants, anticonvulsants, and atypical antipsychotics can be used to treat GAD

[6-8]. However, only 50% of patients experience response with the first-line therapy [9], and less than 20% of patients achieve complete remission even after taking multiple drugs [10]. Therefore, additional novel pharmacological agents are needed to increase treatment option for patients with GAD.

Agomelatine is an antidepressant which was first approved in Europe in 2009 [11]. Its main mechanism of action includes agonist at melatonergic (MT_1 and MT_2) receptors and antagonist at serotonergic 5-HT_{2C} receptor. Animal studies including Vogel conflict procedure, elevated plus-maze procedure, conditioned footshock-induced ultrasonic vocalizations test, social defeat stress test, predator stress test, and the fear learning process suggested anxiolytic properties of agomelatine [12-14]. Studies further showed that agomelatine's anxiolytic property is mainly attributed from its 5-HT_{2C} antagonism, but melatonin receptor may also be involved in decreasing anxiety

[15]. In line with animal models, a study initially showed that agomelatine was effective in treating anxiety symptoms associated with depression [16]. Therefore, numerous randomized, double-blinded, placebo-controlled clinical trials (RCTs) demonstrated that agomelatine could be an effective and safe treatment option for patients with GAD [17,18].

In terms of investigating potential efficacy and safety of a certain drug other than its approved conditions, meta-analysis is an important study method due to its methodological strengths. It can overcome limitation of small sample sizes, increase statistical power for group comparisons, enhance generalizability by including diverse trials conducted in various populations, investigate potential publication biases, and quantify and analyze inconsistencies in results across clinical studies [19-21]. Despite this importance, although multiple expert opinion reviews systemically described potential usage of agomelatine in patients with GAD [9,22], no meta-analysis was conducted to statistically quantify benefits and drawbacks of agomelatine for patients with GAD. Thus, we performed a meta-analysis and investigated its efficacy and safety of agomelatine in the treatment of GAD.

METHODS

Sources of Data

We repeatedly searched PubMed, Embase, Pubmed, PsycINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, and the Cochrane Central Register of Controlled Trials Library for published articles. In terms of clinical trials, ClinicalTrials.gov (www.clinicaltrials.gov) and International Standard Randomized Controlled Trial Number (ISRCTN) registry were explored. The article and clinical trial searches were conducted repeatedly from January 1st to February 15th, 2020 using MeSH terms: "agomelatine," and "anxiety." Reference lists from identified articles and reviews were manually searched to find additional studies. Two authors (S.M.W. and N.K.K.) independently reviewed the abstracts identified from the literature search. Two other authors (H.R.N. and W.M.B.) re-evaluated potentially eligible papers to determine whether they truly met the selection criteria. The last two authors (H.K.L. and Y.S.W.) discussed and reached a consensus for disagreements.

Inclusion Criteria for the Meta-analysis

Primary inclusion criteria were all RCTs investigating the efficacy and safety of agomelatine for the treatment of GAD. To be included in our meta-analysis, studies were required to: 1) be in double-blinded and randomized in design; 2) have placebo as a comparator, regardless of having an active comparator, 3) have clearly described all inclusion and exclusion criteria; 4) compared the outcomes of the use of placebo and agomelatine in patients with GAD. No restrictions were utilized for severity of GAD, sex, treatment basis (i.e., inpatient or outpatient), pharmaceutical, dose range, or study location.

Data Extraction, Quality Assessment, and Risk of Bias

Data including author's names, year of publication, sample size, patients' characteristics (mean age, sex), duration of treatment, dosage, baseline findings, study location country, and study design were extracted using data-collection form. The quality of RCTs was also assessed based on Cochrane Review's recommendations [23]. The risk of bias in individual studies including sequence generation, allocation concealment, the blinding of participants and investigators, the blinding of outcome assessments, incomplete outcome data, selective outcome reporting, and other sources were independently assessed by the two authors (S.M.W. and W.M.B.).

Study Outcomes

The primary outcome measures were change from baseline to study endpoint in total score of Hamilton Anxiety Rating Scale (HAM-A). The secondary efficacy measures were rate of response (50% or more decrement of HAM-A from baseline to endpoint) and remission (7 or less in total HAM-A score at endpoint). In terms of safety and tolerability, total number of adverse events (AEs) and numbers of dropouts due to AEs were included. Other common AEs including liver function test (LFT), nausea, somnolence, headache, nasopharyngitis, and dizziness were included in the meta-analysis.

Statistical Analysis

We used Review Manager Version 5.3 software (Cochrane Collaboration, Oxford, UK) to conduct statistical analysis. In terms of binary measures, odds ratio (OR) with 95% confidence intervals (CI) using the Mantel-Haenszel method was used to present difference

in change from baseline to endpoint between agomelatine and control groups. In addition, standardized mean difference (SMD) using the method developed by Hedges (Hedges g) with 95% confidence intervals (95% CIs) were utilized for continuous measures. The effect size (ES) can be evaluated based on Cohen's classification: small ES = SMD $<$ 0.2, medium ES = SMD of 0.5, and large ES = SMD $>$ 0.8 [24]. In addition, I^2 statistic was used to explore heterogeneity, which evaluates how much of the variance between studies can be attributed to the actual differences between the studies rather than to chance [25]. I^2 of 75$-$100% indicates considerable hetero-

Embase: 51
Pubmed: 133
Psychinfo: 119
CINAHL: 17
Web of science: 164
The Cochrane central register of controlled trials: 2

Total 486 articles were identified

291 articles were duplicates,
152 articles were irrelevant,
and thus excluded

43 full-text articles were reviewed

- 28 articles: patients with depression only or did not involve GAD
- 4 articles: open-label trials or case report
- 5 articles: review
- 2 articles: no placebo

Therefore, 37 articles were excluded
--- 4 articles were finally selected for the meta-analysis since they were randomized, double-blind, placebo-controlled clinical trials (RCT)

Total 4 short-term RCTs were selected

Clinicaltrialgov.com:
Total 21 clinical trials identified
- 21 clinical trials: irrelevant to GAD

ISRCTN registry
Total 21 clinical trials identified
- 17 clinical trials: irrelevant to anxiety disorder
- 4 trials: duplicates of the articles found in Pubmed

Fig. 1. Schematic presentation of studies selected in the present meta-analysis.
GAD, Generalized anxiety disorder; RCT, randomized, double-blinded, placebo-controlled clinical trial; ISRCTN, International Standard Randomized Controlled Trial Number.

geneity, and the heterogeneity threshold was defined as 50% or more in I^2 value and $p <$ 0.1.

