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Efficacy and tolerability of adjunctive gabapentin and memantine in obsessive compulsive disorder: Double-blind, randomized, placebo-controlled trial

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ABSTRACT

Background: In the search for additional pharmacologic treatments of patients with obsessive-compulsive disorders (OCD), the glutamatergic system is attracting growing interest. While adjuvant memantine to a standard medication with a selective serotonin-reuptake inhibitor (SSRI) appears to reduce OCD symptoms, the adjuvant effect of gabapentin is less certain. The aim of the present randomized, double-blind and three-arm clinical trial was therefore to assess whether, compared to placebo, gabapentin (GAB) or memantine (MEM) adjuvant to a standard medication with an SSRI (fluoxetine; FLU) might lead to further improvements.

Methods: A total of 99 outpatients (mean age: 29.59 years; 49.5% females) diagnosed with OCD were randomly assigned to one of the following three conditions: FLU + gabapentin (FLU + GAB); FLU + memantine (FLU + MEM); FLU + placebo (FLU + PLA). Experts rated patients' symptoms of OCD with the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) at baseline, and 4 and 8 weeks later.

Results: YBOCS scores did not decrease over time. No group differences were observed. However, the significant Time by Group interaction showed that Y-BOCS scores decreased significantly over time in the FLU + PLA group. Response rates did not differ between the three study conditions. Typical side-effects were rash (FLU + MEM), drowsiness (FLU + GAB), anxiety (FLU + GAB; FLU + PLA), and drowsiness plus anxiety (FLU + GAB).

Conclusions: The present pattern of results suggests that glutamatergic medications such as gabapentin and memantine adjuvant to a standard treatment with an SSRI have no additional positive impact on patients with OCD, as measured with the Y-BOCS. Additionally, side-effects were reported. Future studies should use more fine-grained tools to assess, for example, patients' sleep and cognitive functioning, and patients' view of symptoms.

1. Introduction

Compared to worldwide prevalence rates for major depressive disorders of 4.7% (Ferrari et al., 2013) and Attention-Deficit/Hyperactivity Disorders of 5.6% (Polanczyk et al., 2007, 2014), prevalence rates for obsessive-compulsive disorders (OCD) are substantially lower in the range 1–3% (Hirschtritt et al., 2017; Ruscio et al., 2010). Furthermore, the DSM 5 (American Psychiatric Association, 2013) no longer defines OCD as an anxiety disorder, but classes it as a disease in itself, emphasising the large overlap between OCD and comorbid tics and hording. While allowing that there are large inter-individual differences, patients with OCD typically report time-consuming, distressing and impairing persistent intrusive thoughts (obsessions), repetitive and ritualistic behaviors (compulsions), excessive anxiety, poor insight,

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and strong avoidance behavior. Likewise, inter-individual differences in symptoms concern the intensity, frequency and duration of anxiety and avoidance, along with the degree of insight into the disease (American Psychiatric Association, 2013; Hirschtritt et al., 2017; Ruscio et al., 2010). Dramatically, patients with OCD not only have a higher number of disability adjusted life-years (DALYs; the number of years lost to disability), than either healthy controls or patients with neurodegenerative disorders (Hirschtritt et al., 2017), but they also report a much poorer quality of life, even after controlling for symptoms of depression and anxiety (Jahangard et al., 2017).

Cognitive-behavioral therapy has been established as the first-line treatment for OCD (O'Neill and Feusner, 2015), and more specifically exposure therapy (Foa and McLean, 2016), though both psychopharmacological and psychotherapeutic interventions are employed in the treatment of these disorders (Hirschtritt et al., 2017; Romanelli et al., 2014; Skapinakis et al., 2016). In this view, in their recent systematic review and meta-analysis, Skapinakis et al. (2016) cautiously concluded that the combination of psychotherapeutic and psychopharmacological interventions is likely to be more effective than are psychotherapeutic interventions alone, at least in severe obsessive-compulsive disorder. Psychopharmacologic treatments mainly involve selective serotonin-reuptake inhibitors (SSRIs) as the mainstay (Skapinakis et al., 2016), followed by clomipramine (Haghighi et al., 2013; Lack, 2012; Pallanti and Quercioli, 2006; Wu et al., 2012). Other options are neuro-modulatory interventions such as repetitive Transcranial Magnetic Stimulation (rTMS; Haghighi et al., 2015; Jahangard et al., 2016; Shayganfard et al., 2016), and more experimental treatments such as adjuvant buprenorphine (Ahmadpanah et al., 2017; Liddell et al., 2013), adjuvant memantine (Ghaleiha et al., 2013; Haghighi et al., 2013; Hirschtritt et al., 2017; Modarresi et al., 2017; Wu et al., 2012), adjuvant N-Acetyl Cysteine (Oliver et al., 2015; Sarris et al., 2015), and, more recently, adjuvant gabapentin (Onder et al., 2008). Gabapentin is an anticonvulsant mainly used to treat epilepsy (Nevitt et al., 2017), refractory chronic cough (Ryan et al., 2018), neuropathic pain (Alles and Smith, 2018), and restless-legs syndrome (Iftikhar et al., 2017; Kim and Hartzema, 2018). As regards using gabapentin to treat OCD, to our knowledge, there is only one open-label study (Onder et al., 2008) and one general recommendation for gabapentin in the treatment of psychiatric disorders (Berlin et al., 2015). Berlin et al. (2015) concluded that gabapentin was not suitable for the treatment of OCD. Onder et al. (2008) randomly assigned 40 outpatients with OCD either to the condition of fluoxetine alone, or to the condition of fluoxetine and gabapentin. Experts rated patients' symptoms of OCD with the YBOCS and CGI (Global Clinical Impression scale) at baseline and then 2,4, and 8 weeks later. While adjuvant gabapentin had reduced symptoms of OCD by the second week, there was no advantage at the end of the study. Accordingly, it appeared that gabapentin adjuvant to an SSRI (here: fluoxetine) had the potential to accelerate treatment response among outpatients with OCD.

