

# Comparison of Antidepressant Responses in Patients with Bipolar vs. Unipolar Depression: A Meta-Analytic Review

## Authors

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## Abstract

**Background:** Since there is considerable uncertainty about therapeutic responses to antidepressants among depressed patients diagnosed with bipolar (BP) vs. unipolar (UP) mood disorders, we have reviewed available studies that compared both types of depressed patients.

**Methods:** Extensive computerized literature-searching identified reports of antidepressant studies involving both BP and UP depressed patients. We used random-effects meta-analysis to compare short-term drug responses by patient type, as well as meta-regression modeling for effects of selected covariates.

**Results:** We identified only 10 studies meeting even liberal inclusion criteria, and they varied greatly in size and design quality. The overall difference in antidepressant responses between BP (n=863) and UP (n=2226) disorder patients was

not significant (pooled RR=1.05; CI: 0.96–1.15;  $p=0.34$ ). Based on meta-regression, we also found no difference in responses based on diagnosis or subtype, subjects/study, % women, average age, or length of treatment based on meta-regression. Risk of manic-switching averaged 2.50 vs. 0.275%/week among BP vs. UP disorder patients, including co-treatment with mood stabilizers in 70% of BP patients.

**Comments:** The findings suggest little difference in antidepressant responses by diagnostic type, sex, or other factors considered, but a substantial risk of mania and hypomania with BP disorders. However, data pertaining to the fundamental question of antidepressant response among BP vs. UP depressed patients were strikingly limited, and support only tentative conclusions. Additional, well-designed, prospective trials of matched BP and UP depression patients and controlled treatment are required.

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## Introduction

There has been intense discussion of possible systematic differences in therapeutic responses to antidepressants between patients diagnosed with unipolar major depressive disorder (UP-MDD) vs. the several types of bipolar disorder (BPD). In general, there appears to be a broad clinical impression that acutely depressed BPD patients respond to antidepressant treatment less favorably than those with UP-MDD, have a higher risk of mood-switching, or are difficult to study owing to the clinical and therapeutic complexity in BPD [1–4]. BP depression is often complicated by the presence of complex and shifting mixtures of depressive, dysphoric-agitated, hypomanic, or psychotic features, as well as common co-morbidity with anxiety and substance-use disorders [5]. This clinical complexity, common instability over time, as well as risk of

inducing manic or mixed states [6], and the tendency to receive multiple psychotropic drugs at one time [7], can greatly complicate the conduct and interpretation of findings regarding antidepressant treatment in BPD patients and limit their comparability to UP-MDD patients [5, 8–10]. Contradictory findings have been reported regarding treatment responses in acute BP-depression [11, 12] and in its long-term prophylaxis [13, 14].

In addition, the hypothesis that BP depression responds relatively poorly to treatment may or may not extend to BP-II disorder and other conditions that appear to be clinically intermediate between typical BP-II and UP major mood disorders – presenting clinically as recurrent episodes of depression but sharing sometimes subtle characteristics usually associated with BPD [15–17]. Indeed, a proposed criterion to support such disorders as lying within a “bipolar spectrum” is the

sharing of relatively poor treatment response of intermediate syndromes with more classic forms of BPD of types I or II or of UP-MDD [8,15–18].

Head-to-head trials comparing antidepressant treatment responses in patients with BP vs. UP depression appear to be uncommon, though they should be helpful in resolving the long-standing, basic question about comparable efficacy [4,11,13,17,18]. Since the question remains important and unresolved, we carried out an extensive computerized literature search followed by meta-analysis of the findings to test for substantial differences in responses to antidepressant treatment of acute major depression between cases diagnosed as BP vs. UP disorders. In view of the apparent rarity of such direct comparisons, we employed liberal criteria to include as many potentially relevant studies as possible.