We applied fixed-effects or random-effects models appropriately to perform analyses of primary and secondary measures. A random-effects model was used when I^2 indicated significant heterogeneity among study results ($I^2 >$ 50% and $p <$ 0.1). Studies showed that the random-effects model allows for sampling variability with and between studies, and smaller studies are weighted more whereas larger studies are weighted less. Thus, it is suggested to provide a more balanced analyses than the fixed effect model [26,27].

RESULTS

Study Characteristics

Electronic searches yielded a total of 486 articles. After a preliminary review, 443 papers were excluded because they were either duplicates or irrelevant to our meta-analysis. The remaining 43 full-text articles were retrieved for a more detailed evaluation. After removing 28 articles not involving GAD, 4 open label or case studies, 5 reviews, and 2 clinical trials not having placebo, only 4 studies remained. Of the 21 records obtained from ClinicalTrials.gov, all were irrelevant to GAD. Among 21 clinical trials identified from ISRCTN, 17 clinical trials were irrelevant, and 4 trials involved RCT of GAD, but they were duplicates of the articles found in Pubmed. Thus, 4 articles were finally selected for the meta-analysis since they were randomized, double-blind, placebo-controlled clinical trials (Fig. 1).

Table 1 presents main characteristics of these 4 RCTs. All studies were multi-centered, multinational trials conducted outside of US. Three were short-term clinical trials with 12 weeks of study duration [17,28,29]. One trial involved a 26-week double-blinded, placebo-controlled trial in GAD patients who showed optimal remission with agomelatine [18]. A total of 1,024 participants were included, and number of patients included in placebo group and agomelatine groups were 442 and 582 respectively. Three studies used identical dose of agomelatine, 25$-$50 mg/day [17,18,28]. However, in one study, the agomelatine group was further randomized into agomelatine 10 mg/day or 25 mg/day [29].

The risk of bias assessment showed that all studies included were good in quality in terms of their method-
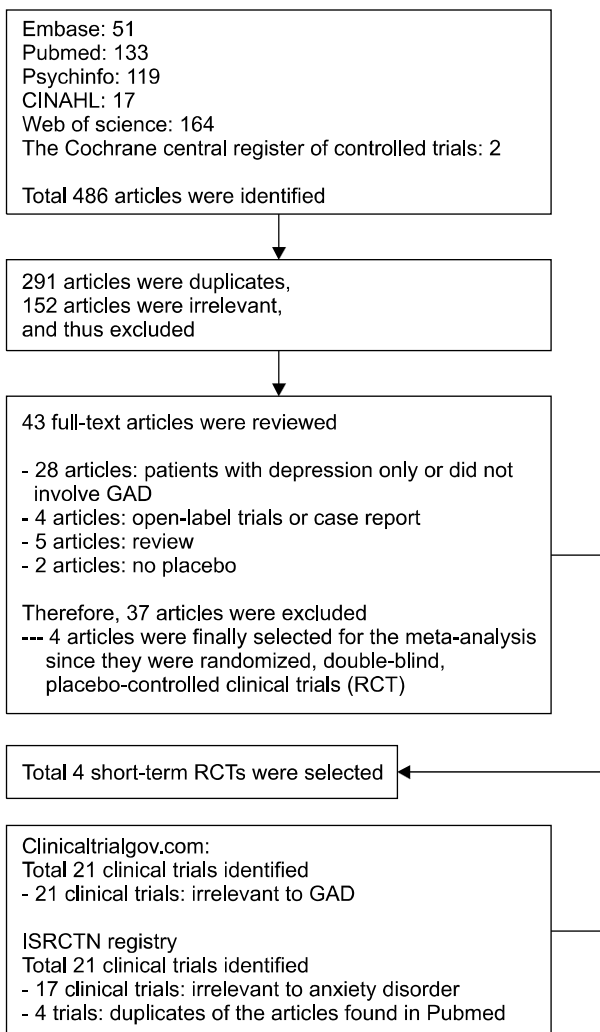
Table 1. Summary of RCTs of agomelatine for the treatment of generalized anxiety disorder

Study	Drugs (mg/d)	Patient (n)	Mean age (yr)	Duration (wk)	Baseline MADRS	Hamilton Anxiety Rating Scale				Study location
						Baseline	Mean change[a]	Response[b]	Remission[c]	
Stein *et al.* 2008 [17]	PBO	58	41.7	12	11.7 ± 2.1	28.6 ± 3.8	−13.2 ± 9.5	27 (46.6)	13 (22.4)	S. Africa, FN
	AGO (25−50)	63	41.7		11.6 ± 2.9	29.0 ± 4.4	−16.6 ± 8.9	42 (66.7)	26 (41.3)	
Stein *et al.* 2012 [18]	PBO	113	47.0	26	NA	6.0 ± 2.6	3.6 ± 8.4	NA	NA	CN, DN, ET, FN,
	AGO (25−50)	112	45.9		NA	5.9 ± 2.7	−1.6 ± 7.7	NA	NA	HG, and SW
Stein *et al.* 2014 [28]	PBO	131	43.0	12	12.3 ± 2.4	28.2 ± 3.4	−10.6 ± 9.5	48 (36.6)	26 (19.9)	FN, RU, PL, CZ,
	AGO (25−50)	139	43.6		12.0 ± 2.4	28.6 ± 4.0	−15.6 ± 9.4	89 (64.0)	51 (36.7)	SL, AG, S. Korea
Stein *et al.* 2017 [29]	PBO	140	44.1	12	11.5 ± 2.6	28.8 ± 3.6	−6.9 ± 9.2	32 (22.9)	18 (12.9)	FN, RU, PL, SL,
	AGO total	268	43.9		11.6 ± 2.4	28.8 ± 3.7	−15.91 ± 8.19	164 (61.2)	88 (32.9)	Ukraine
	AGO (10)	130	43.6		11.8 ± 2.4	28.6 ± 3.5	−13.87 ± 8.7	67 (51.5)	33 (25.4)	
	AGO (25)	138	44.1		11.4 ± 2.4	29.0 ± 3.7	−18.7 ± 7.7	97 (70.3)	55 (39.9)	

Values are presented as number (%) or mean ± standard deviation.
RCT, randomized, double-blind, placebo-controlled trials; MADRS, Montgomery and Åsberg Depression Rating Scale; SD, standard deviation; PBO, Placebo; AGO, Agomelatine; NA, not applicable; S. Africa, South Africa; FN, Finland; CN, Canada; DN, Denmark; ET, Estonia, HG, Hungary; SW, Sweden; RU, Russia; PL, Poland; CZ, Czech Republic; SL, Slovakia; AG, Argentina; S. Korea, South Korea; HAM-A, Hamilton Anxiety Rating Scale.
[a]Primary efficacy measure; [b]Response: 50% or more decrement of HAM-A from baseline to endpoint; [c]Remission: 7 or less in total HAM-A score at endpoint.

