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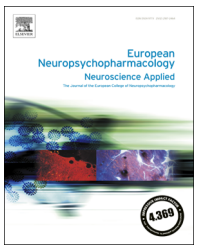

Comparative evaluation of vortioxetine as a switch therapy in patients with major depressive disorder

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Abstract
Switching antidepressant therapy is a recommended strategy for depressed patients who neither respond to nor tolerate an initial pharmacotherapy course. This paper reviews the efficacy and tolerability of switching to vortioxetine. All three published studies of patients with major depressive disorder (MDD) switched from SSRI/SNRI therapy to vortioxetine due to lack of efficacy or tolerability were selected. Vortioxetine was evaluated versus agomelatine directly (REVIVE) and versus sertraline, venlafaxine, bupropion, and citalopram in an indirect treatment comparison (ITC) from switch studies retrieved in a literature review. Vortioxetine's impact on SSRI-induced treatment-emergent sexual dysfunction (TESD) was assessed directly versus escitalopram (NCT01364649) in stable patients with MDD. Vortioxetine's tolerability in the switch population was compared to the overall MDD population. Vortioxetine showed significant benefits over agomelatine on efficacy, functioning, and quality-of-life outcomes, with fewer withdrawals due to adverse events (AEs) (REVIVE). Vortioxetine had numerically higher remission rates versus all therapies included (ITC). Withdrawal rates due to AEs were significantly lower for vortioxetine versus sertraline, venlafaxine, and bupropion, and numerically lower versus citalopram. Switching to vortioxetine was statistically superior to escitalopram in improving TESD (NCT01364649). Tolerability was similar in the switch and overall MDD populations. These findings suggest that vortioxetine is an effective switch therapy for patients with MDD whose response to SSRI/SNRI therapy is inadequate. Vortioxetine was well tolerated and, for patients with a history of TESD,

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showed significant advantages versus escitalopram. Vortioxetine appears to be a valid option for patients with MDD who have not been effectively treated with first-line pharmacotherapies.

1. Introduction

Clinical practice shows that 40–60% of patients with major depressive disorder (MDD) do not respond adequately (e.g., do not achieve $\geq$ 50% reduction in depression rating scores) to first-line pharmacotherapies (Bauer et al., 2013; Rush et al., 2006a) and approximately one-third will not remit even after a course of up to 4 sequential treatment steps (Rush et al., 2006a). Tolerability problems also undermine antidepressant pharmacotherapy; nonadherence and premature discontinuation of medication because of side effects are two of the most common reasons that therapy fails in current practice (Ashton et al., 2005; Masand, 2003).

On average, half of patients (46–52%) discontinue taking their antidepressant medication as prescribed by the end of the first six months of pharmacotherapy (Sansone and Sansone, 2012). In one study, in which 60% of patients had completely discontinued treatment, the most common reasons were lack of efficacy (44%), not liking the way the drug made them feel (36%), lack of interest in sex (22%), tiredness (17%), and weight gain (15%) (Ashton et al., 2005). Furthermore, loss of interest in sex was reported by 47% of all patients prescribed an antidepressant, with inability to have an erection and difficulty reaching orgasm considered to be "extremely difficult to live with" by 25% and 24% of the patients, respectively. Although there are few studies assessing patient self-reported reasons for noncompliance, sexual dysfunction is a commonly reported side effect associated with treatment. A systematic review of the clinical trial data showed that treatment with sertraline, venlafaxine, citalopram, paroxetine, fluoxetine, imipramine, phenelzine, duloxetine, escitalopram, and fluvoxamine was associated with rates of treatment-emergent sexual dysfunction (TESD) that were significantly greater than placebo and that ranged between 25% and 80% (Serretti and Chiesa, 2009). Thus, a large proportion of patients with MDD need to switch therapies during the course of treatment.

In contemporary practice, switching antidepressants is one of the more commonly used strategies when the initial course of antidepressant therapy is either ineffective or poorly tolerated. Indeed, in the UK Clinical Practice Research Datalink database analysis, in the group of patients receiving second-line treatment, switching occurred in 39% of cases (Lamy et al., 2015). A recent multisite study conducted in Spain found that psychiatrists switched 40% of patients who were not well treated with their initial therapy to another antidepressant (Garcia-Toro et al., 2012). They added a second antidepressant for 24% of patients, while the remainder received augmentation (18%) or mixed strategies (19%). A survey of psychopharmacologists in the United States revealed similar treatment patterns (Goldberg et al., 2015).

Once the decision has been made to switch antidepressants due to a lack of efficacy or tolerability problems, there is limited evidence to guide the choice of which new agent to prescribe (American Psychiatric Association (APA), 2010; Gaynes et al., 2012; National Collaborating Centre for Mental Health (NCCMH), 2010; Santaguida et al., 2012; Tadic et al., 2016). A recent meta-analysis found few randomized controlled trials that assessed switching after nonresponse and an absence of high-quality data to support switching versus continuing on the same antidepressant (Bschor et al., 2016). Only a small number of head-to-head studies have assessed the efficacy and tolerability of different antidepressants as switch therapy in individuals who discontinue treatment due to lack of efficacy or intolerable side effects (Kasper and Hajak, 2013; Lenox-Smith and Jiang, 2008; Montgomery et al., 2014; Rush et al., 2006b). Only one study (Jacobsen et al., 2015a) has undertaken a direct comparison of switch therapies in patients with TESD, one of the most bothersome side effects of antidepressant pharmacotherapy (Ashton et al., 2005).

Vortioxetine is an approved antidepressant with a multimodal mechanism of action different from that of SSRIs and SNRIs. Vortioxetine has been evaluated as switch therapy using both direct and indirect analyses in patients who experienced inadequate response to SSRI or SNRI therapy and in patients who discontinued therapy because of intolerable TESD. The objective of this review is to summarize the evidence pertaining to using switch therapy in both of these patient populations.

2. Relative efficacy as switch therapy

2.1. Direct treatment comparison

The REVIVE study (Montgomery et al., 2014) (NCT01488071) was a prospective, randomized, double-blind, flexible-dose, 12-week study to assess vortioxetine efficacy versus agomelatine in patients with MDD who had experienced an inadequate treatment response after receiving a SSRI or SNRI for a minimum of 6 weeks. Eligible patients were directly switched to vortioxetine (10 or 20 mg/day, n=252) or agomelatine (25 or 50 mg/day, n=241). Agomelatine was chosen as the comparator because, like vortioxetine, it has a mechanism of action that is different from SSRIs and SNRIs (Stahl, 2014). The antidepressant effects of agomelatine are thought to be mediated by its actions as a potent agonist at melatonin MT_1 and MT_2 receptors and as a neutral antagonist at 5-HT_{2C} receptors (Guardiola-Lemaitre et al., 2014). This agent is currently not approved for the treatment of MDD in the US, but received that indication from the European Medicines Agency in 2009.

In the primary efficacy analysis, the mean change from baseline in the Montgomery-Åsberg Depression Rating Scale