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Comparison of mania patients suitable for treatment trials versus clinical treatment

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Abstract

It remains uncertain whether bipolar disorder (BPD) patients in randomized-controlled trials (RCTs) are sufficiently representative of clinically encountered patients as to guide clinical-therapeutic practice. We compiled inclusion/exclusion criteria by frequency from reports of 21 RCTs for mania, and applied them in a pilot study of patients hospitalized for DSM-IV BPD manic/mixed states to compare characteristics and clinical responses of patients who did versus did not meet exclusion criteria. From 27 initially identified inclusion/exclusion criteria ranked by citation frequency, we derived six inclusion, and 10 non-redundant-exclusion factors. Of 67 consecutive patients meeting inclusion criteria, 15 (22.4%) potential “research subjects” met all 10 exclusion criteria. The remaining 52 “clinical patients” differed markedly on exclusion criteria, including more psychiatric co-morbidity, substance abuse, involuntary hospitalization, and suicide attempts or violence, but were otherwise similar. In both groups responses to clinically determined inpatient treatments were similar, including improvement in mania ratings. Based on applying reported inclusion/exclusion criteria for RCTs to a pilot sample of hospitalized-manic patients, those likely to be included in modern RCTs were similar to patients who would be excluded, most notably in short-term antimanic-treatment responses. The findings encourage further comparisons of subjects included/excluded from RCTs to test potential clinical generalizability of research findings. The pilot study is limited in numbers and exposure times with which to test for the minor differences between “research subjects” and “clinical patients.”

Keywords

bipolar disorder; randomized-clinical trial; inclusion exclusion criteria; mania

INTRODUCTION

Evidence of efficacy and safety of pharmacotherapies for bipolar disorder (BPD) patients relies heavily on randomized-controlled trials (RCTs) as well as less well-controlled clinical studies. However, major uncertainties arise in translating experimental therapeutics research into clinical practice. Uncertainties reflect: (a) case-selection biases implied by inclusion/exclusion criteria for research samples; (b) uncertain relevance of formal, symptom-based rating scale findings to typically complex, unstable, and individually variable presentations of clinical morbidity; and (c) limited testing of clinical effectiveness of treatment, as opposed to technical

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or statistical “efficacy.” Studies of treatment efficacy in BPD patients, even in acute mania, typically rely on short-term demonstrations of superiority of symptom-based ratings of clinical improvement with active versus placebo treatment, and rarely test for full and sustained clinical recovery (Baldessarini and Tarazi 2005; Harvey, 2006). RCTs are widely considered to provide superior evidence on which to base clinical policies and individual treatment decisions—a reputation based largely on superior internal validity expected through randomization to alternative treatment conditions and blinded assessments (Braslow *et al.*, 2005; Dans *et al.*, 1998; Olschewski *et al.*, 1992). Nevertheless, external validity of RCT findings is not always clear, and their generalizability to broader clinical circumstances may be quite limited (Braslow *et al.*, 2005; Vieta and Carne, 2005).

BPD patients encountered clinically often manifest complex and changing co-morbid psychiatric, substance use, or medical conditions (Regier *et al.*, 1990; Singh and Zarate, 2006), high rates of suicide attempts, accidents, and other violent or reckless behavior (Baldessarini, 2002; Khalsa *et al.*, 2008; Simon *et al.*, 2007), and medical complications of prolonged treatment itself (Baldessarini and Tarazi, 2005; Fagiolini *et al.*, 2005; Ösby *et al.*, 2001). They may also deny or minimize illness and cooperate inconsistently with treatment (Cassidy *et al.*, 2001; Ghaemi and Pope, 1994; Kruger *et al.*, 2000; MacKinnon *et al.*, 2002). Such characteristics lead to exclusion of many BPD patients from trials in efforts to limit variability, early drop-outs, and potentially poor responses to treatment (Simon *et al.*, 2004). As few as one in 10–20 potential subjects may be recruited into RCTs, especially those involving long-term observation and potential randomization to placebo (Baldessarini, 2002; Bowden *et al.*, 1997). Moreover, drop-out rates often are $\geq 50\%$, especially in protocols lasting ≥ 6 months (Baldessarini *et al.*, 2000; Bowden *et al.*, 1997, 2000), but even in trials as brief as 3–4 weeks for acute BPD episodes (Licht, 2001; Tohen *et al.*, 1999, 2000). Such selection practices make it likely that BPD patients enrolled in trials may differ greatly from clinically encountered patients. Nevertheless, very few RCT reports detail subject characteristics prior to randomization, rarely compare those excluded versus enrolled (Licht, 2002; Licht *et al.*, 1997), and the treatment responses and clinical outcomes of those excluded are unknown.

