Antidepressant-Associated Mood Elevations in Bipolar II Disorder Compared With Bipolar I Disorder and Major Depressive Disorder: A Systematic Review and Meta-Analysis

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Objective: Antidepressant-associated manic and hypomanic episodes have been reported in bipolar I disorder but are rare in major depressive disorder (MDD). Several lines of evidence suggest that bipolar II disorder is a distinct illness from bipolar I disorder and MDD. The risk of antidepressant-associated mood elevations (AAME) in bipolar II disorder relative to bipolar I disorder and MDD is unknown.

Data Sources: We conducted a computer-aided MEDLINE search encompassing the dates 1949 to February 2008, using the keywords *antidepressant and mania*, *antidepressant and hypomania*, *antidepressant and bipolar*, *fluoxetine and bipolar*, *fluvoxamine and bipolar*, *sertraline and bipolar*, *paroxetine and bipolar*, *citalopram and bipolar*, *escitalopram and bipolar*, *venlafaxine and bipolar*, *mirtazapine and bipolar*, *bupropion and bipolar*, *monoamine oxidase inhibitor and bipolar*, *phenelzine and bipolar*, *tranylcypromine and bipolar*, *tricyclic and bipolar*, *imipramine and bipolar*, *amitriptyline and bipolar*, *nortriptyline and bipolar*, and *desipramine and bipolar*.

Study Selection: All prospective English-language studies, including randomized, controlled trials (RCTs), open-label studies, and naturalistic treatment reports, were eligible for inclusion. We located 13 studies, including 7 RCTs, that reported rates of antidepressant-associated mood elevations in bipolar I disorder versus bipolar II disorder, and 5, including 4 RCTs, that reported rates in bipolar II disorder versus MDD.

Data Extraction: Data were combined to estimate mean switch rates and subjected to meta-analysis to determine the relative risks of antidepressant-associated mood elevations in bipolar I disorder versus bipolar II disorder and in bipolar II disorder versus MDD.

Data Synthesis: The mean rates of antidepressant-associated mood elevations in studies comparing bipolar I disorder and bipolar II disorder were 14.2% and 7.1%, respectively, in acute trials (less than 16 weeks), and 23.4% and 13.9%, respectively, in maintenance studies. The mean rates in reports comparing bipolar II disorder and MDD were 8.1% and 1.5%, respectively, in acute trials, and 16.5% and 6.0%, respectively, in maintenance studies. The relative risk (RR) of antidepressant-associated mood elevations was greater in bipolar I disorder than bipolar II disorder (RR = 1.78, 95% CI = 1.24 to 2.58, p = .002), and higher in bipolar II disorder than MDD (RR = 2.77, 95% CI = 1.26 to 6.09, p = .01). Mood elevations occurred almost exclusively into hypomania in MDD and bipolar II disorder, while patients with bipolar I disorder experienced manias and hypomanias with similar frequencies.

Conclusions: The risk of antidepressant-associated mood elevations in bipolar II disorder is intermediate between that in bipolar I disorder and MDD.

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The depressive pole of bipolar II disorder is overwhelmingly responsible for its substantial burden. Patients with bipolar II disorder spend one third to one half of their lives with syndromal or subsyndromal depression and experience depressive symptoms up to 35 times more frequently than they experience hypomania.[1,2] Bipolar II disorder is, for many patients, best conceptualized as a depressive illness, with hypomanic episodes generally infre-

quent, brief, and mild.[1] Studies in family practice[3] and specialty[4] settings suggest that 18.5% of primary care patients with depression and 40% of depressed patients in specialty settings suffer from bipolar II disorder. Thus, bipolar II disorder is very likely the most common cause of depression after major depressive disorder (MDD).

In clinical practice, antidepressants are frequently prescribed to treat depressive episodes in patients with bipolar II disorder.[5] While considerable controversy has surrounded the use of antidepressant medications in bipolar disorder, related to their potential liability in precipitating manic and hypomanic episodes, this concern is based primarily on data from patients with bipolar I disorder. Consequently, North American clinical practice guidelines generally recommend that antidepressants be used with caution and for brief periods in the treatment of acute bipolar I disorder depression.[6–8] Whether this caution is also warranted in bipolar II disorder is unclear. A number of lines of evidence, including genetic,[9] family history,[10] treatment,[11–13] and long-term follow-up studies,[14] suggest that bipolar I disorder and bipolar II disorder are distinct illnesses and that bipolar II disorder may be intermediate between bipolar I disorder and MDD in some regards. MDD is distinguished from bipolar disorder by an absence of manic and hypomanic episodes, and numerous clinical trials confirm that it is associated with a very low rate of antidepressant-associated mood elevations.[15] In fact, it has been argued that the rate of mood elevations in MDD falls within the error rate of misdiagnosis of bipolar disorder as MDD and that antidepressant-associated mood elevations are thus unique to bipolar illness.[15]

The rate of antidepressant-associated mood elevations in bipolar II disorder relative to bipolar I disorder and MDD is unknown. While there has been a perception among clinicians and researchers that bipolar II disorder is associated with a lower likelihood of antidepressant-associated mood elevations than bipolar I disorder, the only systematic review of this topic[16] included just 1 prospective clinical trial and 3 retrospective studies. The purpose of the current report is to compare the rate of antidepressant-associated mood elevations in bipolar II disorder to those in bipolar I disorder and MDD, utilizing data from prospective studies.

