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 (MT1 and MT2) receptors and antagonist at serotonergic 5-HT2C 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-HT2C antagonism, but melatonin receptor may also be involved in decreasing anxiety...
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 systematically 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. 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, dosage 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, I² 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]. I² of 75–100% indicates considerable heterogeneity, and the heterogeneity threshold was defined as 50% or more in I² 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 I² indicated significant heterogeneity among study results (I² > 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 (age, yr) | Duration (wk) | Baseline MADRS | Hamilton Anxiety Rating Scale | Study location |
|----------------|--------------|---------------------|---------------|----------------|-------------------------------|----------------|
|                |              |                     |               |                | Baseline | Mean change | Response | Remission |
| Stein et al.   | 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 |
| 2008 [17]      | AGO (25 – 50)| 63                  | 41.7          | 12             | 11.6 ± 2.9 | 29.0 ± 4.4 | −16.6 ± 8.9 | 42 (66.7) | 26 (41.3) |                       |
| Stein et al.   | PBO          | 113                 | 47.0          | 26             | NA         | 6.0 ± 2.6  | 3.6 ± 8.4  | NA         | NA         | CN, DN, ET, FN,       |
| 2012 [18]      | AGO (25 – 50)| 112                 | 45.9          | NA             | 5.9 ± 2.7  | −1.6 ± 7.7 | NA         | NA         | HG, and SW          |
| Stein et al.   | 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,      |
| 2014 [28]      | AGO (25 – 50)| 139                 | 43.6          | 12             | 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.   | 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,      |
| 2017 [29]      | AGO total    | 268                 | 43.9          | NA             | 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.

*Primary efficacy measure; †Response: 50% or more decrement of HAM-A from baseline to endpoint; ‡Remission: 7 or less in total HAM-A score at endpoint.

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### 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 (I² = 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 (I² = 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 (I² = 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...
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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.

| Study or subgroup | Agomelatine | Placebo | Std. Mean difference IV, random, 95% CI | Year |
|-------------------|-------------|---------|----------------------------------------|------|
|                   | Mean SD Total | Mean SD Total | Weight |
| 1.1.1 Total group |             |          |                                        |      |
| Stein et al. 2008 [17] | -16.6 8.9 63 | -13.2 9.5 58 | 22.6% | -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] | -16.91 8.2 268 | -8.9 9.2 140 | 26.2% | -1.05 [-1.27, -0.83] | 2017 |
| Subtotal (95% CI) | 431 | 303 | 95% CI, 95% confidence interval |
| Heterogeneity: Tau² = 0.13; Chi² = 25.01, df = 3 (p < 0.0001); I² = 88% Test for overall effect: Z = 2.89 (p = 0.004) |

1.1.2 Subgroup analysis 1

| Study or subgroup | Agomelatine | Placebo | Std. Mean difference IV, random, 95% CI | Year |
|-------------------|-------------|---------|----------------------------------------|------|
|                   | Mean SD Total | Mean SD Total | Weight |
| 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% |
| Heterogeneity: Tau² = 0.00; Chi² = 2.23, df = 2 (p = 0.33); I² = 10% Test for overall effect: Z = 4.56 (p < 0.00001) |

1.1.3 Subgroup analysis 2

| Study or subgroup | Agomelatine | Placebo | Std. Mean difference IV, random, 95% CI | Year |
|-------------------|-------------|---------|----------------------------------------|------|
|                   | Mean SD Total | Mean SD Total | Weight |
| 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] | -16.91 8.2 268 | -8.9 9.2 140 | 35.3% | -1.05 [-1.27, -0.83] | 2017 |
| Subtotal (95% CI) | 470 | 329 | 100.0% |
| Heterogeneity: Tau² = 0.12; Chi² = 14.96, df = 2 (p = 0.0006); I² = 87% Test for overall effect: Z = 3.10 (p = 0.002) |

Test for subgroup differences: Chi² = 1.73, df = 2 (p = 0.42); I² = 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 | Placebo | Odds ratio M-H, fixed, 95% CI |
|-------------------|-------------|---------|-------------------------------|
|                   | Events Total | Mean Total | Weight |
| 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% |
| Total events | 295 107 |
| Heterogeneity: Chi² = 4.50, df = 2 (p = 0.11); I² = 56% Test for overall effect: Z = 4.50 (p < 0.00001) |