Fig. 2. Risk of bias in individual studies included in the meta-analysis.

ologies (Fig. 2). Publication bias could not be tested because there were too few studies for the various outcomes examined and all RCTs included were published studies.

Efficacy

Primary endpoint: Mean change of HAM-A

The result of the meta-analysis regarding the primary endpoints, mean change of HAM-A total score from baseline to study endpoint, are presented as forest plots (Fig. 3). Agomelatine (SMD, −0.56 [95% CI, −0.94 to −0.18], $p <$

0.0001) more significantly improved HAM-A total scores than placebo. Significant heterogeneity was reported ($I^2 =$ 88%, $p < 0.0001$), so we used random effect model. A subgroup analysis was conducted to explain this heterogeneity. We hypothesized that heterogeneity occurred due to lack of overlap of confidence interval caused from one study having high SMD, Stein *et al.* 2017 [29] (SMD of −1.05). After excluding the study by Stein *et al.* 2017 [29], the heterogeneity became insignificant ($I^2 =$ 10%, $p = 0.33$) while significant superiority of agomelatine over placebo remained with lower effect size (SMD, −0.39 [95% CI, −0.56 to −0.22]). The study by Stein *et al.* 2014 [28] had a different design; GAD patients who showed significant remission from agomelatine were randomized to placebo to agomelatine. Thus, an additional subgroup analysis was conducted after excluding this study, which showed that the effect size of agomelatine became greater (SMD, −0.66 [95% CI, −1.08 to −0.24]), but the heterogeneity remained significant ($I^2 = 87\%$, $p =$ 0.0006) (Fig. 3).

Secondary endpoint: Rate of response and remission

One study (Stein *et al.* 2017 [29]) was not included in the secondary endpoint analysis, because it did not investigate difference between agomelatine and placebo in response or remission rate. The ORs of agomelatine over placebo for response and remission rates were 3.75 (95% CIs, 2.76 to 5.09; $p < 0.00001$) and 2.74 (95% CIs, 1.93
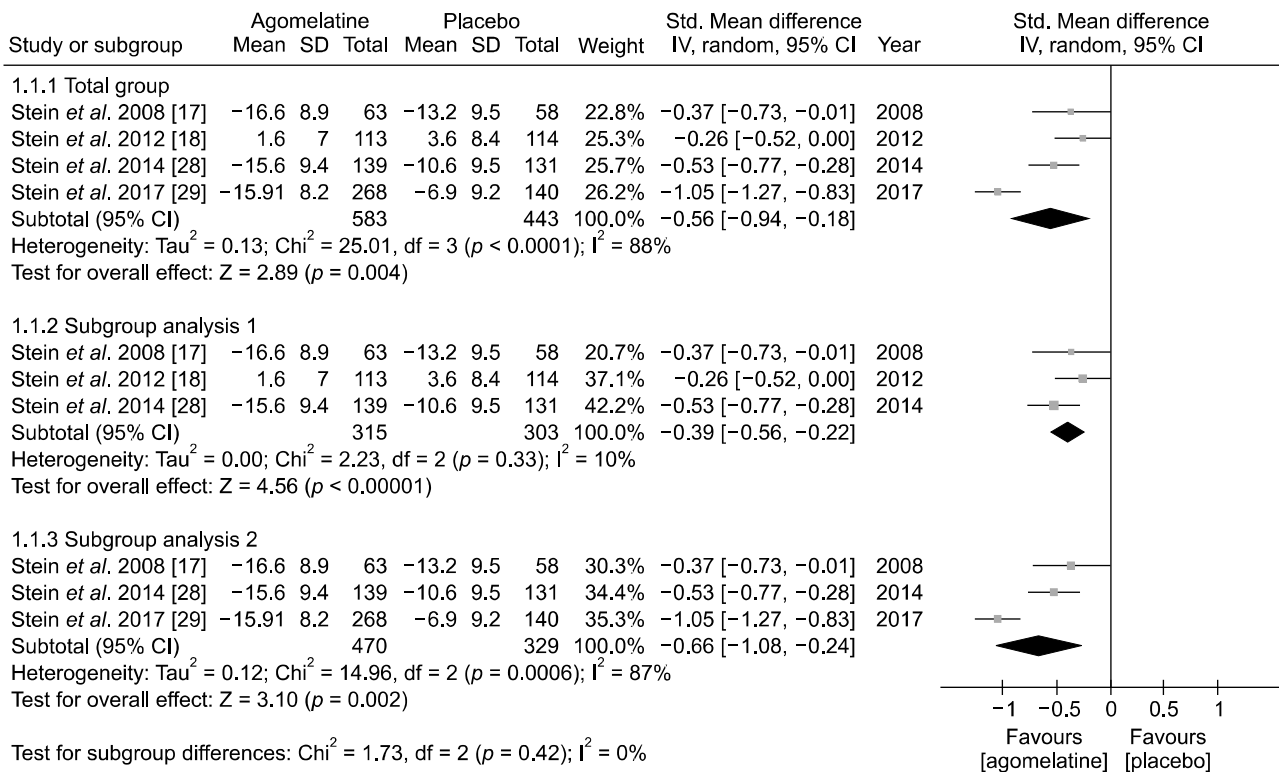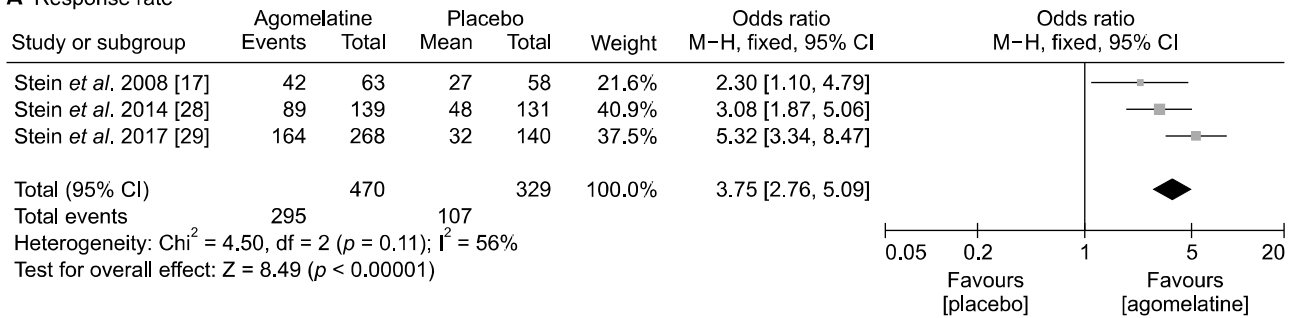
Study or subgroup	Agomelatine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean difference IV, random, 95% CI	Year
1.1.1 Total group									
Stein et al. 2008 [17]	−16.6	8.9	63	−13.2	9.5	58	22.8%	−0.37 [−0.73, −0.01]	2008
Stein et al. 2012 [18]	1.6	7	113	3.6	8.4	114	25.3%	−0.26 [−0.52, 0.00]	2012
Stein et al. 2014 [28]	−15.6	9.4	139	−10.6	9.5	131	25.7%	−0.53 [−0.77, −0.28]	2014
Stein et al. 2017 [29]	−15.91	8.2	268	−6.9	9.2	140	26.2%	−1.05 [−1.27, −0.83]	2017
Subtotal (95% CI)			583			443	100.0%	−0.56 [−0.94, −0.18]	

