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Efficacy and safety of agomelatine (10 or 25 mg/day) in non-depressed out-patients with generalized anxiety disorder: A 12-week, double-blind, placebo-controlled study

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Abstract
Agomelatine is efficacious in reducing symptoms and preventing relapse in placebo-controlled trials in generalised anxiety disorder (GAD). Nevertheless, fixed dose studies of agomelatine in GAD have not been undertaken. To determine the minimally effective optimal dose of agomelatine in GAD, the efficacy of two doses of agomelatine (10 and 25 mg/day) was investigated in a 12-week, placebo-controlled, double-blind, international study in patients with a primary diagnosis of GAD. The primary outcome measure was the Hamilton Anxiety scale (HAM-A). The study was undertaken in 35 clinical centers in Finland, Russia, Poland, Slovakia and Ukraine from August 2013 to January 2015. 131 out-patients were included in the agomelatine 10 mg group, 139 in the agomelatine 25 mg group, and 142 in the placebo group. Both doses of agomelatine were associated with significant decreases in the HAM-A at week 12 (difference *versus* placebo of 7.16 ± 1.00 at 10 mg and 11.08 ± 0.98 at 25 mg, $p < 0.0001$). Significant effects on all secondary measures were found for both doses at week 12; including

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psychic and somatic HAM-A subscales, response rate, remission on the HAM-A, and functional impairment. Findings were confirmed in subsets of more severely ill patients on all endpoints. The low placebo response rate observed in this study was consistent with an increase in the quality of data collected. Agomelatine was well-tolerated by patients, with minimal distinctions from placebo. There was a dose effect of agomelatine, with a greater placebo-agomelatine difference in the agomelatine 25 mg group, compared to the agomelatine 10 mg group.The present data support early work indicating the efficacy and tolerability of agomelatine in the treatment of GAD.

1. Introduction

Generalized anxiety disorder (GAD) is a chronic condition characterized by excessive anxiety, worry and somatic symptoms. Symptoms may fluctuate during the course of the illness, with baseline anxiety traits being compounded by GAD symptoms (so-called "double anxiety") (Rickels and Schweizer, 1998). GAD is the most common anxiety disorder in primary care practice (Hoffman et al., 2008; Wittchen et al., 2011), and is often associated with both comorbidity (including comorbidity of major depression and other anxiety disorders) and morbidity (including psychosocial impairment and economic costs) (Hoffman et al., 2008). While a number of different medication classes have demonstrated efficacy in the management of GAD (Bandelow et al., 2014), many patients fail to respond to, cannot tolerate, or develop discontinuation symptoms after use of such medications (Kapczinski et al., 2003).

The mechanism of action of agomelatine suggests that it may be useful in both major depressive disorder (MDD) and GAD (de Bodinat et al., 2010; Guardiola-Lemaitre et al., 2014). Anxiety symptoms are common in major depression (Fava et al., 2006; Stein and Hollander, 2002) and a range of work has demonstrated that in patients with MDD agomelatine is significantly more efficacious than both placebo and several comparator antidepressants in reducing anxiety symptoms (Hale et al., 2010; Kasper et al., 2010; Kennedy and Emsley, 2006; Lemoine et al., 2007; Loo et al., 2002; Olié and Kasper, 2007; Stein et al., 2013). In these studies, the favourable effects of agomelatine were seen on both the HAMA psychic and somatic sub-scores and were also observed in MDD patients with higher baseline anxiety.

Several agomelatine trials have focused on GAD. The efficacy and tolerability of agomelatine in treating GAD has been demonstrated using doses of 25–50 mg daily in a placebo-controlled phase II study (Stein et al., 2008), in a phase III study with escitalopram as active control (Stein et al., 2014), and in a relapse prevention study (Stein et al., 2012). In a recent study in MDD, symptom reduction in response to a dose of agomelatine 10 mg daily versus placebo reached statistical significance (Kennedy et al., 2014). In accordance with the requirement of EMA to ascertain the lowest effective dose of a medication, additional data on the efficacy of agomelatine 10 mg versus 25 mg daily in GAD would further optimize recommendations regarding dosage in this patient population.

The primary objective of this study was therefore to investigate the short-term (12-week) efficacy of 2 doses of agomelatine (10 and 25 mg/day) compared to placebo in reducing symptoms of GAD, as assessed by the Hamilton Anxiety Scale (HAM-A) in non-depressed out-patients. The secondary objectives were to assess the potential clinical benefit of agomelatine on a broad array of clinical measures including response and remission rates as well as functional impairment, and to provide additional data on the tolerability and safety of agomelatine.

2. Experimental procedures

2.1. Patients

A total of 412 physically healthy male and female outpatients, aged 18 (or legal age of majority in the relevant country) and over, with a primary diagnosis of GAD according to DSM-IV-TR criteria (American Psychiatric Association, 2000) and having provided signed informed consent, were recruited between August 2013 and January 2015 in Finland (6 centres), Russia (6 centres), Poland (9 centres), Slovakia (6 centres), and Ukraine (8 centres). The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki.

The Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) was used to diagnose GAD (DSM-IV-TR criteria) and potential comorbid disorders. Patients were required to have a HAM-A (Hamilton, 1959) total score $\geq$ 22, a score $\geq$ 2 on both HAM-A items 1 and 2, HAM-A items 1+2 $>$ 5, a Hospital Anxiety and Depression (HAD) (Zigmond and Snaith, 1983) Anxiety score $>$ Depression score at selection and inclusion, and a Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) score $\leq$ 16 at selection. Patients with a decrease greater than 20% on the HAM-A total score between selection and inclusion were excluded.

Patients with current (within 6 months prior to the selection visit) anxiety disorders other than GAD, including panic disorder, posttraumatic stress disorder, agoraphobia, social phobia, obsessive-compulsive disorder according to DSM-IV-TR criteria and confirmed by the MINI, were excluded. Regarding specific phobia, only patients with symptoms present almost daily or which could interfere with study evaluation were excluded. Patients with anxiety symptoms due to a general medical condition or substance use were also excluded. Patients with other psychiatric disorders including major depressive disorder, drug or alcohol abuse dependence, severe personality disorders, a history of psychotic disorder, neurological disorders, and suicide risk (as judged by the clinician, a score $>$ 3 on item 10 of the MADRS, or who had made a suicide attempt within the past year), were excluded. Women of childbearing potential without effective contraception, pregnant women, and patients with severe or uncontrolled organic disease, likely to interfere with the conduct of the study were also