REVIEW

Evidence-Based Pharmacotherapy of Generalised Anxiety Disorder: Focus on Agomelatine

Dan J. Stein

ABSTRACT

Recent network meta-analyses support the use of pharmacotherapy in patients with generalised anxiety disorder (GAD). Compared with placebo, drug treatment can improve symptoms and quality of life, and is more effective in preventing relapse. Selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors are generally considered the first-line agents of choice in GAD, but in some patients, an alternative evidence-based treatment with a different mechanism of action may also be considered (e.g. those with severe GAD, inadequate response, adverse effects and/or contraindications). One example is agomelatine, a melatonin receptor agonist and serotonin 2C (5-HT_{2C}) receptor antagonist, which has been shown to have efficacy that is greater than placebo in patients with GAD, and to have a tolerability profile that compares favourably with that of escitalopram. Both agomelatine and escitalopram are efficacious in treating patients with GAD, including those with severe symptoms.

Keywords: Agomelatine; Anxiety disorders; Serotonin 5-HT2C receptor; Serotonin uptake inhibitors

D. J. Stein (✉)
SAMRC Unit On Risk and Resilience in Mental Disorders, Department of Psychiatry and Neuroscience Institute, Groote Schuur Hospital, University of Cape Town, Anzio Road, Cape Town 7925, South Africa
e-mail: dan.stein@uct.ac.za

Key Summary Points

Why carry out this review?

Generalised anxiety disorder (GAD) is a prevalent psychiatric disorder typically treated with selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors.

Patients in whom these agents are ineffective or poorly tolerated require alternative treatments; this review summarises novel agents with alternate mechanisms of action, and includes more detailed discussion of the melatonin receptor agonist and serotonin 2C receptor antagonist agomelatine.

What was learned from the review?

Of several therapeutic drugs with a mechanism of action beyond targeting serotonergic pathways, only the anticonvulsant pregabalin has been granted regulatory approval (in Europe) for the treatment of GAD.

Although not approved in this indication, agomelatine is another such agent with therapeutic evidence supporting its efficacy and safety in the treatment of GAD.

DIGITAL FEATURES

This article is published with digital features, including a video abstract, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14959524.

INTRODUCTION

Pharmacotherapy has long been a mainstay of treatment in generalised anxiety disorder (GAD). Since the 1970s, each successive decade has brought new treatment options: either completely new chemical entities with novel mechanisms of action or established psychopharmacological agents with new evidence of efficacy against anxiety symptoms. This narrative review summarises these developments and emphasizes key advances as well as future areas for investigation, with a particular focus on agomelatine.

The main classes of drugs used to treat GAD are shown in Table 1. Benzodiazepines (BZDs), while effective and fast-acting in the treatment of GAD, have now largely been supplanted by the selective serotonin reuptake inhibitors (SSRIs; e.g. escitalopram) and serotonin–norepinephrine reuptake inhibitors (SNRIs; e.g. venlafaxine) because of the well-documented risks of dependence and other adverse outcomes associated with BZDs. A range of current clinical guidelines list SSRIs and SNRIs as first-line choices in GAD [1–6]; they are effective and well tolerated in many but not all patients.

Tricyclic antidepressants have similar efficacy to BZDs in the treatment of GAD; however, their slower onset of anxiolytic action and range of clinical adverse effects, such as those associated with muscarinic receptor antagonism, limit their wider use. Buspirone is an azapirone with efficacy over the short term (4–9 weeks), but that may be less effective than BZDs [7], hydroxyzine is an antihistamine with the potential for sedation [8], trifluoperazine is a first-generation antipsychotic agent that was approved in the USA for short-term treatment of GAD [9] and used in patients not responsive to safer agents, but subsequently withdrawn from the US market for reasons unrelated to efficacy or safety [10], and pregabalin is a gamma-aminobutyric acid (GABA)-ergic agent [11], which received European Medicines Agency but not US Food and Drug Administration approval (Table 1). Second-generation ('atypical') antipsychotics (SGAs) are used off-label for anxiety (quetiapine showing significant benefit in GAD [12, 13]), but have failed to gain regulatory approval for the treatment of GAD because of safety concerns.

