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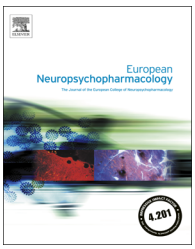

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The efficacy of agomelatine in previously-treated depressed patients

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Abstract
Objective: Post-hoc analysis of two randomized controlled trials with agomelatine was undertaken to compare data on pretreated versus untreated patients with major depressive disorder.
Method: Selected trials were Olié and Kasper (2007), a placebo-controlled trial, and Kasper et al. (2010), a randomized, double-blind comparison with sertraline.
Results: A total of 40% and 57.7% of patients had been pretreated with antidepressants in the placebo-controlled trial and sertraline-controlled trial, respectively. In the previously-treated patients in the placebo-controlled study, the mean decrease in the total score on the HAM-D_{17} over 6 weeks was significantly greater with agomelatine than placebo (delta=4.43, P=0.005) and 67.5% of patients were responders. In the previously-treated patients of the sertraline-controlled study, the improvement on the HAM-D_{17} total score remained numerically higher with agomelatine (delta=1.63, P=0.124), with 55.2% responders. In both studies, agomelatine was well tolerated.
Conclusion: Data from the subset of previously treated depressed patients, who can be considered more difficult to treat, indicate that agomelatine, due to its different mode of action, demonstrated antidepressant efficacy, and favorable side effect profile—with proven benefits in first-line treatment—is also an effective candidate for patients with major depressive disorder previously treated with other antidepressants.

1. Introduction

Major depressive disorder (MDD) is a serious mood disorder that is often chronic and associated with significant morbidity, mortality, social impairment, and patient suffering. Approximately 20% of the general population in Europe as well as the United States and Canada are affected by a depressive episode at some time in their life (Kessler et al., 2010; Patten, 2009; Wittchen et al., 2011).

Despite a broad spectrum of available therapeutic options, in particular, selective serotonin (5-HT) reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), and noradrenaline reuptake inhibitors (NARIs), only 60% of patients with MDD receive treatment (Hasin et al., 2005),

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and between 30% and 50% of patients fail to respond to the first antidepressant prescribed (Brent et al., 2008; Ruhé et al., 2006).

One major concern with these treatments—also with the newer medications—is the delayed onset of a clinical benefit, which results in patients discontinuing their antidepressant treatment during the first weeks of treatment. Almost one-third of patients who fail to improve with their first treatment stop taking their medication, frequently within the first 2 weeks (Warden et al., 2007), and up to 42% of patients discontinue medication within the first month (Olfson et al., 2006). Both clinical trials and "real world" studies consistently show that poor tolerability is associated with increased discontinuation of the prescribed medication (Hotopf et al., 1997; Linden et al., 2000). In a naturalistic setting, 55% of the patients on SSRIs reported at least one bothersome side effect within the first 3 months of starting treatment, and these patients were about three times more likely to discontinue medication (Bull et al., 2002).

Although there is still no full understanding of a common mechanism of action for all antidepressants, newer agents are generally considered to be more targeted. Nevertheless, all available agents—including tricyclics, monoamine oxidase inhibitors, and mirtazapine–do act through the same mechanism of action, which involves modulation of monoaminergic neurotransmission at the synaptic level (Morilak and Frazer, 2007; Papakostas, 2008). Findings from meta-analyses of randomized trials, as well as reviews, indicate a similar spectrum of adverse events with all agents (e.g., nausea, insomnia, somnolence, fatigue, sexual dysfunction, weight gain, withdrawal syndrome), but different frequencies of specific adverse events (Papakostas, 2008).