Heterogeneity: Tau^2 = 0.13; Chi^2 = 25.01, df = 3 (p < 0.0001); I^2 = 88%
Test for overall effect: Z = 2.89 (p = 0.004)

1.1.2 Subgroup analysis 1									
Stein et al. 2008 [17]	−16.6	8.9	63	−13.2	9.5	58	20.7%	−0.37 [−0.73, −0.01]	2008
Stein et al. 2012 [18]	1.6	7	113	3.6	8.4	114	37.1%	−0.26 [−0.52, 0.00]	2012
Stein et al. 2014 [28]	−15.6	9.4	139	−10.6	9.5	131	42.2%	−0.53 [−0.77, −0.28]	2014
Subtotal (95% CI)			315			303	100.0%	−0.39 [−0.56, −0.22]	

Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.23, df = 2 (p = 0.33); I^2 = 10%
Test for overall effect: Z = 4.56 (p < 0.00001)

1.1.3 Subgroup analysis 2									
Stein et al. 2008 [17]	−16.6	8.9	63	−13.2	9.5	58	30.3%	−0.37 [−0.73, −0.01]	2008
Stein et al. 2014 [28]	−15.6	9.4	139	−10.6	9.5	131	34.4%	−0.53 [−0.77, −0.28]	2014
Stein et al. 2017 [29]	−15.91	8.2	268	−6.9	9.2	140	35.3%	−1.05 [−1.27, −0.83]	2017
Subtotal (95% CI)			470			329	100.0%	−0.66 [−1.08, −0.24]	

Heterogeneity: Tau^2 = 0.12; Chi^2 = 14.96, df = 2 (p = 0.0006); I^2 = 87%
Test for overall effect: Z = 3.10 (p = 0.002)

Test for subgroup differences: Chi^2 = 1.73, df = 2 (p = 0.42); I^2 = 0%

Fig. 3. Mean changes of Hamilton Anxiety Scale total score from baseline to end point between agomelatine and placebo treatment groups. SD, standard deviation; std, standardized; 95% CI, 95% confidence interval; IV, inverse variance.

A Response rate

Study or subgroup	Agomelatine Events	Total	Placebo Mean	Total	Weight	Odds ratio M−H, fixed, 95% CI
Stein et al. 2008 [17]	42	63	27	58	21.6%	2.30 [1.10, 4.79]
Stein et al. 2014 [28]	89	139	48	131	40.9%	3.08 [1.87, 5.06]
Stein et al. 2017 [29]	164	268	32	140	37.5%	5.32 [3.34, 8.47]
Total (95% CI)		470		329	100.0%	3.75 [2.76, 5.09]
Total events	295		107			

Heterogeneity: Chi^2 = 4.50, df = 2 (p = 0.11); I^2 = 56%
Test for overall effect: Z = 8.49 (p < 0.00001)

B Remission rate

Study or subgroup	Agomelatine Events	Total	Placebo Mean	Total	Weight	Odds ratio M−H, fixed, 95% CI
Stein et al. 2008 [17]	26	63	13	58	19.5%	2.43 [1.10, 5.39]
Stein et al. 2014 [28]	51	139	26	131	41.6%	2.34 [1.35, 4.06]
Stein et al. 2017 [29]	88	268	18	140	38.9%	3.31 [1.90, 5.78]
Total (95% CI)		470		329	100.0%	2.74 [1.93, 3.88]
Total events	165		57			

Heterogeneity: Chi^2 = 0.85, df = 2 (p = 0.65); I^2 = 0%
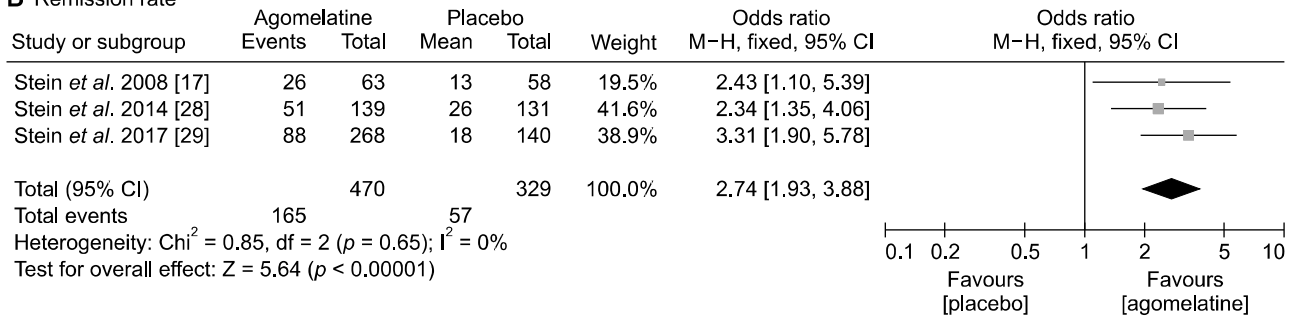Test for overall effect: Z = 5.64 (p < 0.00001)

Fig. 4. Secondary efficacy measure: rate of (A) response and (B) remission between agomelatine and placebo. M−H; Mantel−Haenszel; 95% CI, 95% confidence interval.

to 3.88; $p < 0.00001$), respectively (Fig. 4). For both, fixed model was utilized because no significant heterogeneity was noted.