Given these circumstances, we systematically compiled inclusion and exclusion criteria from reports of modern RCTs for mania and ranked them by frequency. We then applied the extracted criteria to a pilot sample of hospitalized-manic patients to distinguish those considered: (a) potential subjects for a controlled trial of a novel antimanic agent, or (b) as patients likely to be excluded from such a study. We hypothesized, specifically, that BPD patients likely to be included in a trial would be younger, less severely ill, less likely to have co-morbid conditions, higher functioning, hospitalized fewer days, and treated with fewer psychotropic medicines and at lower average daily doses. A particularly important aim was to compare clinical responses between patients likely to be included versus excluded from clinical trials, under conditions in which both groups were evaluated and observed throughout index hospitalizations, with particular emphasis on mania ratings.

METHODS

Inclusion/exclusion criteria

We used computerized literature searching of the Medline® database for 1998–2008 (search terms: bipolar disorder, mania, randomized-controlled trial, treatment) to develop a sample of modern RCTs for patients diagnosed with DSM-IV mania or mixed states. For each trial report, we extracted lists of inclusion and exclusion criteria by investigator consensus, and ranked them by frequency to develop a list of non-redundant criteria so as to characterize current research practices. Some exclusion criteria were not considered owing to their infrequency or redundancy, or were included in more general criteria (notably, receiving long-acting

antipsychotics, recent participation in other trials, or having previous poor responses to specific antimanic treatments).

Subjects and categorization

Following review and approval for confidential and anonymous use of aggregate clinical data by the McLean Hospital IRB, we examined medical records of inpatients prescribed antipsychotic, antimanic, or mood-stabilizing medicines during 3-month (March–May) periods in 2002 and in 2004, and given a clinical DSM-IV diagnosis at discharge of mania or a mixed manic-depressive state. Next, we systematically extracted demographic, clinical, and treatment response data, including estimated ratings on standard symptom-rating scales. Following these data collection, to avoid bias, we then separated patients considered: (a) likely to be included or (b) excluded from participation in a hypothetical, brief RCT of a novel antimanic agent, based on the inclusion/exclusion criteria derived from recent research reports. Inclusion criteria were met by all subjects accepted for further consideration, who were then divided, based on exclusion criteria, into subgroups of potential *research subjects* versus *clinical patients* unlikely to be accepted in controlled trials of experimental treatments.

Clinical assessments

We assessed clinical status at hospital admission and discharge by applying, by investigator consensus, the Clinical Global Impression (CGI; Guy, 1970), Global Assessing of Functioning (GAF; American Psychiatric Association, 2000), Young Mania Rating Scale (YMRS; Young *et al.*, 1978), and Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979) to clinical records, as detailed previously (Centorrino *et al.*, 2005, 2008). We also considered clinical characteristics that might distinguish *research subjects* versus *clinical patients* but not overlap with exclusion criteria.

Data analyses

For bivariate contrasts between research and clinical subgroups we used simple descriptive statistics (with Bonferroni corrections for multiple comparisons), ANOVA methods, paired *t*-tests, contingency tables (χ^2), or Fisher's exact tests (*p*), reporting data as difference measures between "clinical" and "research" patients and their 95% confidence intervals (CI). We then considered multivariate logistic regression modeling to estimate odds ratios (OR) and their 95% CI. A priori, primary outcome measures were rates of improvement (%/day) of YMRS and CGI scores. Statistical analyses were based on commercial software (Statview-5,® SAS Corporation, Cary, NC; Stata-8,® Stata Corporation, College Station, TX).