In the search for faster acting antidepressants and improved tolerability, non-monoaminergic mechanisms have also been explored. An alternative approach focused on circadian rhythms, which are perturbed in depression (Boivin, 2000; Germain and Kupfer, 2008; Souêtre et al., 1989). Since melatonin itself is ineffective in MDD, naphthalene derivatives of melatonin were tested, and agomelatine was identified as the most promising compound (Yous et al., 1992). Agomelatine is a melatonergic (MT_1/MT_2) receptor agonist and a 5-HT_{2C} receptor antagonist whose antidepressant efficacy and good tolerability as first-line treatment have been shown in several clinical studies either versus placebo or versus other antidepressants (de Bodinat et al., 2010; Hale et al., 2009; Kasper et al., 2010; Kasper and Hamon, 2009; Kennedy and Emsley, 2006; Lemoine et al., 2007; Lôo et al., 2002; McAllister-Williams et al., 2010; Montgomery and Kasper, 2007; Olié and Kasper, 2007). In line with its receptor profile and effect on circadian rhythms, agomelatine restores to normal the disturbed sleep–wake cycle and the rest–activity rhythm early in the treatment in depressed patients (Kasper et al., 2010; Quera Salva et al., 2007). The tolerability and safety profile of agomelatine is generally more favorable than that of standard treatment options, and includes freedom from weight gain and the serotonin syndrome, a low risk of sexual dysfunction (Kennedy et al., 2008), a low incidence of gastrointestinal adverse events, as well as the absence of discontinuation symptoms upon withdrawal (Montgomery et al., 2004).

Agomelatine has never been analyzed in previously-treated depressed patients who can be considered more resistant to treatment, thus a post-hoc analysis of two randomized controlled trials in the agomelatine trial program was initiated in order to obtain data in pretreated versus untreated patients.

2. Experimental procedures

Patient data were analyzed from two randomized, double-blind, multicenter clinical trials. Both studies were chosen because they both applied the same methodology and study design, both were European studies, and both used interactive voice response systems (IVRS). Furthermore, both studies were authored by Kasper. The first trial (Olié and Kasper, 2007) was a placebo-controlled study in which patients meeting inclusion criteria at screening were randomized at Week 0 to agomelatine or placebo. After 2 weeks of treatment, patients with an insufficient improvement, based on a predetermined cut-off on the 17-item Hamilton Depression Rating Scale (HAM-D) total score and their global improvement score on the Clinical Global Impression scale (CGI-I), had their agomelatine dose adjusted from 25 mg/day to 50 mg/day for the remaining 4 weeks (Figure 1). Placebo patients with an insufficient improvement were continued on placebo.

The second trial (Kasper et al., 2010; sertraline-controlled study) was a parallel-group study in which eligible patients were randomly assigned to receive agomelatine or sertraline for a 6-week treatment period. After 2 weeks, a dose increase from agomelatine 25 mg/day to agomelatine 50 mg/day or from sertraline 50 mg/day to sertraline 100 mg/day was possible in the case of insufficient improvement according to predefined criteria. In both studies, these criteria were the same and the dose increase was applied centrally using an IVRS, with investigators and patients being blind to them. In both studies, visits took place at selection, Week 0 (randomization), and Weeks 2, 4, and 6 (Figure 1). More detailed descriptions of the methodologies of these two trials have been reported previously (Kasper et al., 2010; Olié and Kasper, 2007).

In both studies, previously treated patients were defined as patients who had been treated with antidepressants at least once during the year before the inclusion.

All patients in the two original studies participated with informed, voluntary written consent, and both studies were approved by local Human Subjects Review (ethics) Committees.

2.1. Statistical analysis

Symptom severity was assessed at Weeks 0, 2, 4, and 6 using the 17-item HAM-D. The CGI-I score was assessed at Weeks 2, 4, and 6. The primary depression efficacy measure was the HAM-D total score assessed in the intention-to-treat (ITT) population using the last observation carried forward (LOCF) approach over Weeks 0–6.

Adverse events were recorded at each clinic visit and safety analyses included patients who took at least one dose of study treatment.

Efficacy analyses were performed on the ITT population (all included and randomized patients having taken at least one dose of the study medication and having at least one post-baseline efficacy assessment: HAM-D total score for the placebo-controlled trial, and an efficacy assessment [other than relative to actigraphy and sleep-wake diary] for the sertraline-controlled trial) and in the subpopulations of patients previously treated and not-previously-treated with antidepressants (at least once) during the year before inclusion in the study.

For all efficacy variables, the two-sided Student's *t* test for independent samples was used to analyze the differences between agomelatine and the placebo-treated or sertraline groups. The difference in HAM-D total score was also studied, using a two-way analysis of covariance with factors treatment, center (as random effect),