Safety and Tolerability

Safety and tolerability of 4 RCTs for agomelatine are presented in Table 2. Total AEs were higher in agomelatine group than in placebo group, but they were statistically not significant (OR, 1.25; 95% CIs, 0.96 to 1.62; $p = 0.1$). Dropout rate due to adverse event also did not significantly differ between two groups (Fig. 5). In terms of commonly observed side effects, agomelatine showed significantly higher incidence of LFT increment (OR, 3.13; 95% CIs, 1.26 to 7.78; $p = 0.01$) and nausea (OR, 3.27; 95% CIs, 1.18 to 9.11; $p = 0.02$) (Fig. 6). Lastly, agomelatine did not cause clinically significant somnolence,
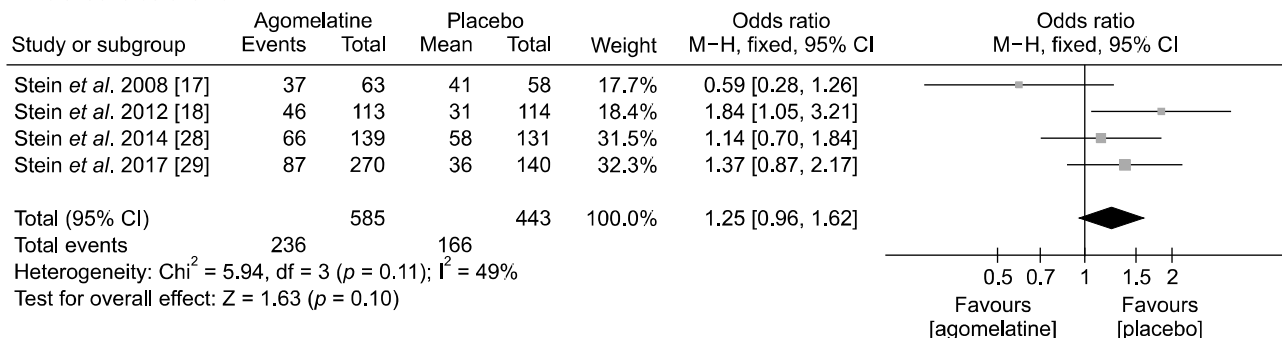
Table 2. Safety and tolerability of 4 RCTs of agomelatine for the treatment of generalized anxiety disorder

Study	Drugs (mg/d)	Patient (n)	At least 1 AE	Increased LFT	Nausea	Somnolence	Headache	NPT	Dizziness	Dropout due to AE	SAE Patient	SAE Critical illness
Stein et al. 2008 [17]	PBO	58	41 (70.7)	0	1 (1.7)	-	9 (15.5)	10 (17.2)	2 (3.4)	0	0	0
	AGO (25−50)	63	37 (58.7)	2 (3.2)	3 (4.8)	-	9 (14.3)	7 (11.1)	5 (7.9)	1	0	0
Stein et al. 2012 [18]	PBO	114	31 (27.2)	5 (4.4)	0 (0)	2 (1.8)	3 (2.6)	6 (5.3)	3 (2.6)	2 (1.8)	0	0
	AGO (25−50)	113	46 (40.7)	13 (11.5)	5 (4.4)	3 (2.7)	12 (10.6)	6 (5.3)	4 (3.5)	0	0	0
Stein et al. 2014 [28]	PBO	131	58 (44.3)	0	1 (0.8)	1 (0.8)	14 (10.7)	7 (5.3)	4 (3.1)	4 (3.1)	4 (3.1)	0
	AGO (25−50)	139	66 (47.5)	2 (1.4)	5 (3.6)	3 (2.2)	10 (7.2)	6 (4.3)	3 (2.2)	3 (2.2)	1 (0.7)	0
Stein et al. 2017 [29]	PBO	140	36 (25.7)	0	2 (1.4)	1 (0.7)	9 (6.4)	1 (0.7)	3 (2.1)	2 (1.4)	2 (1.4)	0
	AGO (10−25)	270	87 (32.2)	2 (0.7)	5 (1.9)	6 (2.2)	15 (5.6)	8 (3.0)	4 (1.5)	4 (1.5)	4 (1.5)	0

Values are presented as number (%).
RCT, randomized, double-blind, placebo-controlled trials; AE, adverse events; LFT, liver function test; NPT, nasopharyngitis; SAE, serious adverse events; PBO, placebo; AGO, agomelatine.

A Total adverse events

Study or subgroup	Agomelatine Events	Total	Placebo Mean	Total	Weight	Odds ratio M−H, fixed, 95% CI
Stein et al. 2008 [17]	37	63	41	58	17.7%	0.59 [0.28, 1.26]
Stein et al. 2012 [18]	46	113	31	114	18.4%	1.84 [1.05, 3.21]
Stein et al. 2014 [28]	66	139	58	131	31.5%	1.14 [0.70, 1.84]
Stein et al. 2017 [29]	87	270	36	140	32.3%	1.37 [0.87, 2.17]
Total (95% CI)		585		443	100.0%	1.25 [0.96, 1.62]
Total events	236		166			

Heterogeneity: $Chi^2 = 5.94$, df = 3 ($p = 0.11$); $I^2 = 49\%$
Test for overall effect: $Z = 1.63$ ($p = 0.10$)

Odds ratio M−H, fixed, 95% CI
0.5 0.7 1 1.5 2
Favours [agomelatine]　Favours [placebo]

B Dropout due to adverse events

Study or subgroup	Agomelatine Events	Total	Placebo Mean	Total	Weight	Odds ratio M−H, fixed, 95% CI
Stein et al. 2008 [17]	1	63	0	58	5.3%	2.81 [0.11, 70.31]
Stein et al. 2012 [18]	0	113	2	114	25.8%	0.20 [0.01, 4.18]
Stein et al. 2014 [28]	3	139	4	131	41.9%	0.70 [0.15, 3.19]
Stein et al. 2017 [29]	4	270	2	140	27.0%	1.04 [0.19, 5.74]
Total (95% CI)		585		443	100.0%	0.77 [0.30, 2.00]
Total events	8		8			

Heterogeneity: $Chi^2 = 1.51$, df = 3 ($p = 0.68$); $I^2 = 0\%$
Test for overall effect: $Z = 0.53$ ($p = 0.60$)