As regards memantine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, this has been employed in a series of previous studies as adjuvant medication to a pharmacologic treatment of symptoms of OCD (Ghaleiha et al., 2013; Haghighi et al., 2013; Pasquini and Biondi, 2006; Wu et al., 2012). Both Ghaleiha et al. (2013) and Haghighi et al. (2013) observed in randomized, placebo-controlled clinical trials that adjuvant memantine improved symptoms of OCD, compared to placebo. To explain the superior effect of memantine compared to placebo, it is assumed that symptoms of OCD are the result of the disruption to glutamatergic transmission, the main excitatory transmitter in the brain. Specifically, changes in glutamate levels and distribution are believed to be key to the development and maintenance of OCD symptoms (Ghaleiha et al., 2013; Pasquini and Biondi, 2006; Stewart et al., 2010). Accordingly, memantine, an NMDA receptor antagonist, has the potential to reducing glutamatergic excitotoxicity and thus protecting against the excitotoxic destruction of cholinergic neurons (Pasquini and Biondi, 2006). Accordingly, also in the present study, we assumed that adjuvant memantine would improve symptoms of OCD, compared to placebo.

There appear to be several options for the psychopharmacological treatment of OCD though more effective approaches to these disorders are still needed (Grant et al., 2016), above all because the overall remission rates remain poor (Albert et al., 2017). The aims of the present double-blind and placebo-controlled clinical trial were therefore to further investigate whether, and if so to what extent, either adjuvant memantine or adjuvant gabapentin with an SSRI (fluoxetine; FLU) might have a positive impact on symptoms of OCD over a period of eight weeks treatment.

The following two hypotheses and one research question were formulated. First, following others (Ghaleiha et al., 2013; Haghighi et al., 2013; Modarresi et al., 2017) we expected that, compared to placebo, adjuvant memantine would alleviate symptoms of OCD. Second, following Onder et al. (2008), we expected that, compared to placebo, adjuvant gabapentin would lead to an early improvement in symptoms of OCD. Next, we treated as exploratory the question of whether adjuvant memantine and adjuvant gabapentin have comparable effects compared to placebo.

We believe that the present results have the potential to increase psychopharmacological treatment options for patients with OCD given that, compared to healthy controls, they have not only higher scores for depression and anxiety, but also lower scores for quality of life.

2. Method

2.1. Procedure

Outpatients diagnosed with OCD were approached to participate in the present randomized, double-blind and placebo-controlled three-arm study. Participants were fully informed about the study aims, the study design and the anonymous data gathering. Thereafter, participants signed a written informed consent, and were then randomly allocated either to the FLU + gabapentin (FLU + GAB), the FLU + memantine (FLU + MEM), or the FLU + placebo (FLU + PLA) condition. Experts rated patients' severity of OCD with the Yale-Brown Obsessive-Compulsive Scale (YBOCS) at baseline, and 4 and 8 weeks later. Side-effects were assessed using a patient-completed form. The Ethics committee of the Kermanshah University of Medical Sciences (KUMS) approved the entire study (Code: kums.rec.1395.86; code of the Iranian Clinical Trial Register: IRCT2016062623705N6), which was conducted in accordance with the rules laid down in the Declaration of Helsinki and its later amendments.

2.2. Sample and inclusion and exclusion criteria

As in a previous study (Haghighi et al., 2013) patients were enrolled in the study, if the following inclusion criteria were met: (1) diagnosis by a psychiatrist of current OCD according to the DSM 5 (American Psychiatric Association, 2013); (2) Yale–Brown Obsessive Compulsive Scale (Y-BOCS) score of 15 points or higher (see below); (3) no comorbid psychiatric disorders; (4) no systemic disorders such as diabetes, hypertension, hyper- or hypothyroidism; (5) no alcohol and other drug use; (6) age between 20 and 40 years; (7) medication for at least three weeks prior to the beginning of the study (and continued throughout the study) of fluoxetine; (8) written informed consent (see also Table 1).

Patients were not enrolled in the study if: (1) the above-mentioned inclusion criteria were not met; (2) female participants were pregnant or breast-feeding or intended to become pregnant during the period of the study; (3) there were concomitant treatments such as rTMS, N-Acetyl Cysteine, buprenorphine, other sleep, or mood, or arousal-altering drugs, or psychotherapy. Patients were withdrawn from the study, if adverse effects were reported or observed, or if patients indicated the wish to withdraw (see Fig. 1).