METHOD

Search Strategy

We conducted a computer-aided MEDLINE search for the period 1949 to February 2008 to locate published reports that compared rates of antidepressant-associated mood elevations in bipolar I disorder versus bipolar II disorder and in bipolar II disorder versus MDD. Search terms included *antidepressant and mania*, *antidepressant and hypomania*, *antidepressant and bipolar*, *fluoxetine and bipolar*, *fluvoxamine and bipolar*, *sertraline and bipolar*, *paroxetine and bipolar*, *citalopram and bipolar*, *escitalopram and bipolar*, *venlafaxine and bipolar*, *mirtazapine and bipolar*, *bupropion and bipolar*, *monoamine oxidase inhibitor and bipolar*, *phenelzine and bipolar*, *tranylcypromine and bipolar*, *tricyclic and bipolar*, *imipramine and bipolar*, *amitriptyline and bipolar*, *nortriptyline and bipolar*, and *desipramine and bipolar*. We scanned the bibliographies of selected papers and relevant review articles to locate other reports. For publications in which rates of antidepressant-associated mood elevations were not specifically reported or were not reported separately for bipolar I disorder, bipolar II disorder, and/or MDD, we contacted the authors for further information.

Eligibility Criteria

In order to capture the full range of studies from which data on antidepressant-associated mood elevations are available, we employed broad inclusion criteria. All English-language prospective studies of antidepressant use in bipolar I disorder and bipolar II disorder, bipolar II disorder and MDD, or bipolar I disorder, bipolar II disorder, and MDD that reported rates of antidepressant-associated mania and/or hypomania separately for 2 or more of these illnesses were eligible for inclusion. No other restrictions regarding sample size or study methodology were stipulated, and thus randomized controlled trials (RCTs), single-blind trials, open-label studies, and naturalistic treatment reports that followed a defined sample of patients over time were eligible for inclusion. Retrospective studies, or prospective studies in which antidepressant-associated mood elevations were retrospectively ascertained, were excluded, as were trials that reported rates of antidepressant-associated mood elevations in patients prescribed non-antidepressant compounds such as stimulants or thyroid supplements. We considered studies with a duration < 16 weeks to represent acute treatment, and those ≥ 16 weeks in duration to be maintenance studies.

Data Extraction and Analysis

To ensure accuracy, 2 reviewers (D.J.B. and M.M.N.) independently extracted data regarding rates of antidepressant-associated mood elevations from the studies selected for inclusion and entered them into Review Manager 4.2.10 (The Cochrane Collaboration, Oxford, United Kingdom). Meta-analyses were performed using relative risk (RR) as a metric. We chose a priori to analyze data using a random-effects rather than a fixed-effects model because of heterogeneity in the clinical samples and methodologies of the studies we selected. Heterogeneity was nonetheless assessed post hoc using χ^2 and I^2 statistics. Our primary outcome was the RR of antidepressant-associated mood elevations in bipolar I disorder and bipolar II disorder, as ascertained from prospective studies

reporting on antidepressant use in both illnesses. Secondary outcome measures included the RR of antidepressant-associated mood elevations in bipolar II disorder and MDD in reports comparing them, the risk of antidepressant-associated mood elevations during acute and maintenance studies, and the risk of mood elevations into both mania and hypomania. We also conducted sensitivity analyses to examine the robustness of our findings by limiting the analyses to RCTs, to trials employing newer (i.e., nontricyclic and non–monoamine oxidase inhibitor) antidepressants, to studies in which all patients received mood-stabilizing medications, and to trials in which mood stabilizers were not used. Finally, as we speculated that the difficulty inherent in detecting mild mood elevations might result in erroneously low rates of antidepressant-associated mood elevations in bipolar II disorder, we also repeated the analysis including only trials that measured antidepressant-associated mood elevations using sensitive cutoff scores on mania rating scales, which we defined as a Young Mania Rating Scale (YMRS) score of 14 or a similarly sensitive score on another mania rating scale.

RESULTS

Studies Included in the Analysis

We identified 13 prospective studies,[17–29] including a total of 777 patients, that reported rates of antidepressant-associated mood elevations in bipolar I disorder (N = 462) and bipolar II disorder (N = 315) separately (Table 1). They included 7 RCTs, 2 single-blind clinical trials, 1 open-label trial, and 3 naturalistic follow-up studies. One additional RCT[30] reported 10-week data for a 1-year maintenance RCT already included.[27] To avoid duplication of data, the 10-week results were included only in the sensitivity analysis of acute-phase reports.