Therefore, additional medications with novel mechanisms of action and better tolerability may provide useful therapeutic

Table 1 Pharmacotherapies used in the off-label treatment of generalised anxiety disorder (GAD), except where otherwise stated

Class	Abbreviation	Important example(s)	Approved for use in GAD (market(s)) [38]	Efficacy/tolerability
Anticonvulsants	–	Pregabalin	Yes (EU, ROW)[a]	Pregabalin considered a second-line option [1]
		Tiagabine	No	
Azapirones	–	Buspirone	No	May be less effective than BZD despite good tolerability profile
Benzodiazepines	BZD	Alprazolam	Yes (USA)	Efficacious; significant adverse events
		Lorazepam	No	
Melatonin receptor agonists	MRA	Agomelatine	No	Efficacy data available; good tolerability profile
Noradrenergic and specific serotonergic antidepressants	NaSSA	Mirtazapine	No	Limited data available
Norepinephrine–dopamine reuptake inhibitors	NDRI	Bupropion	No	Limited data available
First-generation antipsychotics	FGA	Trifluoperazine	No	Withdrawn from US market
Second-generation antipsychotics	SGA	Quetiapine	No	Not approved for use in GAD because of adverse events
Serotonin–norepinephrine reuptake inhibitors	SNRI	Desvenlafaxine	No	SSRIs and SNRIs considered first-line agents for GAD; each agent has specific adverse event profile
		Duloxetine	Yes (USA, ROW)[b]	
		Venlafaxine	Yes (China, Europe, UK, USA, ROW)[c]	
Selective serotonin reuptake inhibitors	SSRI	Escitalopram	Yes (USA, EU)	
		Fluoxetine	No	
		Sertraline	No	
		Vortioxetine	No	

Table 1 continued

Class	Abbreviation	Important example(s)	Approved for use in GAD (market(s)) [38]	Efficacy/tolerability
Tricyclic antidepressants	TCA	Amitriptyline	No	Efficacious, but disadvantageous adverse event profiles
		Imipramine	No	
		Nortriptyline	No	

EU European Union, *GAD* generalised anxiety disorder, *ROW* rest of world, *UK* United Kingdom, *USA* United States

[a] Argentina, Brazil, Hong Kong, India, Indonesia, Malaysia, Mexico, Russia, Singapore, Switzerland, Thailand, Turkey, Ukraine

[b] Argentina, Australia, Canada, Czech Republic, Denmark, Hong Kong, Iceland, Ireland, Israel, Liechtenstein, Malaysia, Mexico, Netherlands, New Zealand, Norway, Portugal, Russia, Singapore, Spain, Switzerland, Thailand

[c] Canada, Ireland, various South American countries

alternatives for the treatment of GAD. A range of newer agents have received attention, including serotonergic agents (e.g. ondansetron, vortioxetine), noradrenergic and specific serotonergic antidepressants (e.g. mirtazapine), norepinephrine–dopamine reuptake inhibitors (e.g. bupropion), beta-blockers (e.g. propranolol), glutamatergic agents (e.g. ketamine), neuropeptides and neurosteroids (e.g. mifepristone), and cannabinoids and herbal agents [14]. However, as noted below, many trials have been negative or had small samples sizes, so that there is limited support for such agents. The melatonin receptor agonist and serotonin 2C (5-HT$_{2C}$) receptor antagonist agomelatine provides another novel mechanism of action, and has consistently been found to be efficacious and well tolerated in GAD, and is discussed in more detail here.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by the author.

EVIDENCE TO SUPPORT PHARMACOTHERAPY IN GAD

Recent network meta-analyses (NMAs) provide useful overviews of the available evidence to support different classes of anxiolytic drug, and individual drugs within those classes [15–17]. In an analysis of 57 clinical trials, Chen et al. found that all classes of pharmacotherapy for GAD were more efficacious (based on changes in Hamilton Anxiety Rating Scale [HAM-A]) than placebo, with the exception of serotonin-modulating drugs and SGAs [15]. The most efficacious drug classes, relative to placebo, were the norepinephrine–dopamine reuptake inhibitors, followed by the noradrenergic and specific serotonergic antidepressant. Importantly, however, the volume of data on these classes was considerably smaller than for SSRIs, SNRIs, BZDs and other classes. BZDs, as a class, showed the smallest efficacy difference versus placebo among the effective drug classes. Most pharmacological interventions had greater treatment effects than psychological interventions [15].

