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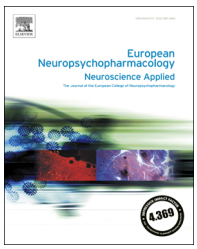

Randomized controlled study of early medication change for non-improvers to antidepressant therapy in major depression - The EMC trial

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Abstract
Patients with Major Depressive Disorder (MDD) and no improvement after two weeks of antidepressant pharmacotherapy have a high risk of treatment failure. The aim of the study was to determine whether an early medication change (EMC) strategy is superior to a guideline-based treatment in MDD patients without improvement after two weeks of antidepressant pharmacotherapy. Eight-hundred-and-eighty-nine patients with MDD were enrolled, 879 patients received the SSRI escitalopram. Of those, 192 patients had no improvement, defined as a reduction of $<20\%$ on the Hamilton Depression Rating Scale (HAMD-17) after 14 days of treatment, and were randomly assigned to open treatment with the EMC strategy ($n=97$; venlafaxine XR for study days 15–56; in case of sustained non-improvement on day 28, lithium augmentation for days 29–56) or TAU ($n=95$; escitalopram continuation; non-responders on day 28 were switched to venlafaxine XR for four weeks, i.e. days 29–56). The primary outcome was remission (HAMD-17 ≤ 7) after 8 weeks of treatment as assessed by blinded raters. Remission

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rates were 24% for EMC and 16% for TAU, which was not significantly different ($p=0.2056$). Sensitivity analyses for the primary and secondary effectiveness endpoints consistently showed favorable results for patients randomized to EMC. The results confirm data from *post-hoc* analyses of clinical trials showing that early non-improvement identifies patients who likely need alternate interventions. However, the herein used two-step switch/augmentation strategy for this risk group was not more effective than the control intervention. Alternate strategies and other design aspects are discussed in order to support researchers addressing the same research question.

1. Introduction

Major Depressive Disorder (MDD) is a severe, highly prevalent and very costly psychiatric disorder that is constantly one of the leading causes of the global burden of diseases because of its substantial morbidity and mortality (Greenberg et al., 2003; Kessler et al., 2003; Murray et al., 2012; Sobocki et al., 2006; Wittchen et al., 2011). Antidepressants are the mainstay of treatment for MDD. However, about two thirds of patients do not benefit sufficiently from the first antidepressant requiring a switch to or an augmentation with a second substance (Rush et al., 2006). Although antidepressants are systematically administered for the treatment of MDD since more than 50 years, there is still uncertainty about the ideal, i.e. minimal duration of treatment to assess the onset of antidepressant action. For decades, common clinical view was that the onset of antidepressant action appears with a delay of 2–4 weeks and can only be fully evaluated after 6–12 weeks. Based on this *delayed onset-hypothesis*, early symptom changes were regarded as unspecific and treatment was continued for several weeks before a medication switch or augmentation was considered (American Psychiatric Association (APA), 2010; Bauer et al., 2013a; DGPPN et al., 2009; Lam et al., 2009; National Institute for Care and Health Excellence, 2010). However, several *post-hoc* analyses of clinical trials suggest that a drug non-response can already be observed within the first 14 days of treatment, and that this early poor outcome is highly predictive for treatment outcome after 6–8 weeks (Henkel et al., 2009; Hennings et al., 2009; Katz et al., 2004; Nierenberg et al., 2000; Papakostas et al., 2006; Posternak and Zimmerman, 2005; Stassen et al., 2007; Szegedi et al., 2003, 2009; Tadić et al., 2010b; Taylor et al., 2006; van Calker et al., 2009). For the clinical decision making of utmost importance, patients who do not improve within the first two weeks and continuing the initial treatment, become stable remitters in only 4 percent of cases, indicating that it might be reasonable to change the treatment strategy after two weeks of unsuccessful treatment (Szegedi et al., 2009).

The Early Medication Change (EMC) trial is the first prospective and confirmative randomized controlled clinical study in patients with MDD to test the hypothesis that an early medication change (EMC) is superior to guideline-based antidepressant treatment in patients with MDD and no improvement after two weeks of antidepressant pharmacotherapy.

2. Experimental procedures

2.1. Participants

Methods and design of the EMC Trial have been described in detail previously (Tadić et al., 2010a). In short, all study participants provided written informed consent at enrollment into the protocol treatment. The ethics committee at the State Chamber of Physicians of Rhineland Palatinate and the German Federal Institute for Drugs and Medical Devices (BfArM) approved the trial protocol. A Data and Safety Monitoring Committee (DSMC) supervised the trial progress to ensure safety of subjects and research integrity.

Adult patients (age 18–65 and <60 years at the time of the first depressive episode)-treated as in-patient or in a day hospital-at one of the eight participating centers in Germany with a primary diagnosis of nonpsychotic MDD (DSM-IV; American Psychiatric Association (APA), 1994) and a sum score ≥ 18 on the Hamilton Rating Scale for Depression (HAMD-17; Hamilton, 1960) at study entry were enrolled between September 2009 and March 2014. Minimal exclusion and broad inclusion criteria were used to maximize generalizability. Patients with a primary diagnosis of bipolar, psychotic, obsessive-compulsive, eating disorder or substance dependence (if it required inpatient detoxification), and female patients who were pregnant or breast-feeding were excluded from the study, as well as those with general medical conditions contraindicating the use of any protocol medication, or a clear history of non-response or intolerance in the current major depressive episode to any protocol antidepressant. Concurrent axis I disorders were assessed by the MINI International Neuropsychiatric Interview (Sheehan et al., 1998), axis II disorders by the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II, Fydrich et al., 1997).

2.2. Protocol treatment

After inclusion and-if necessary-washout of not allowed drugs, patients received the selective serotonin reuptake inhibitor escitalopram for 14 days. Non-improvers, defined by a decrease of $<20\%$ on the HAMD-17 between baseline and day 14 were randomly assigned to open treatment with