In 10 of the 13 studies, data regarding antidepressant-associated mood elevations were provided in the published report. In the remaining 3,[25,28,29] the authors provided the information on request. All 13 trials reported on the use of concomitant mood-stabilizing medications; 75.4% of patients received concomitant mood stabilizers. Nine publications reported on antidepressant-associated mood elevations during acute treatment (< 16 weeks), and 5 provided data from maintenance treatment (≥ 16 weeks). One trial[23] involved treatment with either antidepressants (N = 33) or electroconvulsive therapy (N = 11); all other trials involved treatment with antidepressant medication only. Two studies were excluded from the analysis. We were unable to obtain data regarding rates of mood elevations in bipolar I disorder and bipolar II disorder in 1 study[31] that did not report them separately. A second trial[32] randomly assigned patients to treatment with either 2 mood stabilizers or a mood stabilizer plus an antidepressant but did not specify the number of patients with bipolar I disorder and bipolar II disorder randomly assigned to the antidepressant arm.

Five prospective studies,[20,22,33–35] including 325 patients, were located that reported rates of antidepressant-associated mood elevations in bipolar II disorder (N = 140) and MDD (N = 185) (Table 2). In all studies, data regarding antidepressant-associated mood elevations were provided in the published reports. Four[20,33–35] were RCTs, and 1 was a naturalistic follow-up study.[22] Three publications[20,33,35] reported data from acute treatment with antidepressants, and 2 were maintenance studies.[22,34] All trials reported on the use of concomitant mood-stabilizing medications; 8.3% of patients received concomitant mood stabilizers. One study[36] was excluded because, while prospective in design, it reported a post hoc reanalysis of data from an antidepressant trial in which information on antidepressant-associated mood elevations was apparently generated retrospectively by chart review.

Two publications, an acute-phase RCT[20] and a long-term naturalistic follow-up study,[22] reported data on antidepressant-associated mood elevations in bipolar I disorder (N = 13 in both studies combined), bipolar II disorder (N = 104), and MDD (N = 125). Both of these studies are also included in the reports comparing bipolar I disorder versus bipolar II disorder and bipolar II disorder versus MDD listed above.

Bipolar I Disorder Versus Bipolar II Disorder

Rates of antidepressant-associated mood elevations in reports comparing bipolar I disorder and bipolar II disorder are enumerated in Table 1. In acute treatment trials, the mean rate across studies for bipolar I disorder was 14.2% (range, 0%–60%), compared to a mean of 7.1% (range, 0%–25%) for bipolar II disorder. In maintenance trials, the mean rate for bipolar I disorder was 23.4% (range, 11.9%–37.5%), while the mean for bipolar II disorder was 13.9% (range, 0%–18.6%). Three studies[17–19] reported switch rates of 0% for both bipolar I disorder and bipolar II disorder. In all other reports, rates of antidepressant-associated mood elevations were greater in bipolar I disorder than in bipolar II disorder. Eleven[17–22,24,26–29] of 13 studies, including 673 patients, provided information on the number of bipolar I and bipolar II patients prescribed mood-stabilizing medications (see Table 1). In these reports, 90.2% of patients with bipolar I disorder and 51.4% of patients with bipolar II disorder received concomitant mood stabilizers.

The RR of antidepressant-associated mood elevations in bipolar I disorder versus bipolar II disorder is shown in Figure 1. The risk of mood elevations was significantly greater in bipolar I disorder than bipolar II disorder (RR = 1.78, 95% CI = 1.24 to 2.58, p = .002). The risk of antidepressant-associated mood elevations was also greater in bipolar I disorder than bipolar II disorder in maintenance studies (RR = 1.82, 95% CI = 1.19 to 2.79,

Table 1. Studies Comparing Antidepressant-Associated Mood Elevations in Patients With BDI and BDII

Study	Design	Duration	N		Antidepressant	Concomitant Medication
			BDI	BDII		
Pickar et al,[20] 1982	Randomized, double-blind trial	4 weeks	5	12	N = 3 clorgyline N = 7 pargyline N = 7 phenelzine	None
Himmelhoch et al,[21] 1991	Randomized, double-blind trial	16 weeks	24	32	N = 28 imipramine N = 28 tranylcypromine	None
Benazzi,[22] 1997	Naturalistic treatment study	3–6 months	8	92	SSRIs were the first-line treatment. An SSRI-TCA combination or a switch to TCA was utilized only if there was no response	Small doses of benzodiazepines were used. Mood stabilizers were not prescribed except following episodes of AAME
Henry et al,[23] 2001	Naturalistic treatment study	≥ 6 weeks	31	13	N = 33 antidepressants N = 11 ECT	75% of patients received Li, VPA, or CBZ singly or in combination. 59% also received neuroleptics and benzodiazepines. Data on medication use were not provided separately for BDI and BDII patients
Normann et al,[18] 2002	Randomized, double-blind trial comparing LTG to placebo. All patients received open-label paroxetine	9 weeks	4	3	Paroxetine	3 BDI patients received LTG. 1 BDI patient and all BDII patients received placebo. Lorazepam and oxazepam were permitted for insomnia or agitation
McIntyre et al,[17] 2002	Randomized, single-blind clinical trial comparing topiramate to bupropion	8 weeks	9	9	Bupropion	8 patients received Li, and 10 received VPA. 3 also received SGAs
Joffe et al,[24] 2002	Naturalistic treatment study	≥ 1 year	23	14	Bupropion	All patients received ≥ 1 mood stabilizer
Vieta et al,[25] 2002	Randomized, single-blind trial	6 weeks	44	16	N = 30 venlafaxine N = 30 paroxetine	95% of patients received ≥ 1 of Li, VPA, CBZ, or "other" mood stabilizer. Data were not provided separately for BDI and BDII
Schaffer et al,[28] 2006	Randomized, double-blind trial comparing LTG to citalopram	12 weeks	7	3	Citalopram	All patients received ≥ 1 of Li, VPA, or CBZ. 3 patients received risperidone, 3 gabapentin, 4 benzodiazepines, 1 zopiclone, and 1 buspirone

