

How real are patients in placebo-controlled studies of acute manic episode?

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Abstract

Objective: To determine whether the results from placebo-controlled studies conducted in patients with manic episode can be generalised to a routine population of hospitalised acute manic patients. **Methods:** A list of four most prevalent inclusion and the nine most prevalent exclusion criteria was constructed for participation in previous randomised-controlled trials (RCTs). On the basis of this list, a consecutive series of 68 patients with 74 episodes of acute mania who had been referred for routine treatment were retrospectively assessed to determine their eligibility for a hypothetical but representative randomised controlled trial. **Results:** Only 16% of the manic episodes would qualify for the hypothetical trial (male episodes 28%, female episodes 10%), whereas 37%, 20% and 27% of the manic episodes would have to be excluded because they did not fulfil one, two or at least three of the inclusion or exclusion criteria. The most common exclusion criterion was “no use of contraceptives”. If this criterion was not taken into account, 28% of the male episodes and 33% of the female episodes would qualify for inclusion in the hypothetical study. Apart from the use of contraceptives, no significant differences between male and female episodes were observed in the reasons for exclusion: 11% suicidal ideation, 29% prior mood stabilising medication, 1% depot medication, 22% other axis I diagnosis, 27% internal disease somatic disease, 5% neurological disorder, 15% alcohol use disorder and 10% drug use disorder. **Conclusion:** Only a small percentage acute manic episodes in a routine mental hospital seem to qualify for a standard placebo-controlled RCT. It could be argued, however, that certain exclusion criteria (e.g. no use of contraceptives) are not very likely to reduce the external validity of a standard RCT. In contrast, some other exclusion criteria (e.g. comorbid alcohol and drug use disorders) may have resulted in an overestimation of the efficacy of anti-manic medications. These notions should be taken into account when evaluating the results of RCTs in bipolar patients with an acute manic episode.

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1. Introduction

Recently, the external validity of trials in depression and schizophrenia has been disputed. Zimmerman et al. (2002) showed that subjects treated in antidepressant trials may represent a minority of patients treated for major depression in routine clinical practice. Similarly, Posternak et al.

(2002) showed that the standard exclusion criteria used in recently conducted antidepressant efficacy trials may reduce the generalisability of the results from these trials. Finally, Hofer et al. (2000) studied the possible reasons for selective sampling of patients with schizophrenia for a clinical trial of an investigational anti-psychotic and found that suicidal or violent patients and those with a history of compliance difficulties may be underrepresented in clinical trials.

New compounds for the treatment of moderate to severe manic episodes have been tested in placebo controlled trials since the early nineties (Pope et al., 1991; Bowden et al., 1994; Tohen et al., 1999; Tohen et al., 2002; Keck et al., 2003). The criticisms relating to the external validity of

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the results of the depression/schizophrenia studies may also be relevant for studies regarding the treatment of acute manic episodes. If the in/exclusion criteria are too strict, generalisability of the results may also be rather limited.

The aim of this study is to examine whether patients who are typically included in clinical trials of acute manic episode are representative of the common acutely manic patient population seen in routine clinical practice. In order to answer this question, a consecutive series of patients referred for routine treatment of an acute manic episode were retrospectively assessed to determine their eligibility for a hypothetical but representative, randomised-controlled trial (RCT).

The following questions will be addressed: (1) what percentage of the patients with an acute manic episode is eligible for this hypothetical trial; (2) what are the main reasons for exclusion from such a trial; and (3) what are the consequences of these findings for the generalisability of the currently available data from RTCs. As far as we know, there are no similar studies of the generalisability of placebo-controlled trials in acute manic episode.

2. Methods

2.1. Inclusion and exclusion criteria

In order to create a list of commonly used inclusion and exclusion criteria for RCTs in acute manic episode, two authors (JGS and CCG de W) reviewed all inclusion and exclusion criteria of all double-blind placebo-controlled studies that were part of a registration dossier for the indication “acute manic episode”. These studies had been submitted to the Medicines Evaluation Board of the Netherlands (MEB) in the period between 1 January 1998 and 31 December 2002. In addition, all recent scientific advise procedures from the Committee for Proprietary Medicinal Products (CPMP) (EMA, 2002) between 1 January 1998 and 31 December 2002 were reviewed for recommended inclusion and exclusion criteria. A total of 11 short-term placebo-controlled studies on the treatment of acute manic episodes lasting 3–6 weeks were identified. Two studies were excluded because the inclusion and exclusion criteria of the protocols were only summarised and not available in detail. In the remaining nine studies, eligibility was limited to male patients and female patients who were not pregnant or not breastfeeding, and aged 18–60/65/70 years. Informed consent of the patients or their legal representatives, guardians or relatives was required in all studies. Moreover, in all studies, the patients had to meet the DSM III ($n=1$) or DSM-IV ($n=7$) criteria of a manic episode or the RDC criteria ($n=1$) of a manic disorder (American Psychiatric Association, 1987; American Psy-

chiatric Association, 1994; Spitzer et al., 1975). Seven studies also included DSM-IV mixed episodes. In all studies, patients were eligible only if they were hospitalised at least at the start of the study, had no relevant internal or neurological disease/disorder and did not fulfil to criteria of an alcohol or drug use disorder. In eight studies, the Young Mania Rating Scale (YMRS) (Young et al., 1978) was used as the rating scale for the inclusion of patients with at least minimum intensity (corresponding to moderate or severe manic symptoms). Eight studies explicitly excluded females not using adequate contraceptives and, in seven studies, suicidal ideation was an explicit exclusion criterion. These and some other less frequently applied exclusion criteria (or inclusion criteria formulated as exclusion criteria) are listed in Table 1. This table shows that the studies differ in eligibility criteria and that there is no uniform set of inclusion and exclusion criteria.

In a consensus meeting (JGS, CCGdeW, TW), it was decided that the 12 criteria applied in at least 6 of the 9 reviewed studies and the exclusion of patients using depot medication prior to the start of the study would be automatically included in the “composed inclusion and exclusion criteria” for the current rating of routine clinical patients with an acute manic episode (see also Table 1).

2.2. Medicines evaluation board

The Medicines Evaluation Board (MEB) is the regulatory authority of the Netherlands. In order to obtain marketing authorisation, pharmaceutical companies are required to submit a dossier to the MEB that includes all clinical trials conducted for a drug under development. Because the dossiers submitted to the MEB are confidential and are property of the pharmaceutical companies, the dossiers were made anonymous.

2.3. Clinical profile of patients with an acute manic episode

Two experienced psychiatrists (JGS, AF) reviewed the discharge letters of all patients who attended our clinic within the period 1 January 1998 to 31 December 2002. These letters contain, among others, the clinical diagnosis of the patients. A resident supervised by an experienced psychiatrist using the DSM multi-axial system makes this diagnosis. This review was limited to patients hospitalised with a primary diagnosis of a manic or mixed episode of a bipolar disorder. Patients with schizoaffective and schizophrenic disorder were excluded.

For each patient, a score sheet was filled out that included an evaluation of the presence or absence of the 12 inclusion and exclusion criteria from the list of “composed inclusion and exclusion criteria” (see Table 1). If no information was available about the presence or absence of

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