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Original Article

Rates of response, euthymia and remission in two placebo-controlled olanzapine trials for bipolar mania

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Objective: Clinically meaningful recovery from acute mania may not be captured by conventionally reported response categorizations. We defined new and stringent criteria for remission in bipolar mania. Using a cohort of patients with acute mania randomized to treatment with either olanzapine or placebo, we contrasted remission rates to findings using previously reported but more lenient categorical outcome measures of response and euthymia.

Methods: We pooled and reanalyzed results through 3 weeks from two published randomized double-blind trials of olanzapine versus placebo for treating acute bipolar mania (1, 2). Response was previously defined as ≥ 50% decrease from baseline to endpoint total Young Mania Rating Scale (3) (Y-MRS) scores, and euthymia as an endpoint total Y-MRS score of ≤ 12. In this report, remission required an endpoint total Y-MRS score of ≤ 7, and an endpoint total Hamilton Depression Rating Scale, (HAM-D21) (4) score of ≤ 7 and an endpoint Clinical Global Impression Scale – Bipolar version, CGI-BP (5), overall severity score of ≤ 2.

Results: Olanzapine treated subjects achieved statistically significantly greater rates of clinical response, euthymia and remission than those assigned to placebo, 55% versus 29.5%, 50% versus 27%, and 18% versus 7%, respectively.

Conclusions: Olanzapine monotherapy resulted in discernable clinical improvements in mania in over 50% of subjects and just under 20% of subjects achieved a near complete resolution of manic and accompanying depressive symptoms after 3 weeks of treatment. Full remission is an important but potentially elusive goal during short-term management of acute mania.

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Clinical trials to evaluate the efficacy of psychotropic medications in patients with acute mania typically use between group mean changes in rating scale scores as the primary efficacy measure, and the proportion of patients showing a 50% or greater decrease in rating scale scores as a secondary efficacy measure. Although these measures provide a signal as to whether or not a given agent is efficacious, and what proportion of patients respond, they do not provide information about the proportion of patients that remit following treatment over a given time period. This is important because although nearly 50–65% of manic patients meet criteria for response at end point in 3–4 week acute mania studies, many 'responders' remain significantly symptomatic. Therefore, a more stringent outcome measure would be useful to identify those manic patients who have achieved not only symptomatic and syndromic remission, but have also returned

to their premorbid level of social and occupational functioning. Indeed, studies of antidepressant medications in patients with unipolar depression now often report the remission rates in addition to reporting on previous efficacy measures.

Therefore, we were interested in determining the proportions of manic patients who meet strict criteria for remission. A literature search failed to reveal any clear cut definition of remission in patients with bipolar mania. The closest outcome we could find to remission was euthymia that was defined as patients scoring 12 or less on total Young Mania Rating Scale (Y-MRS) scores at treatment endpoint (2). One limitation of this definition is that a manic patient entering a clinical trial with a score of 20 could meet criteria for euthymia without meeting the criteria for response (i.e. as response requires a 50% or greater reduction in total Y-MRS scores). Secondly, a subject with mania who for instance begins the clinical trial with a Y-MRS score of 40, and ends with a score of 20 would meet the 50% response criteria, but is significantly symptomatic. Therefore, a more stringent definition of remission should require a lower total Y-MRS score. In the unipolar depression literature, cutoffs of 7 or less on Hamilton Depression Rating Scale (HAM-D) 17 item scale have been used to define remission (6). This relatively low HAM-D score implies minimal to no symptoms. Therefore, we proposed to define remission in bipolar mania as patients having a total score of 7 or less on both the total Y-MRS and the total HAM-D 21 item scales (3, 4). In our clinic, it had been noted that remitted bipolar subjects typically have Y-MRS scored at 7 or less, provided no single item contributes significantly to the overall score. So, prior to the analyzes for this paper, we decided to use a Y-MRS score of 7 or less to define remission. Also, as noted later in the methods, the scores on individual items were forced to be rated at either an absent or minimal level of severity. This prevented any individual subject from achieving a remission score of 7 or less on the Y-MRS scale by having a single item contributing significantly to the score. The reason for adding the low HAM-D total scores was to confirm that the treatment of mania had not resulted in a switch to the opposite affective pole, i.e., depression. Further, as subjects with mixed episodes participated, the HAM-D scores were also important in evaluating any improvement in depressive symptoms. Finally, we proposed that patients should achieve a score of 2 or less on the overall severity item of the Clinical Global Impression-Bipolar version (CGI-BP) scale (5) as this rating's anchor point requires a return to usual social and/or occupational functioning.