## Methods

### Search strategy and study selection

We performed a comprehensive literature search for reports of therapeutic trials of antidepressant treatments for depression that included both UP and BP major affective disorder patients with acute major depression, through May 2010, using searches of MEDLINE/PubMed (from 1955 [19]), EMBASE (from 1988 [20]) and LILACS (from 1982 [21]), as well as the Internet search engines, PsiTri [22] and Google-Scholar [23]. Search terms included various combinations of “antidepressant”, “bipolar depression”, “bipolar disorder”, “controlled trial”, “depression”, “efficacy”, “major depression”, “major depressive disorder”, “randomized controlled trial”, “treatment”, and “unipolar disorder”. We also considered reports cited in identified studies and in recent reviews.

*A priori* inclusion criteria broadly considered peer-reviewed, prospective or retrospective, randomized or non-randomized, blinded or open-label clinical trials involving treatment with any clinically employed antidepressant (with or without other psychotropic medicines or a placebo) and compared rates of response, remission, or improvement in episodes of acute depression between patients diagnosed with UP-MDD vs. BPDs based on standardized international diagnostic criteria (DSM-IV or ICD-10, which are very similar in criteria for major depressive episodes [24]); we also sought information on selection criteria, sex distribution, mean age, type and dose of antidepressant, and duration of treatment. Data from potential studies were extracted independently by the authors, and any discrepancies were resolved by consensus. The primary comparison was antidepressant response vs. diagnosis.

In addition to data extracted from published reports, we also included original data from a collaborating Sardinian mood disorder center [25,26] for type I and type II BPD patients, based on previously characterized diagnostic and assessment methods [27]. These prospectively collected data involved clinical treatments with a range of antidepressants, with or without other psychotropic drugs, based on diagnoses of BPD types I or II, or recurrent UP-MDD, and comparisons of men and women in each diagnostic category.

Data were subjected to random-effects meta-analysis and meta-regression modeling, using Stata-8.0® statistical software (Stata-Corp, College Station, TX), based on reported or estimated ratios of responders to non-responders with antidepressant treatment as the primary outcome for meta-analyses [28,29]. For studies

that reported outcomes as continuous measures of improvements in standard depression symptom severity rating scale scores, we converted % improvement in depression ratings to % responding as a comparable estimate for both UP and BP disorder patients, since the 2 measures are often remarkably similar, and the results are comparable between diagnostic groups [30].

## Results

We identified only 10 studies involving 2226 unique UP-MDD (75.2%) and 863 types I or II or various types of BPD (24.8%) patients (total N=3089) who met even broad inclusion criteria, and involved comparisons of UP vs. BP depressed patients under presumably comparable conditions of observation and similar, though variably controlled, short-term antidepressant treatment (see Table 1 [25,26,31–38]) at standard clinical doses [39]. Most studies had major limitations, including highly variable and sometimes unbalanced numbers of UP and BP (usually with fewer BP) patients in study arms and variable representation or separate reporting of types I and II BPDs, use of retrospective analyses in 6/10 studies, as well as variable information concerning specific antidepressants and other treatments, drug doses, and actual exposure times, as well as dissimilar measures of treatment-response outcomes, and of adverse events including mood-switching (see Table 1).

Nevertheless, in view of the importance of any data pertaining to the question of possible differences in antidepressant response by diagnostic type, we carried out a random-effects meta-analysis of the available findings. This process indicated considerable inter-study variability, and yielded a pooled relative response (RR) value of 1.05 (95% CI: 0.96–1.15) indicating little or no difference by diagnosis ( $z=0.96, p=0.34$ ; see Fig. 1). We also repeated the meta-analysis without the very large study by Möller et al. [35] to avoid its potentially excessive influence on the findings, but again found no overall difference by diagnosis (RR=1.06; CI: 0.94–1.20).

Additional secondary meta-analyses of the few studies (with limited statistical power) involving only type I, II, or varied types of BPD patients also found no significant differences in responses of these BPD patients vs. UP-MDD patients, with overlapping confidence intervals among the BP diagnostic types (UP vs. *BP-I*: RR=1.12 [CI: 0.90–1.39]; UP vs. *BP-II*: RR=1.02 [CI: 0.81–1.29]; UP vs. *various types* of BPD patients: RR=1.00 [CI: 0.48–2.10]).