Separately, Slee and colleagues performed an NMA of 89 trials of individual anxiolytic agents that included more than 25,000 patients with GAD [16]. The most efficacious drugs (again, based on change in HAM-A score) were duloxetine, pregabalin, venlafaxine and escitalopram; interestingly, the SGA quetiapine was found to be more efficacious than duloxetine, but was limited by its poor tolerability. There was favourable evidence in terms of efficacy and tolerability for several other drugs, but the authors highlighted that sample sizes for these agents were small (buspirone, fluoxetine, sertraline, mirtazapine and agomelatine) [16]. Notably, this NMA did not include trials

reported before 1994, and may therefore have excluded a significant volume of relevant data.

Lastly, He et al. conducted an NMA of individual first-line pharmacotherapies (SSRIs and SNRIs) for the treatment of GAD [17], and included 41 trials of at least 4 weeks' duration that used the HAM-A as the main measure of efficacy ($n > 15,000$). With the exception of fluoxetine and vortioxetine, all of the drugs included in the analysis had greater anxiolytic efficacy than placebo. Consistent with the findings of Slee and colleagues [16], drugs with the greatest effect on HAM-A scores, relative to placebo, were duloxetine, escitalopram and venlafaxine [17]; pregabalin was not included in the analysis.

Other meta-analyses of pharmacotherapy for GAD have been useful in indicating that a number of classes of medication are useful for GAD [18], that anxiolytic effects persist beyond the active treatment period [19], that maintenance treatment is effective in preventing relapse [20], and that effective treatment improves quality of life [21]. Much research is needed in this area, including trials of more representative patients [22], including those with significant comorbidity [23], trials of GAD across the patients' lifespan [24, 25], pragmatic trials [26], and trials of drugs that target novel mechanisms of action [14]. Future research may also include work based on translational neuroscience [27], epidemiological studies [28] and big data [29], and should also address the question of whether clinical characterization may improve personalized treatment [30].

NEWER DRUGS: AGOMELATINE

The network meta-analyses discussed here emphasize that there is a robust evidence base supporting the use of established drug classes, particularly SNRIs and SSRIs, in the treatment of GAD. However, there have been few studies focused on severe GAD in particular, and there is a need for newer agents with novel mechanisms of action to ensure that there are different treatment options available for people with GAD, including those who do not respond to or cannot tolerate established therapies [31].

Among these newer agents is agomelatine, which Stein and colleagues systematically compared with placebo and active comparators in patients with GAD [31–35]. Importantly, in the NMA by Slee and colleagues mentioned earlier, agomelatine was the only newer agent to show efficacy compared with placebo in the treatment of GAD [16].

In a preliminary 12-week study in 121 patients with GAD [35], HAM-A score curves for agomelatine (25–50 mg/day) and placebo began to separate after 4 weeks. At week 12, the estimated difference between the treatment groups (in mean change in HAM-A score vs baseline) was − 3.28 (95% confidence interval [− 6.41, − 0.15]; $P = 0.04$). Subsequently, agomelatine (25–50 mg/day) was found to have comparable efficacy to escitalopram (10–20 mg/day), in terms of both reductions in HAM-A scores and response rates, in a randomised placebo-controlled trial ($n = 412$). In this trial, escitalopram was used as the comparator in order to validate the study results. Although both active treatments were superior to placebo in the overall study group and in patients with severe GAD (defined as a baseline HAM-A score $\geq$ 25), fewer agomelatine than escitalopram recipients experienced severe adverse events (AEs; $n = 1$ vs 4, respectively) or AEs that led to treatment discontinuation ($n = 3$ vs 10, respectively).