Definition of AAME	Rate of AAME		Notes
	BDI	BDII	
Hypomania: RDC and mean daily nurses' ward rating for mania = 2–4 for at least 4 of 7 days. Mania: RDC and mean daily nurses' ward rating for mania = 5–15	Mania = 60% (3/5) Hypomania = 0% (0/5) Total = 60% (3/5)	Mania = 8.3% (1/12) Hypomania 16.7% (2/12) Total = 25% (3/12)	0% (0/5) of BDI and 25% (3/12) of BDII patients received clorgyline. 40% (2/5) of BDI and 42% (5/12) of BDII patients received pargyline. 60% (3/5) of BDI and 33% (4/12) of BDII patients received phenelzine. The daily nurses' ward rating for mania is a 15-point scale (0 = symptoms absent to 15 = most severe manic symptoms)
RDC and RMS > 5	Mania = NR Hypomania = NR Total = 37.5% (9/24)	Mania = NR Hypomania = NR Total = 12.5% (4/32)	46% (11/24) of BDI and 53% (17/32) of BDII patients received tranylcypromine. 54% (13/24) of BDI and 47% (15/32) of BDII patients received imipramine
Diagnosed according to DSM-IV criteria using CASH, a structured interview	Mania = 25% (2/8) Hypomania = 0% (0/8) Total = 25% (2/8)	Mania = 0% (0/92) Hypomania = 17.4% (16/92) Total = 17.4% (16/92)	Most patients were treated with SSRI monotherapy. Rates of SSRI-TCA combination or TCA monotherapy were not provided
The MAS was used to assess mood elevations. No cutoff scores for hypomania or mania were provided. Mood elevations also had to meet DSM-IV criteria and duration	Mania = NR Hypomania = NR Total = 29.0% (9/31)	Mania = NR Hypomania = NR Total = 23.1% (3/13)	AAME was less frequent in patients taking Li than in those taking no mood stabilizer. No difference was observed between patients receiving VPA or CBZ and those taking no mood stabilizer. Rates of AAME were 24% with antidepressant and 36% with ECT. Data were not provided separately for BDI and BDII patients regarding mood stabilizer use, antidepressant class, or proportion treated with ECT. 90% of all patients treated with antidepressants received SSRIs
Not specified	Mania = NR Hypomania = NR Total = 0% (0/4)	Mania = NR Hypomania = NR Total = 0% (0/3)	
Patients were assessed with the YMRS at each study visit, but no cutoff scores were provided, and criteria for hypomania and mania switch were not defined	Mania = NR Hypomania = NR Total = 0% (0/9)	Mania = NR Hypomania = NR Total = 0% (0/9)	
DSM-IV criteria for hypomania and mania	Mania = NR Hypomania = NR Total = 13.0% (3/23)	Mania = NR Hypomania = NR Total = 0% (0/14)	The authors assessed whether AAME was likely to be causally related to antidepressant use, based on proximity to antidepressant initiation and change in severity and pattern of mood episodes. However, all mood elevations during antidepressant treatment, whether considered causally related or not by the authors, were included in our analysis. AAME in patients receiving SSRIs was also assessed. However, some patients had > 1 SSRI trial, and the number of trials was not reported separately for BDI and BDII. We were therefore unable to include these data
DSM-IV criteria for hypomania and mania, and YMRS score > 11	Mania = NR Hypomania = NR Total = 9.1% (4/44)	Mania = NR Hypomania = NR Total = 6.3% (1/16)	52% (23/44) of BDI and 44% (7/16) of BDII patients received paroxetine. 48% (21/44) of BDI and 56% (9/16) of BDII patients received venlafaxine
The YMRS was utilized, but the definition of AAME was not specified	Mania = 0% (0/7) Hypomania = 14.3% (1/7) Total = 14.3% (1/7)	Mania = 0% (0/3) Hypomania = 0% (0/3) Total = 0% (0/3)	

(continued)

Table 1 (continued). Studies Comparing Antidepressant-Associated Mood Elevations in Patients With BDI and BDII