RESULTS

Inclusion/exclusion criteria

We identified 21 published reports of brief RCTs for treatments of acute mania to estimate the prevalence of their inclusion and exclusion criteria. This process initially yielded 8 inclusion, and 19 exclusion criteria, considered in rank order of citation to generate a final list of 6 inclusion and 10 exclusion criteria, based on their frequency of use in the reported RCTs, modified by investigator consensus, with simplification to avoid redundancies (Table 1).

Pilot-study subjects

We identified 67 manic or mixed states, type I, DSM-IV BPD patient subjects meeting inclusion criteria for acceptability into RCTs for mania (Table 1). All were adults (*n* = 41, 61.2% women; *n* = 26, 38.8% men), meeting DSM-IV diagnostic criteria for type I BPD in a current manic (*n* = 26, 38.8%) or mixed state (*n* = 41, 61.2%), with (*n* = 43, 64.2%) or without psychotic features, with= an estimated initial mania (YMRS) symptom rating of ≥ 20 , in need

of inpatient-level treatment including use of antimanic medication, and with a past history of at least one prior manic or mixed episode requiring psychiatric hospitalization and treatment with an antimanic or antipsychotic agent that was considered to be effective or clinically successful—all as required by the inclusion criteria applied (Table 1). Voluntary status and ability to consent were required for “research subjects” only.

Following a process of extracting information of interest in characterizing manic patients who met the inclusion criteria and their responses to treatment during hospitalization, we then applied the 10 final exclusion criteria (Table 1) to produce two subgroups of patient subjects who would be likely candidates for a brief RCT of antimanic treatment (“research subjects,” $n = 15$) and those who would be excluded (“clinical patients,” $n = 52$), indicating a “trialintake” rate of 22.4% (15/67). We then compared these subgroups. By definition, whereas “research subjects” had none of the exclusion characteristics, the “clinical patients” had substantial rates of attempts (38.4%), other violent acts (23.1%), or substance abuse (51.9%) within 90 days of index hospital admission, as well as a lifetime co-morbid anxiety disorder diagnosis (19.2%), or were under involuntary status (19.2%; all χ^2 [df 1] ≥ 8.2 , all $p < 0.05$; not shown).

Comparison of likely research subjects versus clinical patients

Aside from confirming expected differences in characteristics arising from exclusion criteria for potential research subjects just summarized, we compared “research subjects” and “clinical patients” for other demographic and clinical characteristics in bivariate contrasts (Table 2). The groups were remarkably similar in *demographic* and *descriptive clinical factors*. Exceptions were that clinical patients showed a slightly greater risk of earlier medical illnesses, shorter lifetime illness, a lower rate of mixed states or psychotic features, slightly lower initial mania rating scores, and higher depression rating scores.

In addition, *treatments* were very similar between subgroups, except that clinical patients were 23.6% more likely to receive ≥ 2 psychotropic agents (Table 2). Finally, based on improvements in symptomatic (YMRS and MADRS) and functional assessments (GAF) during brief hospital treatment, both clinical patients and research subjects showed very similar outcomes. Even the identified minor differences became statistically non-significant when Bonferroni corrections were applied to computed p -values to adjust for chance findings among multiple contrasts.

Finally, improvement in YMRS mania ratings and in CGI-severity scores are typical primary outcome measures in RCTs for mania (see citations for Table 1). YMRS improved only 1.04%/week less among “clinical patients” than “research subjects” (Table 2) and would require ≥ 250 patients/group to reach statistical significance ($p < 0.05$ by unpaired t -test). Changes in CGI differed even less between groups (N would need to be ≥ 2500 /group to reach significance), and were 2% better among “clinical patients” (Table 2). These considerations indicate that type II error is improbable and that huge samples would be required to demonstrate significant differences. Given the lack of significant differences between the groups, multivariate modeling was not pursued.

DISCUSSION

Given continued uncertainty about possible differences between patients who are enrolled versus eligible but excluded from RCTs of novel treatments, it seemed timely to compile leading inclusion/exclusion criteria from modern RCTs for mania, and to compare patients who would or would not meet these criteria. We hypothesized that these subgroups would differ substantially in demographic or clinical variables as well as responses to short-term antimanic treatment. Such comparisons remain rare, but seem essential if research findings are to provide a rational basis for sound, evidence-based clinical practice (Akobeng, 2005; Braslow *et al.*, 2005; Licht, 2002; Licht *et al.*, 1997; Stiegler *et al.*, 2005; Suppes *et al.*, 2005).