Odds ratio M−H, fixed, 95% CI
0.005 0.1 1 10 200
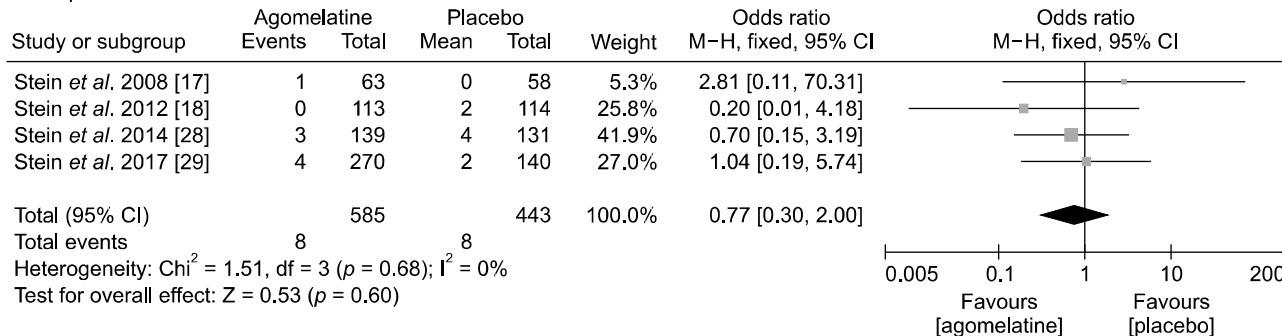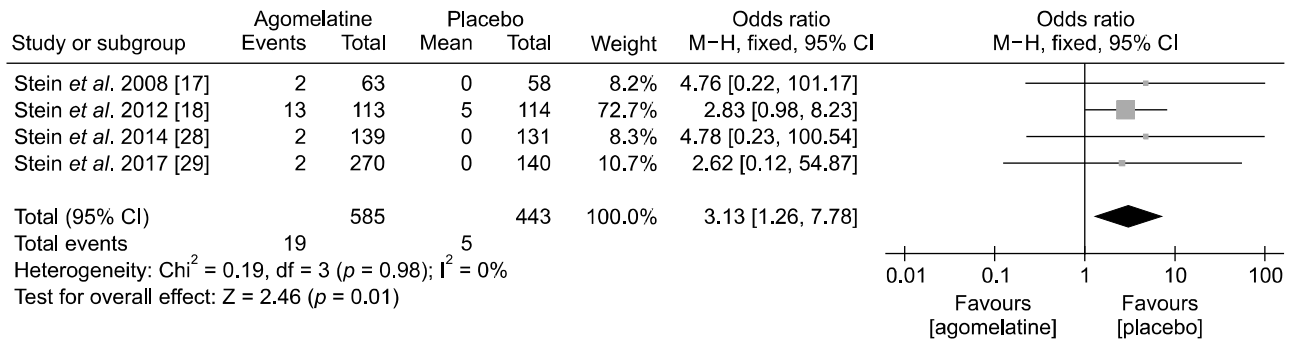Favours [agomelatine]　Favours [placebo]

Fig. 5. Safety and tolerability: number of (A) total adverse events, (B) dropout due to adverse events.
M−H; Mantel−Haenszel; 95% CI, 95% confidence interval.

A Liver function

Study or subgroup	Agomelatine Events	Total	Placebo Mean	Total	Weight	Odds ratio M–H, fixed, 95% CI	Odds ratio M–H, fixed, 95% CI
Stein et al. 2008 [17]	2	63	0	58	8.2%	4.76 [0.22, 101.17]	
Stein et al. 2012 [18]	13	113	5	114	72.7%	2.83 [0.98, 8.23]	
Stein et al. 2014 [28]	2	139	0	131	8.3%	4.78 [0.23, 100.54]	
Stein et al. 2017 [29]	2	270	0	140	10.7%	2.62 [0.12, 54.87]	
Total (95% CI)		585		443	100.0%	3.13 [1.26, 7.78]	
Total events	19		5				

Heterogeneity: Chi^2 = 0.19, df = 3 (p = 0.98); I^2 = 0%
Test for overall effect: Z = 2.46 (p = 0.01)

0.01   0.1   1   10   100
Favours [agomelatine]   Favours [placebo]

B Nausea

Study or subgroup	Agomelatine Events	Total	Placebo Mean	Total	Weight	Odds ratio M–H, fixed, 95% CI	Odds ratio M–H, fixed, 95% CI
Stein et al. 2008 [17]	3	63	1	58	19.7%	2.85 [0.29, 28.20]	
Stein et al. 2012 [18]	5	113	0	114	9.4%	11.61 [0.63, 212.44]	
Stein et al. 2014 [28]	5	139	1	131	19.7%	4.85 [0.56, 42.08]	
Stein et al. 2017 [29]	5	270	2	140	51.3%	1.30 [0.25, 6.80]	
Total (95% CI)		585		443	100.0%	3.27 [1.18, 9.11]	
Total events	18		4				

Heterogeneity: Chi^2 = 2.07, df = 3 (p = 0.56); I^2 = 0%
Test for overall effect: Z = 2.27 (p = 0.02)

0.002   0.1   1   10   500
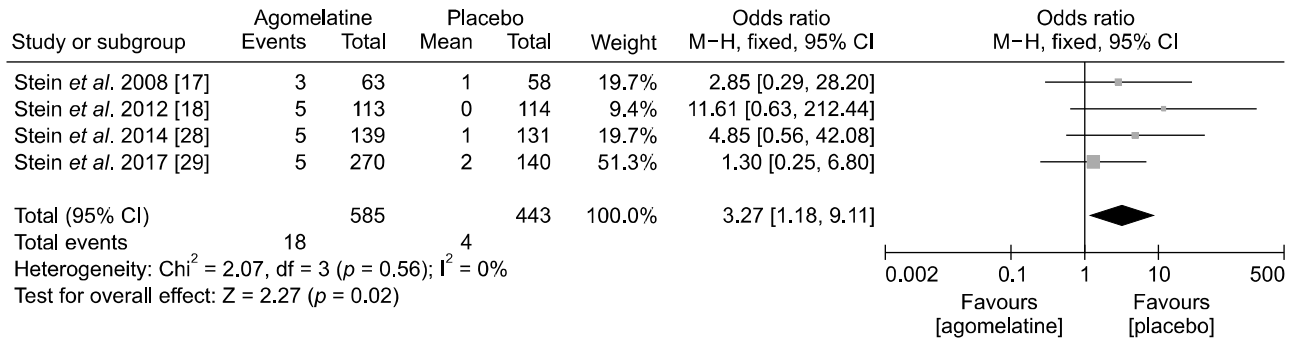Favours [agomelatine]   Favours [placebo]

Fig. 6. Safety and tolerability: rate of (A) liver function test increment, (B) nausea. M–H; Mantel–Haenszel; 95% CI, 95% confidence interval.

headache, nasopharyngitis, and dizziness compared with placebo (Fig. 7).

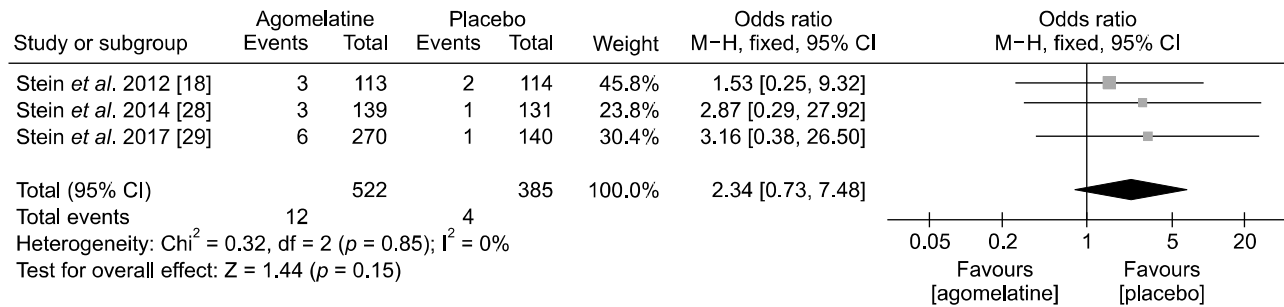## Number Needed to Treat and Number Needed to Harm