Methods

In order to assess the same time period for the different definitions of the three outcome criteria, the datasets from two previously published acute mania trials of olanzapine were pooled. The first study was 3 weeks in duration, and the second was of 4 weeks duration (2), and to facilitate pooling, the data from the 4-week study were truncated at the 3-week time point. Details of these studies have been reported earlier (1, 2). Briefly, subjects providing written and informed consent were recruited from inpatient and outpatient sites including university hospitals, Department of Veterans Affairs facilities, State Hospitals and private practice settings. Diagnosis was based on the Structured Clinical Interview for DSM IV (SCID-P) (7) and the DSM IV (8) criteria for manic or mixed episodes associated with bipolar I disorder. Subjects were required to be inpatients at least initially, and have a total Y-MRS score of at least 20. Other psychotropic medications were discontinued by the day prior to randomization and subjects were randomized to receive either olanzapine or placebo. Olanzapine dosing began at either 10 or 15 mg, and thereafter was flexibly dosed between 5 and 20 mg daily. Lorazepam as rescue medicine was permitted for a maximum of 10 days. Illness psychopathology and severity was assessed using the Y-MRS scale, the HAM-D 21 and the CGI-BP (3–5).

We report results using three different mania outcome definitions: (a) response defined as 50% or greater reduction in total Y-MRS scores, (b) euthymia, as an endpoint Y-MRS total score of ≤ 12 as defined by Tohen et al. (2) and (c) remission as defined in this paper (see Table 1). As noted in Table 1, this definition of mania remission also forces individual items on the Y-MRS scale to be rated at no more than a minimal to mild level of severity, especially the double-weighted items of irritability, speech, content, and disruptive-aggressive behavior. Furthermore, by requiring the HAM-D score to be ≤ 7, the concern about switch to the opposite pole was also addressed. Finally, the definition also provides for the CGI-BP score to be at a level consistent with the ability to function effectively in the subject's usual social and occupational roles providing a dimension of functional outcome. Six secondary analyzes of remission were performed for bipolar disorder subgroups determined by

Table 1. Definitions for clinical response, euthymia and remission in bipolar I mania/mixed episodes

Responder definition	Measure used	Conceptualization
Clinical response	≥50% reduction in Y-MRS total scores from baseline to endpoint.	Discernible clinical improvement in individual subjects. However, a subject starting at a total Y-MRS score of 40 and ending at 20 is considered the same as someone starting at a score of 20 and ending at 10.
Euthymia	Endpoint Y-MRS total scores at ≤12.	In the original paper, Young et al. (3) used a total score of 12.5 to define the lowest severity level for mania corresponding to a global rating of 0–1.5. A cut off of 12 was used to define euthymia by Tohen et al. 2000 (2).
Remission	Total Y-MRS score of ≤7 at endpoint. (The following four items on the Y-MRS scale: irritability, speech, content and disruptive-aggressive behavior were scored at ≤2; and the remaining seven items of the Y-MRS were scored at ≤1) **and** Total HAM-D (21 items) score of ≤7 **and** CGI BP overall total severity score of ≤2.	Near complete resolution of manic and mixed symptoms, and of accompanying depressive symptoms. Also, no switch to depression. Furthermore, a CGI-BP score of ≤2 implies not only few to no symptoms but also effective functioning in the subject's usual social and occupational roles. Finally, no single item on the Y-MRS scale contributed significantly to the remission score in any individual subject.

DSM-IV categorization (8): psychotic, non-psychotic, pure manic, mixed, and with and without a rapid cycling course.

Statistical analyzes

The three outcome definitions were applied to the overall cohort, and the remission definition was applied within diagnostic subgroups, in comparing the two treatment groups (olanzapine versus placebo) using a Cochran-Mantel-Haenszel test stratified by study. Survival analyzes was used to evaluate time to response or euthymia or remission between treatment assignments.

Results

There were 246 patients (men = 124; women = 122) with bipolar I disorder who were included in these analyzes (1, 2). The mean age of the cohort was 39 years (± 10.7 SD.), and nearly 76% were of Caucasian ethnicity. Of these, 176 subjects had pure mania, 70 subjects had a mixed episode, 132 presented with psychotic symptoms, and 85 had a rapid cycling course.

As noted in Fig. 1, olanzapine treatment was statistically superior to placebo using all three definitions; 68/124 (55%) versus 36/122 (29.5%) for response ($\chi^2 = 16.3$, df = 1, p = 0.001), 62/124 (50%) versus 33/122 (27%) for euthymia ($\chi^2 = 13.8$, df = 1, p = 0.001), 22/124 (18%) versus 9/122 (7%) for remission ($\chi^2 = 5.9$, df = 1, p = 0.015). Survival analyzes comparing the treatment groups found no difference in the time to achieve response, euthymia or remission (data not shown).