In the new studies by Tondo et al. [25,26], we also found no difference in response-rates with antidepressant-treatment by diagnostic subtype (*BP-II* [67.3%], *BP-I* [62.2%], *UP* [61.2%];  $\chi^2=2.12$  [df=2],  $p=0.35$ ). There also were no significant differences [25,26] in antidepressant response between men and women across diagnostic groups (*UP* [women/men=61.9%/59.9%=1.03] < *BP-II* [70.1%/62.1%=1.13] < *BP-I* [67.3%/55.7%=1.21], or overall (women/men=63.8%/59.4%;  $\chi^2$  [df=1]=0.29–2.55,  $p=0.59$ –0.11). Of note, however, under similar conditions, we found marked differences by diagnosis, in rates of co-treatment with other psychotropic medicines (most often, lithium, anti-convulsants, antipsychotics, or sedative-anxiolytics: *BP-I* [93.3%] > *BP-II* [82.9%] > *UP-MDD* [62.5%];  $\chi^2=143, p<0.0001$  [25,26].

Overall meta-regression analysis found no relationship of the difference in response between UP and BP disorder patients and factors added one-by-one into the model: [a] diagnostic type or subtype (UP-MDD BP-I, BP-II), [b] total number of subjects,

**Table 1** Antidepressant treatment trials comparing depressed unipolar and bipolar disorder adult patients.

Study [design]	Drugs <sup>a</sup>	Unipolar				Bipolar							
		Weeks Treated	n	% F	Age	Response (%)	Switch (%/week)	n (Dx)	% F	Age	MSS Used	Response (%)	Switch (%/week)
Amsterdam 1998 [R] [31]	VNX	6	30	64.6 <sup>b</sup>	45 <sup>b</sup>	56.7 <sup>c</sup>	0.000	16 (II)	64.6	41 <sup>b</sup>	no	62.5 <sup>c</sup>	0.000
Amsterdam et al. 1998 [P] [32]	FLX	12	80	71.0	41	76.2	0.025	79 (II)	71.0	41	no	60.8	0.317
Amsterdam & Garcia-España 2000 [P] [33]	VNX	12	17	100	41	55.8 <sup>c</sup>	0.000	15 (II)	100	37	no	56.0 <sup>c</sup>	0.000
Möller et al. 2001 [R] [34]	various <sup>d</sup>	16	1755	73.0	54	58.5 <sup>c</sup>	–	277 (I)	63.0	48	Li or CBZ (53%)	56.7 <sup>c</sup>	1.562
Bottlender et al. 2002 [R] [35]	various <sup>e</sup>	9	50	62.0	54	74.0	–	50 (I)	62.0	54	Li (80%), others (30%)	70.0	1.333
Ghaemi et al. 2004 [R] [36]	various <sup>f</sup>	8	19	49.0	38	68.4	0.000	39 (I+II)	63.0	38	CBZ, Li, or VPA (81%)	48.7	0.841
Agosti et al. 2007 [P] [37]	IMI/PNZ	6	125	–	–	61.8	–	25 (I+II)	–	–	no	54.2	–
O'Donovan et al. 2008 [R] [38]	various <sup>g</sup>	ca. 8	17	53.0	35	82.0 <sup>c</sup>	ca. 0.750	17 (I+II+SA) <sup>j</sup>	65.0	29	no	41.2 <sup>c</sup>	ca. 5.875
Tondo et al. 2010a [R] [25]	various <sup>h</sup>	12	133	67.0	44	61.9	0.501	89 (I)	53.0	36	Li (56%), others (19%)	67.3	5.056
Tondo et al. 2010b [R] [26]	various <sup>h</sup>	12	133	67.0	44	61.9	0.501	92 (II)	61.5	44	Li (43%), others (18%)	70.1	6.250
<b>totals/averages</b>	<b>various</b>	<b>10</b>	<b>2226<sup>i</sup></b>	<b>79.3</b>	<b>54</b>	<b>59.9</b>	<b>0.275</b>	<b>863</b>	<b>62.0</b>	<b>42</b>	<b>ca. 42% yes</b>	<b>54.2</b>	<b>2.496</b>

Baseline illness severity was adequately matched between UP and BP cases; diagnoses were based on DSM criteria in 8, and ICD criteria in 2 studies [34, 35]; study designs were prospective [P] or retrospective [R]. Mean % responding are weighted by subject numbers (n). Average switch rates (%/week of antidepressant treatment) weighted (by n): BP-II (2.97) ≥ BP-I (2.28) >> UP (0.028). Switch rate (%/week of antidepressant exposure) was 9; +times greater (2.496/0.275) among all BPD than MDD patients.

