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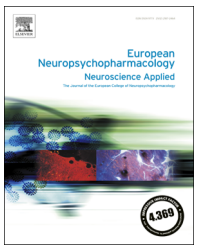

Effectiveness of long-term vortioxetine treatment of patients with major depressive disorder

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Abstract
To investigate the effectiveness, safety, and tolerability of vortioxetine in patients treated at therapeutic doses (5–20 mg/day) for both acute and maintenance treatment, patient-level data were pooled from 5 long-term (52-week), open-label extension studies of major depressive disorder. The mean (±standard deviation) MADRS total score improved from 17.1±10.2 at the start of maintenance therapy to 7.6±8.2 (observed cases [OC]) or 10.3±9.9 (last observation carried forward [LOCF]) at week 52. The mean HAM-A total scores improved from 11.3±6.9 to 6.0±6.0 (OC) or 7.5±6.7 (LOCF) and the mean CGI-S score improved from 3.11±1.20 to 1.94±1.08 (OC) or 2.27±1.26 (LOCF) at week 52. Response and remission rates increased over time. At week 52, the total response rate was 75.4% (n=916/1215, LOCF) and the total remission rate was 60.7% (n=738/1215, LOCF). There were no differences in effectiveness as assessed by MADRS total scores at week 52 in subgroups based on gender, age (<55 vs ≥55 years), baseline HAM-A total score (<20 vs ≥20), baseline MADRS total score (<30 vs ≥30), previous major depressive episodes (MDEs) (<3 vs ≥3) or current MDE duration (<6 vs ≥6 months) at the start of the lead-in studies, or response status (≥50% decrease in MADRS total score during the lead-in study). The most commonly reported adverse event during the maintenance period was nausea.

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1. Introduction

Major depressive disorder (MDD) affects an estimated 350 million individuals globally (World Health Organization (WHO), 2014) and is associated with substantial societal and economic burden (Druss et al., 2009; IsHak et al., 2014; Kessler et al., 2006; Lépine and Briley, 2011). According to the Global Burden of Disease Study 2013 Collaborators (2015), MDD was second only to low back pain in years lived with disability worldwide. As many as 1 in 4 individuals who recover from a major depressive episode (MDE) will have a recurrence within the first year (Solomon et al., 2000). A greater number of previous episodes, more severe depressive symptoms, and longer duration of MDE are predictive of recurrence (Bauer et al., 2015). Long-term treatment (at least 6–9 months) is recommended for patients with MDD who have responded to acute treatment in order to prevent relapse and recurrence (Bauer et al., 2015). Longer prophylactic treatment is recommended for individuals who are at high risk of recurrence; however, evidence supporting maintenance therapy beyond 9 months is limited (Bauer et al., 2015).

Vortioxetine was approved in 2013 in the US for the treatment of adults with MDD and in the European Union for the treatment of an MDE in adults, and subsequently in other countries. The mechanism of action of vortioxetine is related to its multimodal activity, which combines 2 pharmacological actions: direct modulation of receptor activity and inhibition of the serotonin (5-HT) transporter. In addition to inhibiting the 5-HT transporter, vortioxetine is an antagonist at 5-HT_3, 5-HT_7, and 5-HT_{1D} receptors, a partial agonist at 5-HT_{1B} receptors, and an agonist at 5-HT_{1A} receptors (Bang-Andersen et al., 2011; Mork et al., 2012; Westrich et al., 2012).

Vortioxetine is efficacious in the acute treatment of MDD in the 5–20 mg/day dose range (Thase et al., 2016) and has demonstrated longer-term efficacy and prevention of relapse in an MDD relapse-prevention study (Boulenger et al., 2012). In the relapse prevention study, there was a statistically significant difference in favor of vortioxetine vs placebo in the time to relapse of MDD during the first 24 weeks of the double-blind period, with a significantly lower percentage of vortioxetine-treated patients who relapsed (hazard ratio, 2.01; $P=0.0035$), meaning that the risk of relapse was 2 times higher in the placebo group than in the vortioxetine group (Boulenger et al., 2012). Five open-label, long-term (52-week) extension studies (Alam et al., 2014; Baldwin et al., 2012; Filippov and Christens, 2013; Florea et al., 2012; Jacobsen et al., 2014) support the maintenance of effect established during acute treatment phase. The individual extension studies found that patients receiving vortioxetine 2.5 mg/day to 20 mg/day and who had completed a 6- to 8-week vortioxetine clinical trial continued to show improvement in depressive and anxiety symptoms with long-term vortioxetine treatment regardless of prior therapy. Rates of response and remission also increased substantially during the 52-week extension studies.

A pooled analysis of the safety and tolerability of vortioxetine during short-term treatment found that treatment-emergent adverse events (TEAEs) commonly experienced with most antidepressants (e.g., headache, dry mouth, dizziness, constipation, insomnia, somnolence, fatigue, hyperhidrosis) were observed at placebo-like levels with vortioxetine treatment (Baldwin et al., 2016). The TEAEs occurring in $\geq 5\%$ of patients and at twice the frequency of placebo-treated patients were nausea and vomiting. The incidences of potential clinically significant weight change (increase or decrease) and sexual dysfunction (combination of several preferred terms) occurred in $<2\%$ of any vortioxetine-treated group (Baldwin et al., 2016), underscoring the benign safety profile of vortioxetine treatment. In addition, this analysis found that the number needed to harm with vortioxetine treatment ranged from 24 (with vortioxetine 15 mg/day) to 126 (with vortioxetine 5 mg/day).

To investigate the effectiveness, safety, and tolerability of vortioxetine in patients treated at therapeutic doses (5-20 mg/day) during both acute and maintenance treatment, patient-level data were pooled from the 5 long-term (52 weeks), open-label MDD extension studies (Alam et al., 2014; Baldwin et al., 2012; Filippov and Christens, 2013; Florea et al., 2012; Jacobsen et al., 2014). This post hoc analysis was designed to assess whether improvements in depressive and anxiety symptoms continued after acute (6- to 8-week) vortioxetine treatment and whether the effectiveness of long-term vortioxetine treatment was affected by risk factors such as symptom severity, duration of the index MDE, or number of prior MDEs.

2. Experimental procedures

2.1. Studies

Patient-level data were from 5 long-term, open-label, flexible-dose extension studies (NCT00761306, NCT00694304, NCT00707980, NCT01323478, and NCT01152996) that enrolled patients (aged 18-75 years) with MDD who completed 1 of 8 short-term lead-in studies (Alam et al., 2014; Baldwin et al., 2012; Filippov and Christens, 2013; Florea et al., 2012; Jacobsen et al., 2014). Seven of the lead-in studies were of 8-week duration and 1 study (NCT00761306) was of 6-week duration. These studies were conducted in Asia, Australia, Europe, North America (United States and Canada), and/or South Africa. For 2 of the studies (Filippov and Christens, 2013; Florea et al., 2012), only some countries from the lead-in studies could participate due to late start of the extension studies or delayed approvals. In the extension studies, patients were seen at weeks 1, 2, and 4, then every 4 weeks until week 28, and thereafter every 8 weeks until week 52, with a safety follow-up 4 weeks after completion of the extension study (or after early withdrawal).

In the current analysis, Baseline I is defined as the start of active treatment in the lead-in studies and Baseline II is the start of active treatment in the extension studies.

2.2. Patients

In the current post hoc analysis, only patients who were treated with vortioxetine at an approved therapeutic dose (between 5 and 20 mg/day) and who completed the lead-in studies were included.

2.3. Safety and tolerability

Safety and tolerability were assessed by the incidence, nature, and severity of TEAEs that have an onset that occurred after Baseline II