We first identified inclusion and exclusion criteria from recent RCT reports (Table 1), and then applied them in a pilot study based on forming subgroups representing hospitalized-manic patients who probably would or would not be selected as research subjects. Of 67 included pilot-study patients, only 15, or about 1 in 5, also met all 10 of our exclusion criteria and were considered potential “research subjects” likely to meet eligibility criteria for RCTs. This low proportion of eligibility is consistent with observations arising from recent RCTs for mania (Bowden *et al.*, 1995; Licht, 2002). By definition, the remaining 52 “clinical patients” differed markedly with respect to exclusion criteria, including more psychiatric co-morbidity, recent substance abuse, involuntary status, and suicide attempts or violence. However, the subgroups were similar on other demographic, illness history, and current clinical characteristics (Table 2). Of particular importance, their responses to clinically determined inpatient treatments were remarkably similar, including by changes in a priori-defined primary outcome measures (change in YMRS mania and CGI-severity ratings). Contrary to our expectations, these similarities seem to suggest that findings among subjects of RCTs for antimanic treatments might well be highly relevant to clinical practice.

This study is limited in considering only hospitalized, acutely manic patients, not comparing patients included versus excluded from an actual RCT, reliance on medical records rather than direct examinations, sampling at a single psychiatric teaching hospital, and relatively brief treatment exposure (11–13 days, limited mainly by current financial and administrative considerations), and use of uncontrolled treatments and doses that surely were clinically optimized to individual requirements, including individualized polytherapies rarely permitted in controlled trials. Such individualized treatment, and treatment exposures shorter than are encountered in typical RCTs for acute mania (3–4 weeks) may tend to limit differences between the subgroups compared. On the other hand, individualized treatment and brief hospitalizations are realistic conditions of contemporary psychiatric hospital practice, and are those under which the results of modern RCTs and regulatory approvals for new antimanic treatments are actually applied (Centorrino *et al.*, 2005, 2006, 2008). It is less likely that the moderate sample sizes produced misleading, false negative, conclusions, based on statistical considerations reported in the Section Results. Finally, it is important to emphasize that this study involved assessments of clinical characteristics and treatment responses for all included subjects *before* their segregation into research subject and clinical-patient subgroups based on the application of exclusion criteria derived objectively from modern RCTs for mania—in essence, a form of “blinding.”

The potential importance of the study’s findings encourages further comparisons of hospitalized-manic and other BPD patients who would be included or excluded in RCTs. We also strongly encourage routine reporting of comparisons of patients included and excluded from RCTs. Such information can support efforts to develop sound treatment guidelines based on scientific evidence with potential generalizability as well as sound experimental design and internal validity.

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Table 1
Inclusion/exclusion criteria in 21 recent randomized-controlled trials for mania, ranked by citation prevalence (%)

Inclusion	
1	DSM-IV diagnosis of bipolar disorder type I, currently manic or mixed episode, with or without psychotic features (100%)
2	Voluntarily status, ability to consent (100%)
3	Men and women, age ≥18 years (95%)
4	Need for inpatient psychiatric treatment and use of an antimanic or antipsychotic agent (90%)
5	Intake Young Mania Rating Scale (YMRS) total score ≥20 (67%)
6	At least one prior manic or mixed episode requiring hospitalization and short-term treatment with a standard antimanic agent, considered clinically successful (52%)
7	Illness severity supported by rating scales other than YMRS (38%) ^a
8	Duration of manic or mixed episode ≤2 or ≥4 weeks (24%) ^a
Exclusion	
1	Any substance abuse within 3 months, or dependence within 6 months (86%)
2	Clinically significant medical illness, unstable ≥3 months (76%)
3	Any current DSM-IV Axis I diagnosis other than bipolar I disorder (57%)
4	Known intolerance or unresponsiveness to antimanic agents (57%) ^b
5	Suicide attempt or other violence within the last 3 months (57%)
6	Epilepsy, head trauma with loss of consciousness, or progressive neurological disease diagnosed within 12 months (43%)
7	Participating in a clinical treatment trial within 12 months (43%) ^b
8	Use of clozapine within 4 weeks (38%)
9	Receiving of discontinuing an antidepressant within 1 month (38%) ^c
10	Female, breast-feeding, or pregnant (38%)
11	Given a long-acting antipsychotic agent within 6 months (38%)
12	Mania associated with a neuromedical condition or substance exposure (24%) ^a
13	Electroconvulsive therapy (ECT) within 3 months (19%) ^b
14	Mental retardation (IQ <70) (19%)
15	Rapid cycling within 12 months (19%) ^b
16	Prior major treatment non-adherence for ≥30 days (10%) ^d
17	Previous diagnosis of schizophrenia or schizoaffective disorder (5%) ^a
18	Involuntary psychiatric hospitalization or incarceration (5%) ^a
19	History of neuroleptic malignant syndrome (5%) ^a