<sup>a</sup> Drugs: BUP = bupropion; CBZ = carbamazepine; FLX = fluoxetine; IMI = imipramine; LI = lithium carbonate; MAOIs = monoamine oxidase inhibitors; MSS = mood stabilizers; NEZ = nefazodone; PNZ = phenelzine; SNRIs = serotonin and norepinephrine reuptake inhibitors; SRIs = serotonin reuptake inhibitors; TCAs = tricyclic antidepressants; VPA = valproate; antidepressants were given at standard daily doses (39) for an unweighted average of 10 weeks

<sup>b</sup> Sex (F = female), reported for all subjects; average ages are weighted by numbers of subjects

<sup>c</sup> Based on % improvement in HDRS or MADRS depression ratings

<sup>d</sup> Antidepressants used: TCAs > MAOIs > SRIs

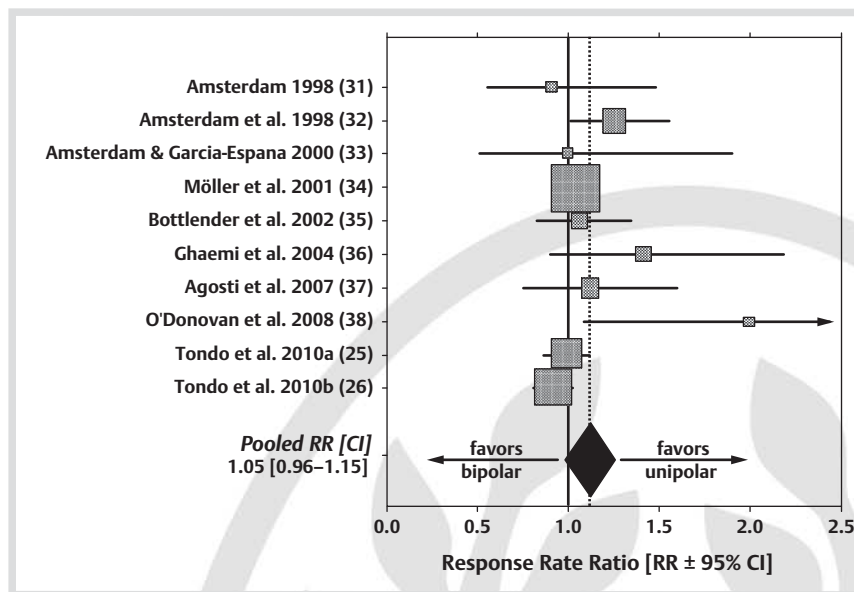
<sup>e</sup> Antidepressants used: TCAs > SRIs > MAOIs

<sup>f</sup> Antidepressants used: SRIs/SNRIs > BUP > MAOIs

<sup>g</sup> Antidepressants used: SRIs/SNRIs > BUP > NEZ > TCAs

<sup>h</sup> Antidepressants used: SRIs/SNRIs > TCAs >> MAOIs > Others; switch rates are for mania or hypomania; in BP-I (59%), BP-II (97%) and UP (100%) switches = hypomania.

<sup>i</sup> Total N excludes 133 UP-MDD patients involved in 2 studies [25, 26]



**Fig. 1** Random-effects meta-analysis of studies comparing antidepressant responses in patients with UP or BP depression ( $n = 10$  comparisons), based on data summarized in **Table 1**, with references in parentheses. The overall pooled RR (1.05, CI: 0.96–1.15,  $p = 0.34$ ) indicates a lack of significant difference in responses of UP and BP disorder patients in acute major depressive episodes.

[c] % women, [d] average age, or [e] duration of treatment (all  $z \leq 1.57$ , all  $p \geq 0.12$ ).

