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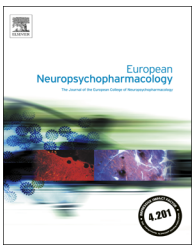

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Placebo response in antipsychotic trials of patients with acute mania
Results of an individual patient data meta-analysis

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Abstract
We examined the role of placebo response in acute mania trials. Specifically, whether placebo response: (1) predicts treatment effect, (2) can be predicted by patient and study characteristics, and (3) can be predicted by a parsimonious model. We performed a meta-analysis of individual patient data from 10 registration studies (n=1019) for the indication acute manic episode of bipolar disorder. We assessed the effect of 14 determinants on placebo response. Primary outcome measures were mean symptom change score (MCS) on the Young Mania Rating Scale (YMRS) and response rate (RR), defined as $\geq$50% YMRS symptom improvement from baseline to endpoint. The overall placebo response was 8.5 points improvement on the YMRS (=27.9%) with a RR of 32.8%. Placebo response was significantly associated with the overall treatment response. Five determinants significantly ($p<0.05$) predicted the placebo response. The multivariate prediction model, which consisted of baseline severity, psychotic features at baseline, number of geographic regions, and region, explained 10.4% and 5.5% of the variance in MSC and RR, respectively. Our findings showed that the placebo response in efficacy trials of antipsychotics for acute mania is substantial and an important determinant of treatment effect. Placebo response is influenced by patient characteristics (illness severity and presence of psychotic features) and by study characteristics (study year, number of geographic regions and region). However, the prediction model could only explain the placebo

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response to a limited extent. Therefore, limiting trials to certain patients in certain geographic regions seems not a viable strategy to improve assay sensitivity.

1. Introduction

Efficacy trials of medicines for psychiatric disorders have a higher failure rate than trials of medicines for other medical disorders (Kemp et al., 2010; Khan et al., 2003a; Nutt and Goodwin, 2011; Vieta and Cruz, 2008; Walsh et al., 2002). These failures mostly become manifest in phase III clinical trials, where drugs are tested for efficacy and safety in the target group in doubled blinded randomised placebo-controlled studies (Nutt and Goodwin, 2011). Unfortunately, it diminishes the likelihood of new medicines becoming available for psychiatric disorders. One of the most frequently cited reasons for the high failure rate is the relatively high placebo response in trials of psychiatric medications (Agid et al., 2013; Kemp et al., 2010; Khan et al., 2003a; Kinon et al., 2011; Vieta and Cruz, 2008; Walsh et al., 2002; Yildiz et al., 2011). This makes it important to understand the role of the placebo response in psychiatric treatment.

Numerous studies have reported on the placebo response in psychiatric trials (Agid et al., 2013; Chen et al., 2010; Cohen et al., 2010; Gispen-de Wied et al., 2012; Khin et al., 2011; Kinon et al., 2011; Mallinckrodt et al., 2011; Post et al., 2000; Sun et al., 2013; Vieta and Carné, 2005), and, contrary to clinical belief, it is even reported to be high in patients with schizophrenia and bipolar disorder (Chengappa et al., 2000; Keck et al., 2000; Storosum et al., 2007; Sysko and Walsh, 2007; Yildiz et al., 2011). However, fewer research has focused on determinants of the placebo response, especially not in trials involving patients with an acute manic episode of bipolar disorder (Chengappa et al., 2000; Keck et al., 2000; Sysko and Walsh, 2007; Vieta and Carné, 2005; Yildiz et al., 2011). In a recent meta-regression analysis of data from 38 placebo-controlled randomized controlled trials involving patients with an acute manic or mixed episode Yildiz et al. (2011), unexpectedly found that symptomatic improvement was similar in the placebo arms of trials of effective and ineffective drugs, and that a higher placebo response was associated with patient (female, older age) and study (more study sites, more recent studies) characteristics (Yildiz et al., 2011). However, as only a limited number of patient and study characteristics were included, and other, not studied, patient and study characteristics might be related to the magnitude of the placebo response, it is important to take these aspects into consideration when designing studies with a low placebo response and a high success potential. Moreover, meta-regression analysis has a relatively low power compared to individual patient data (IPD) meta-analysis, and only the latter allows calculation of the total amount of variance in the placebo response due to patient and study characteristics.

The aim of this study was to examine the magnitude of the placebo response, the effect of the placebo response on the treatment effect, and the role of patient and study characteristics in the prediction of the placebo response in placebo-controlled trials of antipsychotics in patients with acute mania using IPD meta-analysis. More specifically, (1) we tested whether the magnitude of the placebo response predicts the treatment effect, (2) we investigated which patient and study characteristics predict the placebo response, and (3) we identified the most parsimonious model to predict the placebo response.

2. Experimental procedures

2.1. Selection of studies

We included all short-term efficacy studies that assessed antipsychotics and which had been submitted to the Dutch Medicines Evaluation Board (CBG-MEB) during an eleven-year period as part of market authorization application for the indication acute manic episode of bipolar disorder. All studies were double-blind, randomized, placebo-controlled trials involving patients diagnosed with DSM-IV bipolar disorder. Pharmaceutical companies provided their raw patient data, which enabled us to perform a meta-analysis of IPD.

The studies investigated five different types of antipsychotic medication. Active drugs were included and analysed as treatment. Nine studies studied antipsychotic mono-therapy, one study used an add-on, placebo-controlled design. In order to protect the company's interests, the medications investigated are referred to as compounds A to E. We restricted the analyses to the data of patients given a proven effective dose of the medication according to the Summary of Product Characteristics (SmPC) if the drug was registered for the treatment of the acute manic episode; if the drug was not registered for this indication, then expert consensus established whether a dose was effective, based on the doses mentioned in SmPCs for related disorders.

2.2. Assessments

We used the Young Mania Rating Scale (YMRS), an interview-based questionnaire, to assess the severity of the acute manic episode of bipolar disorder. The YMRS comprises 11 items: 7 items are scored on a 0–4 scale and 4 are scored on a 0–8 scale. Total scores ranges from 0 (no symptoms) to 60 (severe symptoms) (Young et al., 1978).

2.2.1. Outcome measures

We used two efficacy outcomes: the standardized difference in mean change score on the YMRS from baseline to follow-up and the percentage responders, with response defined as a decrease $\geq 50\%$ from baseline to follow-up on the YMRS.

The study endpoint was chosen as 3 weeks after baseline, since this is the duration recommended in the EMA Committee for Proprietary Medicinal Products (CPMP) guideline on the clinical investigation of medicinal products for the treatment and prevention of bipolar disorder (CPMP, 2001). If outcome data at week 3 were missing, we used week 4 data in studies that lasted longer than 3 weeks, and if data at week 4 were missing or not available, last observation carried forward (LOCF) was used.