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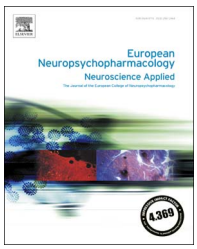

A multi-centre, randomised, double-blind, placebo-controlled clinical trial of methylphenidate in the initial treatment of acute mania (MEMAP study)

Ulrich Hegerl[a,*], Roland Mergl[a], Christian Sander[a], Jens Dietzel[a], Istvan Bitter[b], Koen Demyttenaere[c], Ricardo Gusmão[d,e], Ana Gonzalez-Pinto Arrillaga[f,g], Iñaki Zorrilla[f,g], Adriana García Alocén[f,g], Victor Perez Sola[g,h], Eduard Vieta[g,i], Georg Juckel[j], Ulrich S. Zimmermann[k], Michael Bauer[k], Pascal Sienaert[c], Sónia Quintão[d,e], Marc-Andreas Edel[j], Csilla Bolyos[b], Jose Luis Ayuso-Mateos[g,l,m], Pilar López-García[g,l,m], Michael Kluge[a]

[a]*Department of Psychiatry and Psychotherapy, University Hospital Leipzig, Leipzig, Germany*
[b]*Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary*
[c]*University Psychiatric Center KU Leuven, Leuven, Belgium*
[d]*Departamento de Psiquiatria, Hospital de Egas Moniz, Centro Hospitalar de Lisboa Ocidental, Lisbon, Portugal*
[e]*ISPUP, Instituto de Saúde Pública, Universidade do Porto, Porto, Portugal*
[f]*Department of Psychiatry, Hospital Santiago Apostol, Vitoria, Spain*
[g]*Centro de Investigación Biomédica en Red de Salud Mental. CIBERSAM, Madrid, Spain*
[h]*Department of Psychiatry, Hospital del Mar, Barcelona, Spain*
[i]*Department of Psychiatry, Hospital Clinic, University of Barcelona, IDIBAPS, Barcelona, Spain*
[j]*Department of Psychiatry and Psychotherapy, University of Bochum, Bochum, Germany*
[k]*Department of Psychiatry and Psychotherapy, Technische Universität Dresden, Dresden, Germany*
[l]*Department of Psychiatry, Universidad Autonoma de Madrid, Madrid, Spain*
[m]*Instituto de Investigación Sanitaria Princesa (IP), Madrid, Spain*

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*Correspondence to: Department of Psychiatry and Psychotherapy, University of Leipzig, Semmelweisstr. 10, D-04103 Leipzig, Germany. Fax: +0049 (0)341/97 24539.

E-mail address:

Ulrich.Hegerl@medizin.uni-leipzig.de (U. Hegerl).

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Abstract
Based on many clinical and preclinical findings the 'vigilance regulation model of mania' postulates that an unstable regulation of wakefulness is a pathogenetic factor in both mania and Attention Deficit Hyperactivity Disorder (ADHD) and induces hyperactivity and sensation seeking as an autoregulatory attempt to stabilize wakefulness. Accordingly, stimulant medications with their vigilance stabilizing properties could have rapid antimanic effects similar to their beneficial effects in ADHD. The MEMAP study – a multi-center, double-blind, placebo-controlled and randomized clinical trial (RCT) – assessed the antimanic efficacy and safety of a 2.5-day treatment with methylphenidate (20–40 mg/day). Of 157 screened patients with acute mania, 42 were randomly assigned to receive 20–40 mg per day of methylphenidate in one or two applications, or placebo. The primary outcome was the change in Young Mania Rating Scale (YMRS) sum scores from baseline to day 2.5 in the methylphenidate group compared to the placebo group. A group sequential design was chosen to justify early RCT termination based on efficacy or futility at an interim analysis after inclusion of 40 patients. In the interim analysis, the change from baseline in the YMRS total score at day 2.5 was not significantly different between both groups ($F(1,37)=0.23$; $p=0.64$). Thus, futility was declared for methylphenidate and the RCT was stopped. In summary, although methylphenidate was well tolerated and safe in the full analysis set, it failed to show efficacy in the treatment of acute mania. Trial registration: clinicaltrials.gov (URL: http://www.clinicaltrials.gov; registration number: NCT01541605).

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 IIIb 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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