Items in boldface were applied in the pilot study.

Trials ($N = 21$) analyzed for inclusion/exclusion factors: Janicak *et al.* (1998) (verapamil vs. placebo); Hirschfeld *et al.* (1999) (lithium vs. divalproex); Stoll *et al.* (1999) (omega-3 fatty acids vs. placebo); Tohen *et al.* (1999) (olanzapine vs. placebo); Tohen *et al.* (2000) (olanzapine vs. placebo); Zajecka *et al.* (2002) (divalproex vs. olanzapine); Sachs *et al.* (2002) (RSP vs. HAL vs. placebo); Keck *et al.* (2003a) (aripiprazole vs. placebo); Keck *et al.* (2003b) (ziprasidone vs. placebo); Revicki *et al.* (2003) (divalproex vs. olanzapine); Hirschfeld *et al.* (2004) (risperidone vs. placebo); Weisler *et al.* (2004) (carbamazepine vs. placebo); Bowden *et al.* (2005) (lithium vs. quetiapine vs. placebo); Khanna *et al.* (2005) (risperidone vs. placebo); Potkin *et al.* (2005) (ziprasidone vs. placebo); Smulevich *et al.* (2005) (risperidone vs. placebo); Vieta *et al.* (2005) (aripiprazole vs. placebo); Zarate *et al.* (2007) (tamoxifen vs. placebo); Yildiz-Yesiloglu *et al.* (2008) (tamoxifen vs. placebo); Weisler *et al.* (2006) (divalproex vs. placebo); Zarate *et al.* (2007) (tamoxifen vs. placebo); Yildiz-Yesiloglu *et al.* (2008) (tamoxifen vs. placebo); Bowden *et al.*

^a Item not used due to its implicit or explicit inclusion in other, more general, criteria.

^b Item not used as potentially excessively biasing.

^c Item not used as largely unavoidable among contemporary US BPD patients (Baldessarini *et al.*, 2007a,2007b).

^d Item not used for lack of adequate information.

Table 2
Characteristics of adult hospitalized-manic patients considered suitable as treatment research subjects or not (clinical patients)