Study	Design	Duration	N		Antidepressant	Concomitant Medication
			BDI	BDII		
Altshuler et al,[30] 2006	Randomized, double-blind trial	10 weeks	134	48	N = 66 venlafaxine N = 62 sertraline N = 54 bupropion	All patients received ≥ 1 mood stabilizer, and a mean of 1.96 mood stabilizers. Antipsychotics and benzodiazepines were also permitted. More BDI than BDII patients received VPA and SGAs. Rates of use of Li and CBZ were similar
Leverich et al,[27] 2006	Randomized, double-blind trial	1 year	169	59	N = 86 venlafaxine N = 76 sertraline N = 66 bupropion	All patients received ≥ 1 mood stabilizer, and a mean of 1.96 mood stabilizers. Antipsychotics and benzodiazepines were also permitted
Nolen et al,[19] 2007	Randomized, double-blind trial comparing tranylcypromine and LTG	10 weeks	4	4	Tranylcypromine	All patients received Li, VPA, or CBZ. No other antidepressants, antipsychotics, or benzodiazepines other than lorazepam were permitted
Fonseca et al,[26] 2006	Open-label clinical trial	12 weeks	16	4	Escitalopram	55% of patients received monotherapy with Li, VPA, or CBZ. 45% of patients received combination therapy with Li + VPA/CBZ/OXC. Benzodiazepines and antipsychotics were also permitted
Sachs et al,[29] 2007	Randomized, double-blind, placebo-controlled trial	26 weeks	118	54	Paroxetine Bupropion	All patients received ≥ 1 mood stabilizer (Li, VPA, CBZ, or SGA). Except for other antidepressants, all other clinically indicated medications were permitted

Abbreviations: AAME = antidepressant-associated mood elevation, BDI = bipolar I disorder, BDII = bipolar II disorder, CASH = Comprehensive Assessment of Symptoms and History CBZ = carbamazepine, CGI-BP = Clinical Global Impressions-Bipolar Disorder Severity of Illness scale, ECT = electroconvulsive therapy, Li = lithium, LTG = lamotrigine, MAS = Bech-Rafaelson Mania Rating Scale, NR = not reported,

p = .006), and there was a trend toward a greater risk in bipolar I disorder in acute phase trials (RR = 1.94, 95% CI = 0.98 to 3.81, p = .06). Other sensitivity analyses revealed similar results when analyses were confined to RCTs (RR = 1.87, 95% CI = 1.24 to 2.84, p = .003), studies involving newer antidepressants (RR = 1.65, 95% CI = 1.06 to 2.57, p = .03), studies in which all patients received mood stabilizers (RR = 1.69, 95% CI = 1.04 to 2.75, p = .03), and trials in which mood stabilizers were not utilized (RR = 2.28, 95% CI = 1.16 to 4.48, p = .02). The results remained significant when the analysis was limited to trials that used sensitive cutoff scores on mania rating scales to detect antidepressant-associated mood elevations (RR = 2.57, 95% CI = 1.06 to 6.21, p = .04) (data not shown for sensitivity analyses).

Six studies[19,20,22,26,28,30] specified whether mood elevations were into mania or hypomania (Table 1). In these 6 trials, switches into both mania (6.3%) and hypomania (8.0%) were relatively common in bipolar I disorder patients. In bipolar II disorder, by contrast, switches were almost exclusively into hypomania (11.7%), while manic switches were rare (0.6%).

Bipolar II Disorder Versus MDD

Rates of antidepressant-associated mood elevations in reports comparing bipolar II disorder and MDD are listed in Table 2. In acute treatment trials, the mean rates for bipolar II disorder and MDD were 8.1% (range, 0%–25%), and 1.5% (range, 0%–6.7%), respectively. In maintenance trials, the mean rates were 16.5% (range, 9.1%–17.4%) and 6.0% (range, 5.8%–7.1%) for bipolar II disorder and MDD, respectively. One study[33] reported no mood elevations in bipolar II disorder or MDD. In 3 reports,[20,22,34] the rate was greater in bipolar II disorder, and in 1 report[35] it was greater in MDD. Four[20,22,33,34] of 5 studies, including 302 patients, provided information on the use of concomitant mood-stabilizing medications separately for bipolar II disorder and MDD (see Table 2). In these reports, 4.5% of patients with bipolar II disorder and 4.7% of patients with MDD received mood stabilizers.

