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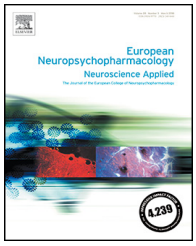

12-week double-blind randomized multicenter study of efficacy and safety of agomelatine (25–50 mg/day) *versus* escitalopram (10–20 mg/day) in out-patients with severe generalized anxiety disorder

Dan J. Stein[a,*], Jon-Paul Khoo[b], Antti Ahokas[c], Marek Jarema[d], Michael. Van Ameringen[e], Livia Vavrusova[f], Cyril Höschl[g], Michael Bauer[h], Istvan Bitter[i], Sergey N. Mosolov[j], Valérie Olivier[k], Sophie Matharan[k], Françoise Picarel-Blanchot[k], Christian de Bodinat[k]

[a] *University of Cape Town Department of Psychiatry & MRC Unit on Risk and Resilience in Mental Disorders, Groote Schuur Hospital, Anzio Road, Cape Town 7925, South Africa*
[b] *Toowong Specialist Clinic – Level 2, 54 Jephson Street, Toowong, QLD 4066 Australia*
[c] *Mehilainen Clinic, Runeberginkatu, 47 A, 00260 Helsinki, Finland*
[d] *Institute of Psychiatry and Neurology, 3rd Department of Psychiatry, Sobieskiego 9, 02-0957 Warszawa, Poland*
[e] *Department of Psychiatry and Behavioural Neurosciences, McMaster University, 1057 Main St. West, Suite L02, Hamilton, Ontario L8S 1B7, Canada*
[f] *Private Psychiatric Practice – Vavrušová Consulting s.r.o., Záporožská 12, 851 01 Bratislava, Slovakia*
[g] *National Institute of Mental Health, Topolová 748, 250 67 Klecany, Czechia*
[h] *Department of Psychiatry and Psychotherapy, University Hospital Carl Gustav Carus, Fetscherstr. 74, 01307 Dresden, Germany*
[i] *Department of Psychiatry and Psychotherapy, Semmelweis University, Balassa u. 6, H-1083 Budapest Hungary*
[j] *Department for Therapy of Mental Disorders, Moscow Research Institute of Psychiatry, 3, Poteshnaya street, 107076 Moscow, Russia*
[k] *Institut de Recherches Internationales Servier (IRIS), 50 rue Carnot, 92284 Suresnes Cedex, France*

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* Corresponding author.
E-mail address: dan.stein@uct.ac.za (D.J. Stein).

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KEYWORDS
Agomelatine;
Escitalopram;
Generalized anxiety disorder

Abstract
Treatment of severely symptomatic patients with generalized anxiety disorder (GAD) raises particular concerns for clinicians.
This 12-week double-blind study evaluated the efficacy of agomelatine (25-50 mg/day) in the treatment of patients with severe GAD, using escitalopram (10-20 mg) as active comparator. The primary outcome measure was the change from baseline of the total score on the Hamilton Anxiety scale (HAM-A) at week 12. Secondary outcome measures included rate of response to treatment (at least 50% score reduction from baseline) in the HAM-A psychic and somatic anxiety sub-scores, Clinical Global Impression severity and change scores, the Toronto Hospital Alertness Test, the Snaith-Hamilton Pleasure Scale, and the Leeds Sleep Evaluation Questionnaire Scores.
Sixty one clinical centers (Australia, Canada, Czech Republic, Finland, Germany, Hungary, Poland, Russia, Slovakia) participated from April 2013 to February 2015.
Patient characteristics and demographic data were comparable between treatment groups. Both treatments were associated with a clinically significant decrease in HAM-A total score at week 12; the non-inferiority of agomelatine *versus* escitalopram was not demonstrated (E(SE) = −0.91(0.69), 95%CI = [−2.26, 0.44], $p = 0.195$). At week 12, the response rate was 60.9% in the agomelatine group, and 64.8% in the escitalopram group. In both treatment arms, HAM-A psychic and somatic anxiety scores decreased, alertness and sleep parameters improved, and ability to experience pleasure increased. In these secondary outcome measures, there were no significant differences between the treatment groups. Agomelatine was well-tolerated, with a lower incidence of adverse events than escitalopram.
Agomelatine and escitalopram are efficacious in treating GAD patients with severe symptoms.

Introduction

Generalized anxiety disorder (GAD) has a lifetime prevalence of 3.7% across the globe (Ruscio et al., 2017) and is the most common anxiety disorder in primary care (Hoffman et al., 2008; Kessler et al., 2002, 2005; Wittchen, 2002; Wittchen et al., 2011). GAD is characterized by anxiety and worries that are difficult to control, and by accompanying psychic and somatic symptoms including sleep disturbance. GAD is an impairing illness, and when symptoms are severe patients may demonstrate significant disability with considerable social and occupational dysfunction (Kessler et al., 2005; Wittchen et al., 2011). Severe GAD may be associated with increased risk for suicidality (Norton et al., 2008), and is associated with lower response rates to some forms of treatment (Haby et al., 2006).

While several medications have shown efficacy for GAD (Bandelow et al., 2012), many patients fail to respond to, cannot tolerate, or develop discontinuation symptoms after use of such compounds (Kapczinski et al., 2003). Agomelatine has a mechanism of action and tolerability profile that differs from that of currently approved therapies for GAD (de Bodinat et al., 2010; Guardiola-Lemaitre et al., 2014) and so is an attractive option for the treatment of this disorder. Its efficacy and tolerability in treating GAD has been demonstrated using doses of 25-50 mg daily in three short-term placebo-controlled studies, including one with escitalopram as an active control (Stein et al., 2017, 2014, 2008, 2013), and in a relapse prevention study (Stein et al., 2012).

Notably, agomelatine was efficacious in reducing symptoms in a subset of patients with severe GAD (Stein et al., 2014). Of particular interest was a signal in this subset of severely ill participants that agomelatine was perhaps more efficacious than the escitalopram, a selective serotonin reuptake inhibitor (SSRI) (Stein et al., 2014). Given that care of this population raises particular clinical concerns and that there have been few prior trials of pharmacotherapy for severe GAD (Liebowitz et al., 2003; Matza et al., 2010), it would be useful to obtain additional data regarding the efficacy of agomelatine in an appropriately powered sample of patients with severe GAD.

The primary objective of the present study was to investigate the short-term (12-week) efficacy of agomelatine (25-50 mg/day) compared to escitalopram (10-20 mg) in reducing GAD symptoms, assessed by the HAM-A, in out-patients with severe illness. Escitalopram was chosen as an active comparator given its demonstrated efficacy in the treatment of GAD (Baldwin et al., 2006; Davidson et al., 2004; Goodman et al., 2005; Stein et al., 2005) and as it had previously been used as an active control in a GAD trial of agomelatine (Stein et al., 2014). The secondary objectives were to assess the potential clinical benefits of these two treatments on a broad array of clinically relevant measures including response rate, alertness, subjective sleep, and anhedonia, and to provide supplementary data on their tolerability.

Experimental procedures

Patients

A total of 523 physically healthy male and female outpatients, aged between 18 and 65 years old inclusive, with a primary diagnosis of GAD according to DSM-IV-TR criteria (American Psychiatric Association, 2000), were

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