Number needed to treat (NNT) and number needed to harm (NNH) were also computed because they can quantify the effect sizes of clinically relevant benefits and harms of a certain drug [30]. By doing so, they have advantage of allowing clinicians to intuitively relate effect size difference back to real-world concerns of clinical practice [31]. For response rate, the risk difference between agomelatine and placebo was 0.32 (95% CIs, 0.25 to 0.38). Thus, NNT can be calculated as 3.13. The risk difference between agomelatine and placebo for remission was 0.19 (95% CIs, 0.13 to 0.25) yielding NNT of 5.26. For safety and tolerability, NNH for nausea and LFT increment was analyzed because they were significantly higher than placebo. The risk difference for nausea and LFT increment was 0.02 (95% CIs, 0.01 to 0.04) and 0.03 (95% CIs, 0.01 to 0.05) yielding NNT of 50 and 33.3.
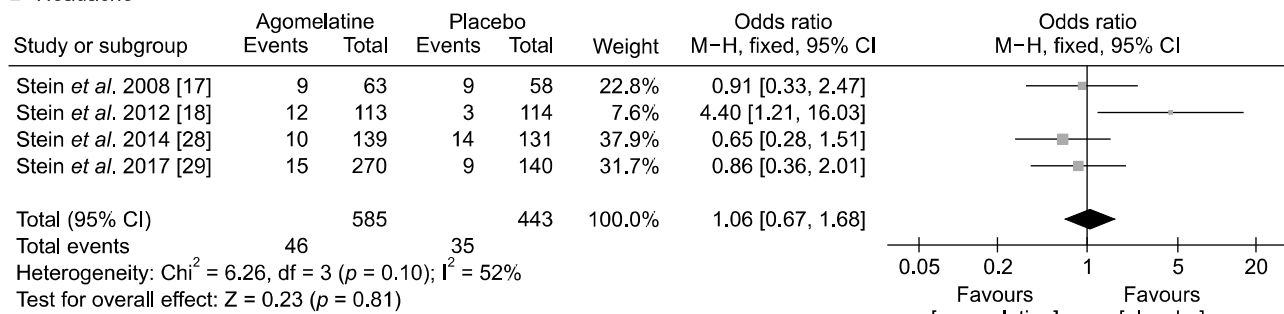
DISCUSSION

Despite multiple pharmacological agents available, a large proportion of patients with GAD achieve neither adequate response nor complete remission [32]. The 5-HT_{2C} receptor antagonistic property of agomelatine's mechanism of action suggests its potential role in the treatment of GAD [22,33]. Thus, we aimed to investigate the efficacy and safety of agomelatine in the treatment of GAD by conducting a meta-analysis of RCTs.

Our results found 4 RCTs, and the meta-analysis demonstrated the statistically superior efficacy of agomelatine compared with placebo for the treatment of GAD. The differences in terms of mean changes in HAM-A total scores from baseline to endpoint (SMD, −0.56) was not small with median effect size according to Cohen's classification [34]. This effect size is comparable to the previous study showing SMD of pregabalin, hydroxyzine, venlafaxine, benzodiazepines and SSRIs vs. placebo in GAD as 0.50, 0.45, 0.42, 0.38, and 0.36, respectively [35]. The ORs of agomelatine over placebo for response and remission rates were also notable with 3.75 and 2.74 respectively. In addition, the NNT for response and re-
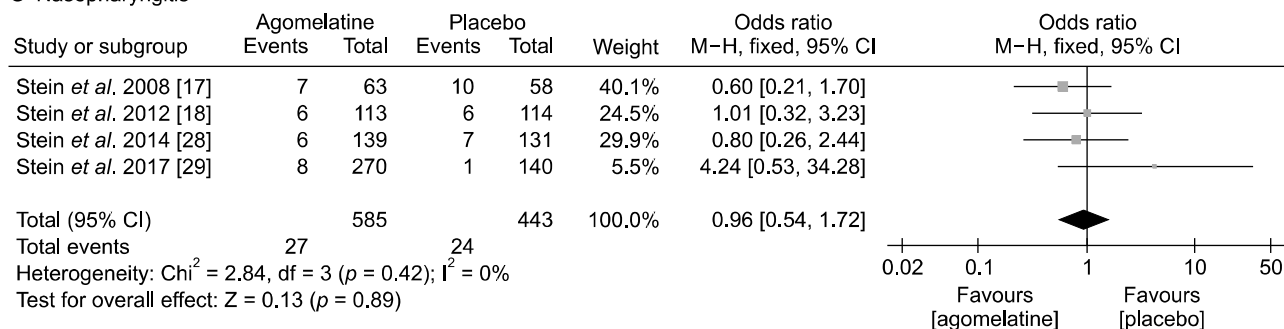
A Somnolence

Study or subgroup	Agomelatine Events	Total	Placebo Events	Total	Weight	Odds ratio M–H, fixed, 95% CI	Odds ratio M–H, fixed, 95% CI
Stein *et al.* 2012 [18]	3	113	2	114	45.8%	1.53 [0.25, 9.32]	
Stein *et al.* 2014 [28]	3	139	1	131	23.8%	2.87 [0.29, 27.92]	
Stein *et al.* 2017 [29]	6	270	1	140	30.4%	3.16 [0.38, 26.50]	
Total (95% CI)		522		385	100.0%	2.34 [0.73, 7.48]	
Total events	12		4				

Heterogeneity: Chi^2 = 0.32, df = 2 (p = 0.85); I^2 = 0%
Test for overall effect: Z = 1.44 (p = 0.15)

0.05   0.2   1   5   20
Favours [agomelatine]   Favours [placebo]

B Headache

Study or subgroup	Agomelatine Events	Total	Placebo Events	Total	Weight	Odds ratio M–H, fixed, 95% CI	Odds ratio M–H, fixed, 95% CI
Stein *et al.* 2008 [17]	9	63	9	58	22.8%	0.91 [0.33, 2.47]	
Stein *et al.* 2012 [18]	12	113	3	114	7.6%	4.40 [1.21, 16.03]	
Stein *et al.* 2014 [28]	10	139	14	131	37.9%	0.65 [0.28, 1.51]	
Stein *et al.* 2017 [29]	15	270	9	140	31.7%	0.86 [0.36, 2.01]	
Total (95% CI)		585		443	100.0%	1.06 [0.67, 1.68]	
Total events	46		35				

Heterogeneity: Chi^2 = 6.26, df = 3 (p = 0.10); I^2 = 52%
Test for overall effect: Z = 0.23 (p = 0.81)

0.05   0.2   1   5   20
Favours [agomelatine]   Favours [placebo]

