A multi-centre, randomised, double-blind, placebo-controlled clinical trial of methylphenidate in the initial treatment of acute mania (MEMAP study)


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Received 18 January 2017; received in revised form 19 September 2017; accepted 3 November 2017

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https://doi.org/10.1016/j.euroneuro.2017.11.003
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1. Introduction

Treatment response of patients with acute mania with antipsychotic agents, benzodiazepines or lithium often requires high dosages and occurs with a delay of several days (Goikolea et al., 2013; Grande et al., 2016). Recently the ‘vigilance regulation model of mania’ has been proposed which suggests that stimulant medications could be a treatment option similar to their beneficial effects in ADHD (Hegerl et al., 2009; Hegerl and Hensch, 2014). This model is based on a variety of clinical as well as preclinical findings which suggest that an unstable regulation of vigilance (vigilance=“brain arousal”) is an important pathogenetic factor not only in ADHD but also in mania. Manic symptoms are interpreted as an autoregulatory attempt of the organism to stabilize vigilance by creating a stimulating environment (Hegerl and Hensch, 2014). Indeed, our research group and others have found unstable vigilance regulation with rapid transitions to EEG drowsiness patterns and sleep stages in mania (Van Sweden, 1986; Ulrich, 1994; Small et al., 1999; Schönknecht et al., 2010). Furthermore, destabilizing vigilance (e.g. by sleep deficits or therapeutic sleep deprivation) can trigger mania in vulnerable subjects (Wu and Bunney, 1990; Plante and Winkelman, 2008; for further references see Hegerl and Hensch, 2014); in contrast, stabilizing vigilance (e.g. by prolonged sleep) could be shown to have antimanic effects (e.g., Frank et al., 2005). In line with this concept antimanic effects of stimulant medications have been reported in several case reports and case series (e.g., Beckmann and Heinemann, 1976; Garvey et al., 1987; Schönknecht et al., 2010; for review see Hegerl et al., 2009 as well as Hegerl and Hensch, 2014). A pilot study (Bschor et al., 2001) even demonstrated reduction of manic symptoms already two hours after onset of treatment with methylphenidate in a patient with acute mania and unstable vigilance regulation (for further arguments for antimanic effects of stimulant medications see Hegerl and Hensch, 2014).

In view of this background, the MEMAP study (Kluge et al., 2013), a RCT was designed to assess the efficacy and safety of short-term treatment with methylphenidate in patients with acute mania.

The primary aim of the RCT was to test the hypothesis that a 2.5 day treatment with methylphenidate immediate release given twice daily has better antimanic effects measured with the Young Mania Rating Scale (YMRS, primary outcome) (Young et al., 1978) than placebo. It was further analysed whether instability of vigilance at baseline predicts response to methylphenidate.

2. Experimental procedures

2.1. Study design overview

Details of the study design have been published elsewhere (Kluge et al., 2013). In short, the MEMAP study is an exploratory, randomized, double-blind, placebo-controlled, international multi-center phase llb RCT. It has been designed to assess the efficacy and safety of the stimulant medication drug methylphenidate (Medikinet®) in the initial 2.5 day treatment of acute mania in patients suffering from bipolar affective disorders. The primary comparison in this RCT was between methylphenidate immediate release given twice daily per os (15 mg at 10 a.m. and 3 p.m. on the first day of treatment (day 1), 20 mg at 9 a.m. and 3 p.m. on day 2 and 20 mg at 9 a.m. on day 3) and placebo (also given twice daily). The lower dose of methylphenidate on day 3 was due to the restriction of treatment duration to 2.5 days and thus a single application at 9 a.m. The patients got the drug only...
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