Factors	Clinical/research				Statistic ^d	p-value
	Research	Clinical	Ratio [95%CI]			
Number (N)	15	52	3.47 [2.46-5.55]	-	-	-
Women (N (%))	10 (66.6%)	31 (59.6%)	0.89 [0.80-0.96]	0.24	0.62	0.62
Current age (years)	41.4 ± 11.5	42.7 ± 13.3	1.03 [1.00-1.12]	0.14	0.71	0.71
Single (N (%))	10 (66.7%)	34 (65.4%)	0.98 [0.92-1.06]	0.01	0.93	0.93
Employed (N (%))	1 (7.6%)	13 (25.0%)	3.29 [2.37-5.19]	(Exact)	0.16	0.16
Education (years)	13.0 ± 3.5	14.1 ± 13.3	1.08 [1.03-1.20]	0.14	0.71	0.71
Clinical presentation (N (%))				5.06	0.24	0.24
Manic	4 (26.7%)	22 (42.3%)	1.58 [1.35-2.00]			
Mixed	11 (73.3%)	30 (57.7%)	0.79 [0.67-0.88]			
Psychotic features (N (%))	11 (73.3%)	32 (61.5%)	0.84 [0.73-0.92]	0.70	0.40	0.40
Age at onset (years)	21.5 ± 7.0	21.7 ± 8.0	1.01 [1.00-1.09]	0.01	0.92	0.92
Years of illness	23.1 ± 17.0	18.5 ± 12.8	0.80 [0.69-0.89]	0.69	0.41	0.41
Hospitalizations/year (%)	0.30 ± 0.34	0.36 ± 0.25	1.20 [1.09-1.38]	0.06	0.79	0.79
Co-morbid disorders (N (%)) ^b						
Prior substance abuse	11 (73.3%)	39 (75.0%)	1.02 [1.00-1.09]	0.01	0.90	0.90
Prior medical illness	7 (46.7%)	40 (76.9%)	1.65 [1.37-2.06]	5.09	0.02	0.02
Prior suicide attempt (N (%)) ^b	3 (20.0%)	23 (44.2%)	2.21 [1.74-3.07]	(Exact)	0.13	0.13
Prior violent behavior (N (%)) ^b	3 (20.0%)	9 (17.3%)	0.86 [0.76-0.94]	(Exact)	0.96	0.96
Polytherapy (N (%)) ^c						
At admission	10 (66.7%)	31 (59.6%)	0.89 [0.80-0.96]	0.24	0.62	0.62
At discharge	10 (66.7%)	47 (90.3%)	1.35 [1.18-1.60]	1.05	0.02	0.02
Mean discharge dose (mg/day) ^d						
Antipsychotics	327 ± 260	432 ± 390	1.32 [1.17-1.56]	0.95	0.33	0.33
Mood Stabilizers	1008 ± 711	1229 ± 1010	1.22 [1.11-1.41]	0.62	0.43	0.43
Index hospitalization (days)	10.8 ± 5.7	13.2 ± 12.5	1.22 [1.11-1.41]	0.51	0.47	0.47
YMRS score						
Admission	30.1 ± 10.3	26.9 ± 10.2	0.89 [0.80-0.96]	1.09	0.30	0.30
Discharge	2.6 ± 3.6	4.3 ± 6.1	1.65 [1.37-2.06]	1.00	0.32	0.32

Factors	Clinical/research				p-value
	Research	Clinical	Ratio [95%CI]	Statistic ^d	
Improvement (%/day) ^e	10.6 ± 5.48	9.56 ± 6.24	0.90 [0.80-0.96]	0.32	0.56
MADRS score					
Admission	18.0 ± 9.4	22.6 ± 10.2	1.26 [1.14-1.48]	2.40	0.12
Discharge	0.3 ± 0.7	3.9 ± 5.6	13.0 [6.04-40.6]	6.33	0.14
Improvement (%/day)	11.3 ± 5.0	9.4 ± 7.3	0.83 [0.73-0.92]	0.87	0.35
CGI score					
Admission	5.8 ± 0.5	6.0 ± 0.8	1.03 [1.00-1.12]	0.92	0.30
Discharge	3.6 ± 0.7	3.6 ± 0.8	1.00 [0.95-1.05]	0.48	0.83
Improvement (%) ^e	37.5 ± 12.7	38.3 ± 16.2	1.02 [1.00-1.09]	0.02	0.87
GAF score					
Admission	28.8 ± 6.2	27.8 ± 7.3	0.97 [0.90-1.00]	0.21	0.64
Discharge	53.2 ± 5.2	51.8 ± 7.2	0.97 [0.90-1.00]	0.49	0.48
Improvement (%)	93.5 ± 48.2	100.1 ± 67.6	1.07 [1.02-1.17]	0.12	0.72

Note: Research criteria leading to exclusion of “clinical patients” are omitted here.

^a Statistics: F-values for continuous measures, and χ^2 or Fisher exact-p (if < 10 subjects/cell) for categorical measures; Bonferroni correction for the 31 contrasts tested would require $p < 0.002$ for significance, but primary outcome measures were improvement in YMRS and CGI scores (requiring $p < 0.05$).

^b Prior: >3 months before index hospitalization.

^c Polytherapy: simultaneous use of ≥ 2 psychotropic agents of any type.

^d Doses: standardized total mg/day: antipsychotics to *chlorpromazine*, anticonvulsants to *lithium* (Baldessarini and Tarazi 2005; Centorrino *et al.*, 2006).

^e A priori primary outcome measures.