Agomelatine improves symptoms of generalised anxiety disorder

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Agomelatine improves symptoms of generalised anxiety disorder

QUESTION

Question: Is agomelatine effective for people with generalised anxiety disorder?

Patients: 121 people, aged 18–65 years, with DSM-IV generalised anxiety disorder (69% female, mean age 42 years) (see online notes for exclusion criteria).

Setting: Five centres in Finland and six centres in South Africa; time period not stated.

Intervention: Agomelatine (n = 63; 25–50 mg/day) or placebo (n = 58) for 12 weeks. Agomelatine dose was increased from 25 to 50 mg/day if there was an insufficient response after 2 weeks. This was done in a blinded fashion, using a dose adjustment algorithm.

Outcomes: Primary outcome: overall anxiety (HAM-A). Secondary outcomes: response (≥50% reduction in HAM-A score); somatic anxiety, psychic anxiety, severity of illness, sleep and disability symptoms (HAM-A subscales, Clinical Global Impressions Scale, Leeds Sleep Evaluation Questionnaire and Sheehan Disability Scale); discontinuation effects in the week after discontinuation (Discontinuation Emergent Signs and Symptoms scale (DESS)). Last observation carried forward (LOCF) and observed case analyses were used; LOCF analyses are reported below.

Patient follow-up: 93% completed treatment; 100% included in LOCF analyses.

METHODS

Design: Randomised controlled trial.

Allocation: Concealed.

Blinding: Double blind.

Follow-up period: 12 weeks (treatment period) plus 1 week after discontinuation.

At 12 weeks, overall anxiety was reduced in both groups but agomelatine was more effective at reducing anxiety than placebo (mean change in HAM-A from baseline −16.6 with agomelatine vs −13.2 with placebo; difference −3.3, 95% CI −6.4 to −0.2; p = 0.04). Agomelatine increased response rate (66.7% with agomelatine vs 46.6% with placebo; p = 0.026) and improved severity of illness compared with placebo by the end of treatment (mean CGI score 2.7 with agomelatine vs 3.2 with placebo; p = 0.049). Agomelatine also improved sleep symptoms, including getting off to sleep (p<0.001), quality of sleep (p = 0.002) and sleep awakening (p=0.0001). Agomelatine was more effective than placebo for disability symptoms on the family subscale (p = 0.055) but not on the work or social subscales (p = 0.069, p = 0.063, respectively). There was no difference in treatment emergent adverse events (38% with agomelatine vs 35% with placebo; p value not reported); discontinuation effects were less likely in people treated with agomelatine than placebo (>1 symptom on the DESS: 40% with agomelatine vs 44% with placebo; p value not reported).

CONCLUSIONS

Agomelatine reduces symptoms of generalised anxiety disorder, including symptoms of insomnia and, to some extent, disability.

ABSTRACTED FROM


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Therapeutics

Generalised anxiety disorder (GAD) is a common, typically persistent and burden-some condition, but many of those who might benefit from treatment are not recognised or treated. Evidence based guidelines for pharmacological management recommend initial treatment with either a selective serotonin reuptake inhibitor (SSRI) or a serotonin–noradrenaline reuptake inhibitor (SNRI). However, there is room for improvement in both the efficacy and tolerability of treatment; response rates can be disappointing, some patients will relapse despite continuing medication and many experience troublesome adverse effects. The exact mechanism of action underlying the antidepressant and anxiolytic efficacy of agomelatine is uncertain. Melatonin agonism alone is unlikely to be responsible, it being more probable that accompanying antagonism of 5-HT2A/2C receptors, which enhances the release of noradrenaline and dopamine within the prefrontal cortex, combines with melatonergic effects to improve mood and correct disturbances of bodily rhythms. Antagonism of 5-HT2A/2C receptors has already been found to be efficacious in acute treatment in patients with GAD but this is the first evidence that agomelatine exerts anxiolytic effects in non-depressed patients. The decline in anxiety symptom severity and the proportion of patients meeting responder criteria is broadly similar to that seen with SSRIs or SNRIs, with a difference of approximately 3 points between agomelatine and placebo on the primary outcome measure at study endpoint, this difference being conventionally regarded as being clinically relevant. The relatively greater effects in relieving somatic (physical) anxiety symptoms when compared with placebo is intriguing, as antidepressant drugs are traditionally viewed as being more efficacious in reducing psychological symptoms. The sample size is probably insufficient to allow complete confidence here. More compelling is the evidence of good overall tolerability and absence of excess discontinuation symptoms after the withdrawal of double blind treatment; if these advantages are replicated, agomelatine could come to occupy an important role in wider practice.

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Competing interests: DSB has received personal honoraria from the manufacturers of agomelatine. ATL has no competing interests to declare.