B Remission rate

| Study or subgroup | Agomelatine | Placebo | Odds ratio M-H, fixed, 95% CI |
|-------------------|-------------|---------|-------------------------------|
|                   | Events Total | Mean Total | Weight |
| Stein et al. 2008 [17] | 26 63 | 13 58 | 19.5% | 2.93 [1.90, 4.50] |
| 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% |
| Total events | 165 57 |
| Heterogeneity: Chi² = 0.85, df = 2 (p = 0.65); I² = 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 |
|----------------|--------------|-------------|---------------|---------------|--------|------------|----------|-----|-----------|------------------|-----|
| Stein et al.   | PBO          | 58          | 41 (70.7)     | 0             | 1 (1.7) | -          | 9 (15.5) | 10 (17.2) | 2 (3.4)     | 0                | 0   |
| 2008 [17]      | AGO (25–50)  | 63          | 37 (58.7)     | 2 (3.2)       | 3 (4.8) | -          | 9 (14.3) | 7 (11.1)  | 5 (7.9)     | 1                | 0   |
| Stein et al.   | 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   |
| 2012 [18]      | 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   |
| Stein et al.   | PBO          | 131         | 58 (44.3)     | 0             | 1 (0.8) | 1 (0.8)    | 14 (10.7)| 7 (5.3)   | 4 (3.1)     | 3 (3.1)         | 0   |
| 2014 [28]      | 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)     | 1 (0.7)         | 0   |
| Stein et al.   | PBO          | 140         | 36 (25.7)     | 0             | 2 (1.4) | 1 (0.7)    | 9 (6.4)  | 10 (7.2)  | 3 (2.1)     | 2 (1.4)         | 0   |
| 2017 [29]      | 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)         | 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 | Placebo Events | Odds ratio M–H, fixed, 95% CI | 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%                          | 1.25 [0.96, 1.62]             |
| Total events | 236                | 166           | 0.5                           | 0.7                           |

Heterogeneity: \( \chi^2 = 5.94, df = 3 \) (\( p = 0.11 \)); \( I^2 = 49\%

Test for overall effect: \( Z = 1.63 \) (\( p = 0.10 \))

#### B Dropout due to adverse events

| Study or subgroup | Agomelatine Events | Placebo Events | Odds ratio M–H, fixed, 95% CI | 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] | 3                  | 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%                          | 0.77 [0.30, 2.00]             |
| Total events | 8                  | 8             | 0.005                         | 0.1                           |

Heterogeneity: \( \chi^2 = 1.51, df = 3 \) (\( p = 0.68 \)); \( I^2 = 0\%

Test for overall effect: \( Z = 0.53 \) (\( p = 0.60 \))

**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.

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**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-
Fig. 7. Safety and tolerability: rate of (A) somnolence, (B) headache, (C) nasopharyngitis, (D) dizziness.

M−H; Mantel–Haenszel; 95% CI, 95% confidence interval.

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

| Study or subgroup | Agomelatine Events Total | Placebo Events Total | Weight | 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: Ch² = 0.32, df = 2 (p = 0.85); I² = 0% |
| Test for overall effect: Z = 1.44 (p = 0.15) |

Favours [agomelatine] Favours [placebo]

| Study or subgroup | Agomelatine Events Total | Placebo Events Total | Weight | 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: Ch² = 6.26, df = 3 (p = 0.10); I² = 52% |
| Test for overall effect: Z = 0.23 (p = 0.81) |

Favours [agomelatine] Favours [placebo]

| Study or subgroup | Agomelatine Events Total | Placebo Events Total | Weight | 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: Ch² = 2.84, df = 3 (p = 0.42); I² = 0% |
| Test for overall effect: Z = 0.13 (p = 0.89) |

Favours [agomelatine] Favours [placebo]

| Study or subgroup | Agomelatine Events Total | Placebo Events Total | Weight | 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: Ch² = 1.63, df = 3 (p = 0.65); I² = 0% |
| Test for overall effect: Z = 0.25 (p = 0.80) |

Favours [agomelatine] Favours [placebo]
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.

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■ 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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