Definition of AAME	Rate of AAME: BDI	Rate of AAME: BDII	Notes
Hypomania: YMRS = 14–19 Mania: YMRS ≥ 20	Mania = 3.7% (5/134) Hypomania = 8.2% (11/134) Total = 11.9% (16/134)	Mania = 0% (0/48) Hypomania = 2.1% (1/48) Total = 2.1% (1/48)	38% (51/134) of BDI and 31% (15/48) of BDII patients received venlafaxine. 34% (45/134) of BDI and 35% (17/48) of BDII received sertraline. 28% (38/134) BDI and 33% (16/48) of BDII patients received bupropion. This study provides 10-week data for the same patients included in Leverich et al[27] below
Hypomania: ≥ 7 days with mild severity of mania using life chart method. Mania: ≥ 2 days with moderate or greater severity of mania using life chart method	Mania = NR Hypomania = NR Total = 30.8% (52/169)	Mania = NR Hypomania = NR Total = 18.6% (11/59)	Some patients had >1 antidepressant trial, and the rate of mood elevations was therefore calculated based on the number of antidepressant trials (N = 169 for BDI and N = 59 for BDII) rather than the number of patients
CGI-BP mania rating of "much worse" or "very much worse" and YMRS score ≥ 14 at any visit	Mania = 0% (0/4) Hypomania = 0% (0/4) Total = 0% (0/4)	Mania = 0% (0/4) Hypomania = 0% (0/4) Total = 0% (0/4)	2 patients also received tranylcypromine in a second trial for patients who did not respond to the first treatment. It was unclear if they were diagnosed with BDI or BDII. No switches were reported
Hypomania: DSM-IV criteria Mania: YMRS score >12 and DSM-IV criteria	Mania = 6.3% (1/16) Hypomania = 12.5% (2/16) Total = 18.8% (3/16)	Mania = 0% (0/4) Hypomania = 0% (0/4) Total = 0% (0/4)	
DSM-IV criteria for hypomania or mania, or intervention by the treating clinician for a clinically significant treatment-emergent mood elevation	Mania = NR Hypomania = NR Total = 11.9% (14/118)	Mania = NR Hypomania = NR Total = 7.4% (4/54)	Equipoise-stratified randomization was employed, such that patients could be randomly assigned to (1) paroxetine vs PBO, (2) bupropion vs PBO, or (3) paroxetine vs bupropion vs PBO based on patient preference. Data regarding individual antidepressants were not provided separately for BDI and BDII patients

Abbreviations continued: OXC = oxcarbazepine, PBO = placebo, RDC = Research Diagnostic Criteria, RMS = Raskin Mania Scale, SGA = second-generation antipsychotic, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, VPA = valproate, YMRS = Young Mania Rating Scale.

The RR of antidepressant-associated mood elevations was greater in bipolar II disorder than MDD when all trials were considered (RR = 2.77, 95% CI = 1.26 to 6.09, p = .01) (Figure 2). Sensitivity analyses revealed that the risk of antidepressant-associated mood elevations remained greater in bipolar II disorder when analyses were limited to maintenance studies (RR = 2.74, 95% CI = 1.17 to 6.39, p = .02) but not acute treatment trials (RR = 2.86, 95% CI = 0.14 to 57.05, p = .49). Additional sensitivity analyses demonstrated significantly greater rates of antidepressant-associated mood elevations in bipolar II disorder when analyses were limited to trials involving newer antidepressants (RR = 2.64, 95% CI = 1.12 to 6.23, p = .03) and trials in which mood stabilizers were not used (RR = 3.38, 95% CI = 1.44 to 7.95, p = .005), but not RCTs (RR = 2.16, 95% CI = 0.37 to 12.70, p = .40) (data not shown for sensitivity analyses). We did not identify any studies in which all patients received mood stabilizers. Finally, only 1 trial assessed antidepressant-associated mood elevations using a sensitive cutoff score on a mania rating scale[20] and reported rates of 25% in bipolar II disorder and 0% in MDD.

Four of 5 studies[20,22,34,35] specified whether mood elevations occurred into mania or hypomania. In bipolar II disorder, hypomania occurred with a substantially greater frequency than mania (14.6% vs. 1.6%, respectively). Mood elevations into hypomania and mania were rare for MDD (3.9% vs. 1.3%).