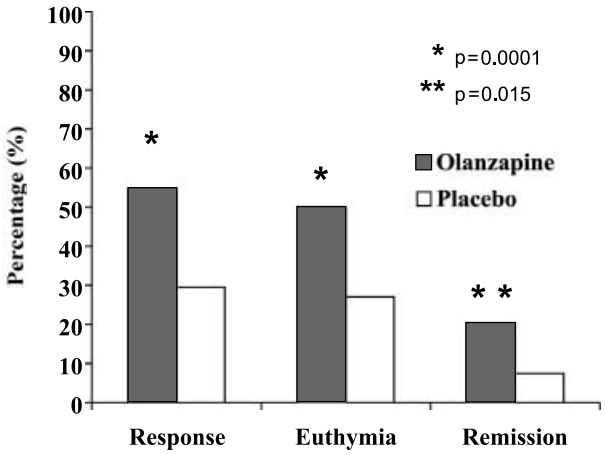

Fig. 1. Rates of response, euthymia and remission in bipolar I mania/mixed episodes.

Remission rates were significantly better on olanzapine versus placebo for groups with pure mania, with psychotic features and without a rapid cycling course (See Table 2). Remission rates did not differ between the treatment groups for those with mixed mania without psychotic features or with a rapid cycling course.

Discussion

Our analyzes found that olanzapine is superior to placebo in the treatment of mania even when stringent criteria are used to define clinically meaningful remission. We found olanzapine to have significantly better outcome rates than placebo for response (55% versus 29.5%), euthymia (50% versus 27%) and remission (18% versus

Table 2. Remission rates to either olanzapine or placebo in subgroups of bipolar I patients

Subgroup	Olanzapine n (%)	Placebo n (%)	Statistics
Pure mania	16/89 (18)	6/87 (7)	$\chi^2 = 4.9$, df = 1, p = 0.027
With psychotic features	14/71 (20)	4/61 (7)	$\chi^2 = 4.8$, df = 1, p = 0.029
Without a rapid cycling course	18/81 (22)	6/80 (7.5)	$\chi^2 = 6.8$, df = 1, p = 0.009
Mixed mania	6/35 (17)	3/35 (9)	NS
Without psychotic features	8/53 (15)	5/61 (8)	NS
With a rapid cycling course	4/43 (9)	3/42 (7.5)	NS

NS = Not statistically significant.

7%). Not unexpectedly, as the definition of outcome became more stringent, the proportion of responders decreased in both treatment groups. Using the strictest definition, among subjects treated with olanzapine after 3 weeks of treatment, one in five subjects achieved a complete recovery of manic and accompanying depressive symptoms, which included resuming their usual occupational and social role functioning. In addition, greater remission rates occurred among olanzapine treated bipolar patients who had psychotic features, pure mania, or were without a rapid cycling course. However, the study was not powered to address these diagnostic subgroups, limiting the generalizability of these secondary subgroup analyzes.

In the face of short hospital stays, the goal of rapidly treating bipolar illness to remission has gained momentum. Most available studies do not address recovery within the short time frames increasingly imposed in clinical practice for hospitalized subjects with mania. Tohen et al. (9), found that nearly 65% of first episode manic patients achieved syndromal recovery within 3 months, and virtually all (97.5%) achieved this status within 2 years. However, Tohen et al. (9) also noted that functional (social and occupational) recovery was only 30% at 6 months and alarmingly only 37.6% at 2 years. Kupfer et al. (10) used a calculated average (over a 4-week period) of ≤ 7 score for either mania, depression or mixed/cycling to define stabilization using the Bech-Rafaelsen Mania Scale. Using that definition, they noted it took a mean of 11 weeks to stabilize following a manic episode, whereas the median was 17 weeks (10). In the present study, instead of using a proxy measure such as the CGI by which to judge social and occupational functioning as in this report, it would have been ideal to have used a more definitive measure. The present data indicate that nearly 20% of patients with acute bipolar mania achieved remission during a 3-week olanzapine treatment period. It is possible that remission rates for mania may be higher with a longer duration of treatment or with combination treatment. Also, studies comparing olanzapine directly with lithium or valproate are needed. Importantly, the issue of sustained and stable remission over 4–8 weeks including psychosocial functional recovery needs to be answered in longer term studies of bipolar disorder. The case for recovery outcomes in unipolar depression and in bipolar depression has been thoughtfully reviewed by Angst and colleagues (11). We clearly need to strive for these goals in bipolar mania too, especially as the majority of subjects in a voluntary bipolar registry reported current unemployment, an indirect indicator of functional outcomes (12). These first analyzes suggest that even with the availability of efficacious treatments, prompt and full remission may elude many patients with bipolar mania at least in the short term.

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