Since the publication of these two studies, subsequent trials have confirmed the efficacy and safety of agomelatine in the treatment of GAD at lower daily dosages (10–25 mg/day) [33], and in a head-to-head trial versus escitalopram in severe GAD [32]. In the latter study, both treatments were associated with clinically significant decreases in HAM-A scores at week 12, and were thus efficacious in treating patients with severe GAD. There were no significant differences between agomelatine and escitalopram in terms of the size of the reductions in HAM-A score from baseline, in either the overall study group (mean ± standard deviation, − 16.0 ± 9.1 vs − 16.9 ± 8.4, respectively) or in more severely anxious patients (− 16.4 ± 9.5 vs − 17.4 ± 8.6, respectively; Fig. 1) [32]. However, the pre-established criteria for non-inferiority of agomelatine versus escitalopram were not met (HAM-A total score
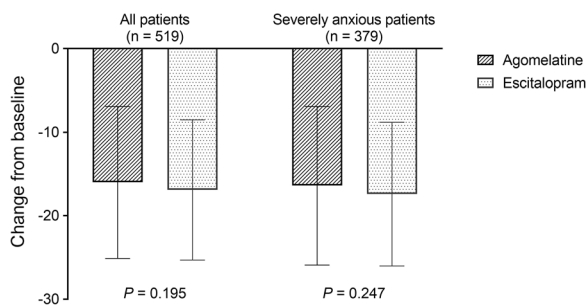
Fig. 1 Mean change between baseline and 12 weeks in Hamilton Anxiety Rating Scale (HAM-A) in a randomised trial comparing agomelatine (25–50 mg/day) versus escitalopram (10–20 mg/day) in the treatment of generalised anxiety disorder [32]. Error bars represent standard deviation. 'Severe anxiety' was defined as patients with a HAM-A total score $\geq$ 25 and a CGI-S (Clinical Global Impression–Severity scale) rating $\geq$ 5 at baseline

estimate, − 0.91; standard error, 0.69; 95% confidence interval − 2.26, 0.44; $P = 0.195$). Agomelatine was associated with a numerically lower incidence of AEs compared with escitalopram (46.9% vs 58.8%) [32].

Maintenance agomelatine treatment has been shown to be more effective than placebo in preventing relapse in patients with GAD [34]. Over a 6-month period, 19.5% of patients receiving agomelatine (25–50 mg/day) experienced relapse, compared with 30.5% of placebo recipients [hazard ratio (HR) 0.582; $P = 0.046$]. Agomelatine was also associated with a significantly lower relapse rate versus placebo in patients with severe GAD (20.8% vs 42.9%; HR 0.407; $P = 0.006$).

Agomelatine has also been found to be efficacious in anxious depression, as discussed in a separate article in this supplement. Symptoms of anxiety are present in 40–50% of patients with major depressive disorder (MDD), and are associated with greater functional impairment and a higher risk of suicide in this patient group [36]. In a pooled analysis of six trials in patients with MDD, agomelatine was found to have a significantly greater effect on HAM-A scores over 6–8 weeks compared with placebo (between-group difference at endpoint, 3.13 points; $P < 0.005$), and a comparable or greater effect versus fluoxetine (1.24 points; $P = 0.137$),

sertraline (2.36 points; $P = 0.016$) or venlafaxine (0.82 points; $P = 0.327$) [36]. Findings were similar for the subgroup of patients with more severe anxiety symptoms.

GAD TREATMENT GUIDELINES

In current guidelines for the management of GAD, SSRIs and SNRIs are typically recommended as first-line agents of choice [1–6]. Agomelatine has also demonstrated efficacy in anxiety symptoms in MDD [36], as well as in GAD [32, 34, 37]. Considering its evidence base in GAD to be comparable to that for escitalopram, the Anxiety Disorders Association of Canada recommends agomelatine as a first-line agent [4]. Agomelatine is considered as a second-line agent (in patients with GAD resistant to SSRI or SNRI treatment) by the Royal Australian and New Zealand College of Psychiatrists [1] and the South African Society of Psychiatrists [6]. Thus, agomelatine has an established place in therapy as an alternative to initial treatment with an SSRI or SNRI, and as an option in patients who do not respond, or have only a partial response, to first-line GAD. Its use in GAD would be off-label since it is not approved for use in this indication.

CONCLUSIONS

The evidence base on pharmacotherapy for GAD has expanded greatly in the last few decades, and supports the use of SSRIs and SNRIs as first-line agents. As not all patients respond to or are able to tolerate these agents, more recently there has also been work on a range of medications with different mechanisms of action (e.g. melatonin receptor agonists, NMDA receptor antagonists, neuropeptides, and neurosteroids). Unfortunately, a number of such trials have failed (e.g., neuropeptides such as L-759274, SSR149415, and BMS-562086 [38]). Indeed, at the current time, for the majority of these medications, evidence of their use in GAD is limited and further research is required. Agomelatine has been shown to be efficacious and well tolerated in patients with GAD,

including those with more severe symptoms, providing physicians and patients alike with another useful option.

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