Bipolar I Disorder Versus Bipolar II Disorder Versus MDD

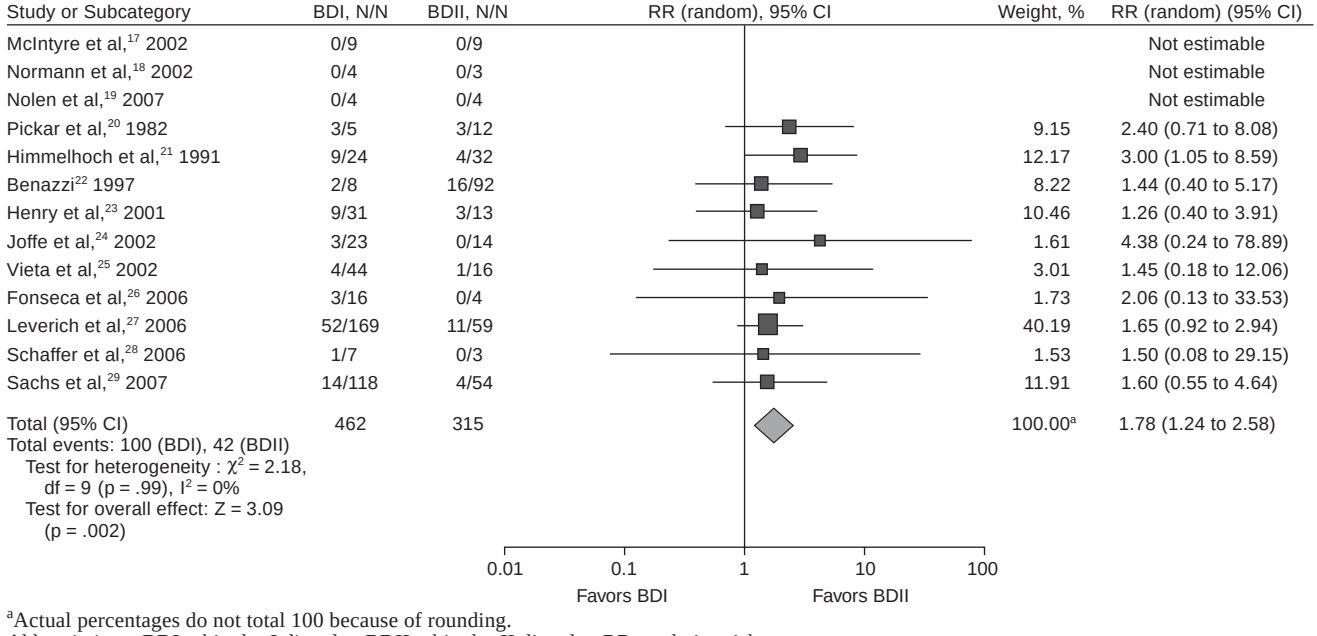
Both reports that provided data on antidepressant-associated mood elevations in bipolar I disorder, bipolar II disorder, and MDD suggested that the rate in bipolar II disorder was intermediate between those in bipolar I disorder and MDD. The rates of antidepressant-associated mood elevations in an acute-phase RCT[20] were 60% for bipolar I disorder, 25% for bipolar II disorder, and 0% for MDD. The rates of antidepressant-associated mood elevations in a naturalistic maintenance study[22] were

Table 2. Studies Comparing Antidepressant-Associated Mood Elevation in BDII and MDD

Study	Design	Duration	N		Antidepressant	Concomitant Medication
			BDII	MDD		
Pickar et al,[20] 1982	Randomized, double-blind trial	4 weeks	12	22	N = 12 clorgyline N = 11 pargyline N = 11 phenelzine	None
Kane et al,[34] 1982	Randomized, double-blind, placebo-controlled trial	Mean of 11 months	11	14	Imipramine	54.5% (6/11) of BDII patients and 57.1% (8/14) of MDD patients received Li
Benazzi,[22] 1997	Naturalistic treatment study	3–6 months	92	103	SSRIs were the first-line treatment. An SSRI-TCA combination or a switch to TCA was utilized if there was no response.	Small doses of benzodiazepines were used. Mood stabilizers were not prescribed except following episodes of AAME
Amsterdam,[33] 1998	Randomized, double-blind trial comparing 2 dosing strategies for venlafaxine	6 weeks	17	31	Venlafaxine	Lorazepam and chloral hydrate
Barbosa et al,[35] 2003	Randomized, double-blind trial comparing LTG to placebo. All patients received open-label fluoxetine 20 mg/d	6 weeks	8	15	Fluoxetine	Oxazepam prn; 13 of 23 patients received LTG 100 mg/d. Data were not provided separately for BDII and MDD patients

Abbreviations: AAME = antidepressant-associated mood elevation, BDI = bipolar I disorder, BDII = bipolar II disorder, CASH = Comprehensive Assessment of Symptoms and History, Li = lithium, LTG = lamotrigine, MDD = major depressive disorder, NR = not reported,

Figure 1. Relative Risk of Antidepressant-Associated Mood Elevations in BDI Versus BDII



[a]Actual percentages do not total 100 because of rounding.
Abbreviations: BDI = bipolar I disorder, BDII = bipolar II disorder, RR = relative risk.

25% for bipolar I disorder, 17.4% for bipolar II disorder, and 5.8% for MDD.