Finally, it is noteworthy that new episodes of mania or hypomania were quite common among BPD patients (**Table 1**), despite limited exposure to antidepressants (averaging 10 weeks), and often with a mood-stabilizer (by approximately 42% of BPD patients [**Table 1**]). Rates of mood-switching (%/week) were similar among BP-I (2.28) and BP-II patients (2.97), but approximately 97% involved hypomania in BP-II patients, and 41% mania+59% hypomania in BP-I cases in studies reporting that information [25,26]. Moreover this risk, as expected, was more than 9-times higher among all BP (2.50%/week) than UP depressed patients (0.275%/week, almost all as hypomania [25,26]). This low observed switch-risk among UP-MDD patients suggests that misdiagnosis of apparent UP-MDD was uncommon.

## Discussion

The present findings underscore 2 important conclusions. First, the number and quality of studies pertaining to direct comparisons of antidepressant responses among acutely depressed UP-MDD vs. BPD patients are strikingly limited. This circumstance is surprising for such a fundamental question that has remained unanswered since introduction of the concept of BPD as a separate subtype of manic-depressive illnesses in the mid-20<sup>th</sup> century, and of modern antidepressants in the 1950s [5,39]. Second, the studies that we did find were limited in number, with variable methodological rigor and independence of subjects sampled, and they provided no basis for support of major differences in antidepressant responses between UP-MDD and BPD patients. This conclusion – though tentative due to the limitations of the available data – is consistent with recent proposals that antidepressant treatment may or may not be as effective in BP depression as in UP-MDD, may be superior with modern antidepressants compared to tricyclics, needs to be employed cautiously and is potentially risky in acute BP-depression, not only due to risk of inducing mania (**Table 1**), but possibly destabilizing the long-term course and leading to treatment-resistance [1–3,40–47], as well as having uncertain but possibly quite limited long-term

benefit, particularly in comparison with mood-stabilizers [3,13,40,45]. Despite much discussion, and with limited directly relevant data, there remains uncertainty to what extent the evidently widespread impression that depressed BPD patients may respond less well to antidepressants than UP-MDD patients pertains to efficacy *per se*, or to concerns about potential mood-destabilizing effects, with or without simultaneous treatment with mood stabilizers, whose protective effects with antidepressant treatment also remain uncertain [6].

It is also important to emphasize that the reported findings may be confounded by limited control over treatments in most of the studies identified, and by their sometimes retrospective designs, with the likelihood that clinical treatment was individualized and adjusted to tolerability so as to favor positive clinical outcomes in some studies. Such uncontrolled variance may well contribute to data that are highly regressed to average outcomes, tending toward a conclusion of “no difference” that may well not represent definitive evidence of similarity of response (type II error). Even such potential limitations leave the possibility that clinical use of antidepressants may be beneficial for some BPD patients; surely it is highly prevalent [48,49]. In general, possible clinical dissimilarities between “depressive” syndromes in UP-MDD vs. BP-I and perhaps BP-II disorders discussed above, as well as marked dissimilarities in their clinical treatment and their risks of antidepressant-associated mania or hypomania ([6], **Table 1**) or destabilization over time [1], may well make comparisons – especially of simple, controlled antidepressant trials without mood-stabilizers – unusually challenging [12,40]. On the other hand, similar responses to antidepressant treatment among UP-MDD and BP-II patients were found in a randomized, controlled trial [32], as well as in several others that may involve somewhat individualized clinical treatments (**Table 1**), underscoring the possibility that these two mood syndromes may be quite similar and distinct from BP-I disorder [50]. In conclusion, given the continued importance of the question of possible diagnostic differences in responses to antidepressant drugs, and in view of the major limitations of available research studies and findings involving direct comparisons of BPD and UP-MDD patients, it seems clear that additional, prospective, controlled trials are needed. Ideally, these would include BP and

UP disorder patients who are properly matched by demographic and clinical characteristics, and with greater control over the types, doses, and exposure-times for antidepressants and over other treatments provided as well as consideration of rates of adverse effects on mood per exposure time, as well as simple antidepressant efficacy.

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The authors had no potential conflicts of interest related to this report.

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