C Nasopharyngitis

Study or subgroup	Agomelatine Events	Total	Placebo Events	Total	Weight	Odds ratio M–H, fixed, 95% CI	Odds ratio M–H, fixed, 95% CI
Stein *et al.* 2008 [17]	7	63	10	58	40.1%	0.60 [0.21, 1.70]	
Stein *et al.* 2012 [18]	6	113	6	114	24.5%	1.01 [0.32, 3.23]	
Stein *et al.* 2014 [28]	6	139	7	131	29.9%	0.80 [0.26, 2.44]	
Stein *et al.* 2017 [29]	8	270	1	140	5.5%	4.24 [0.53, 34.28]	
Total (95% CI)		585		443	100.0%	0.96 [0.54, 1.72]	
Total events	27		24				

Heterogeneity: Chi^2 = 2.84, df = 3 (p = 0.42); I^2 = 0%
Test for overall effect: Z = 0.13 (p = 0.89)

0.02   0.1   1   10   50
Favours [agomelatine]   Favours [placebo]

D Dizziness

Study or subgroup	Agomelatine Events	Total	Placebo Events	Total	Weight	Odds ratio M–H, fixed, 95% CI	Odds ratio M–H, fixed, 95% CI
Stein *et al.* 2008 [17]	5	63	2	58	15.1%	2.41 [0.45, 12.96]	
Stein *et al.* 2012 [18]	4	113	3	114	22.6%	1.36 [0.30, 6.21]	
Stein *et al.* 2014 [28]	3	139	4	131	31.7%	0.70 [0.15, 3.19]	
Stein *et al.* 2017 [29]	4	270	3	140	30.6%	0.69 [0.15, 3.11]	
Total (95% CI)		585		443	100.0%	1.10 [0.52, 2.36]	
Total events	16		12				

Heterogeneity: Chi^2 = 1.63, df = 3 (p = 0.65); I^2 = 0%
Test for overall effect: Z = 0.25 (p = 0.80)

0.1   0.2   0.5   1   2   5   10
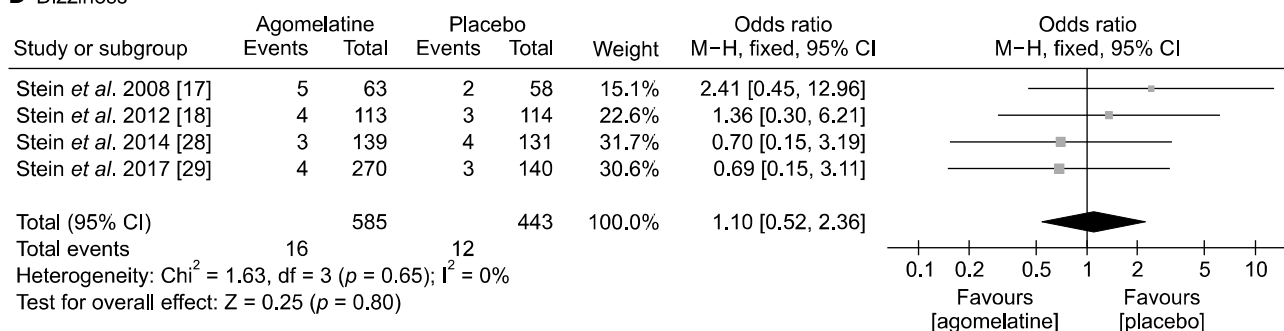Favours [agomelatine]   Favours [placebo]

Fig. 7. Safety and tolerability: rate of (A) somnolence, (B) headache, (C) nasopharyngitis, (D) dizziness. M–H; Mantel–Haenszel; 95% CI, 95% confidence interval.

mission were 3.13 and 5.26 respectively, which corresponds to "somewhat treatable." [31]. However, more RCTs are needed to confirm efficacy and establish more correct effect size of agomelatine in GAD.

In line with previous meta-analysis of agomelatine in the treatment of MDD, agomelatine was generally well tolerated and safe [36,37]. Above all, most of side effects observed in both groups were mild or moderate in

severity. No SAEs led to clinically critical conditions. A trend of higher total AEs was found in agomelatine group than in placebo group, but they were statistically not significant group (OR, 1.25, $p = 0.1$). In addition, dropout rate due to adverse event and rate of somnolence, headache, nasopharyngitis, and dizziness did not differ between the two group. However, the rate of nausea was significantly higher in agomelatine than in placebo group (OR, 3.27; $p = 0.02$). The risk of agomelatine causing liver injury has been well documented [38]. Likewise, our meta-analysis also showed that agomelatine caused significantly higher incidence of LFT increment (OR, 3.13; $p = 0.01$) than placebo. NNH for nausea and LFT increment were 50 and 33.3 respectively. Thus, monitoring of LFT before initiating and during treatment with agomelatine is necessary.

The study contains several limitations. First, our results were based on a total of 4 RCTs with a pooled sample size (agomelatine and placebo) of 1,024 patients only. Therefore, we combined all doses of agomelatine and were unable to undertake meta-regression to understand its dose related efficacy and safety. We were also unable to conduct meta-regression and investigate possible linear relationship between outcome measure and other covariates. Second, all studies were conducted outside North America, so more studies are needed in diverse regions worldwide to increase generalizability. Third, we were not able to find unpublished trials, so there is a possibility of publication bias. Fourth, all 4 studies were financially sponsored by pharmaceutical company owning Valdoxan, a brand name for agomelatine, Servier. Moreover, all 4 trials were led by the same author (Stein) and employees of Servier were also involved as co-authors. Thus, industry bias could have influenced to yield a positive result [39,40].

Despite these limitations, our study has major strengths. To the best of our knowledge, this is the first meta-analysis to evaluate the benefits and risk of agomelatine for treatment of GAD. All RCTs included were multi-centered, multi-national, and carefully designed. The demographics of the studies including age range, mean age, sex ratio, and inclusion criteria were comparable reducing clinical heterogeneity. In addition, despite significant heterogeneity noted, magnitude of the difference in reduction of HAM-A, response rate, and remission rate between agomelatine and placebo was relatively large. Thus, the difference was observed regardless of using fixed or random effect model.

In conclusion, the present meta-analysis suggested that agomelatine may be another treatment option for patients with GAD. However, the results should be interpreted and translated into clinical practice cautiously because only 4 RCTs are conducted worldwide. Thus, our results urge that more adequately powered, well-designed, placebo-controlled clinical trials are clearly needed to confirm agomelatine's clinical utility in treatment of GAD.

■ **Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

■ **Author Contributions**

Sheng-Min Wang and Won-Myong Bahk designed the study. Nak-Young Kim and Hae-Ran Na acquired data, Hyun Kook Lim and Young Sup Woo analysed the data. Finally, Sheng-Min Wang wrote the article, which all authors reviewed and approved for publication.

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