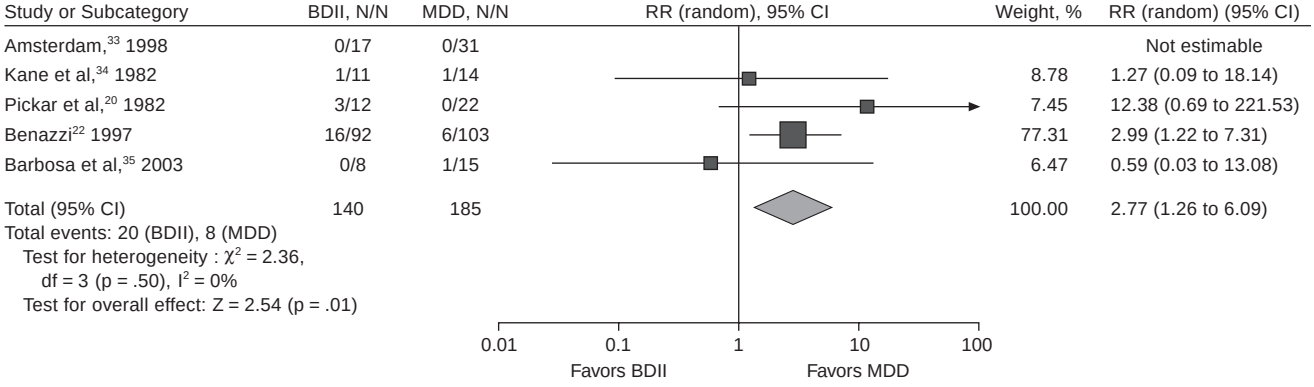
DISCUSSION

Taken together, the results of the studies reviewed here demonstrate that the risk of antidepressant-associated mood elevations in bipolar II disorder is intermediate between those in bipolar I disorder and MDD. Patients with bipolar II disorder are approximately half as likely as patients with bipolar I disorder, and 2 to 3 times more likely than patients with MDD, to experience mood elevations during antidepressant treatment. Mood elevations in bipolar II disorder are less severe than in bipolar I disorder,

Definition of AAME	Rate of AAME		Notes
	BDII	MDD	
Hypomania: RDC and mean nurses' ward rating for mania 2–4 for 4 of 7 days. Mania: RDC and mean daily nurses' ward rating for mania = 5–15	Mania = 8.3% (1/12) Hypomania = 16.7% (2/12) Total = 25% (3/12)	Mania = 0% (0/22) Hypomania = 0% (0/22) Total = 0% (0/22)	25% (3/12) of BDII and 41% (9/22) of MDD patients received clorgyline. 42% (5/12) of BDII and 27% (6/22) of MDD patients received pargyline. 33% (4/12) of BDII and 32% (7/22) of MDD patients received phenelzine
RDC for > 1 week	Mania = 9.1% (1/11) Hypomania = 0% (0/11) Total = 9.1% (1/11)	Mania = 7.1% (1/14) Hypomania = 0% (0/14) Total = 7.1% (1/14)	
Diagnosed according to DSM-IV criteria using CASH, a structured interview	Mania = 0% (0/92) Hypomania = 17.4% (16/92) Total = 17.4% (16/92)	Mania = 1.0% (1/103) Hypomania = 4.9% (5/103) Total = 5.8% (6/103)	
Not specified. No mania rating scales employed	Mania = NR Hypomania = NR Total = 0% (0/17)	Mania = NR Hypomania = NR Total = 0% (0/31)	All subjects received venlafaxine and were blindly assigned to once daily or twice daily dosing
Not specified	Mania = 0% (0/8) Hypomania = 0% (0/8) Total = 0% (0/8)	Mania = 0% (0/15) Hypomania = 6.7% (1/15) Total = 6.7% (1/15)	

Abbreviations continued: RDC = Research Diagnostic Criteria, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Figure 2. Relative Risk of Antidepressant-Associated Mood Elevations in BDII Versus MDD



Abbreviations: BDII = bipolar II disorder, MDD = major depressive disorder, RR = relative risk.

occurring almost exclusively into hypomania in patients with bipolar II disorder.

Our results were most consistent in the analyses comparing antidepressant-associated mood elevations in bipolar I disorder and bipolar II disorder, with the primary analysis and all sensitivity analyses producing similar and statistically significant outcomes. The only exception was the sensitivity analysis limited to acute treatment studies, which demonstrated a statistical trend toward a greater rate of mood elevations in bipolar I disorder (p = .06). The results were less robust in the analyses comparing antidepressant-associated mood elevations in bipolar II disorder and MDD, with the primary analysis and 3 of 5 subanalyses detecting a significant difference in rates of antidepressant-associated mood elevations. We were able to locate only 5 studies that reported on antidepressant-associated mood elevations in bipolar II disorder and MDD, one of which produced rates of mood elevations of 0% for both bipolar II disorder and MDD and thus did not contribute evaluable data to the meta-analysis; several of the sensitivity analyses involved only 2 trials. In addition, sample sizes of most of the bipolar II disorder versus MDD studies were small, except for 1,[22] which was therefore weighted heavily in the analyses in which it was included.

Ten[20–29] of 13 studies comparing rates of antidepressant-associated mood elevations in bipolar I disorder and bipolar II disorder demonstrated them to be more frequent

in bipolar I disorder, while the remaining 3 reported rates of 0% for both illness groups.[17–19] The consistency of the main findings across study types—RCTs, randomized, single-blind trials, open-label clinical trials, naturalistic follow-up studies—makes a strong argument that we are measuring a true difference in the rate of mood elevations between bipolar I disorder and bipolar II disorder. The diverse methodologies of the studies included in our analysis may be viewed as both limiting and advantageous. The shortcomings of studies other than RCTs—lack of random assignment to treatment, absence of blinding of subjects and investigators, failure to control all variables except the intervention of interest—are well known to clinicians. However, while RCTs remain the gold-standard method for assessing the efficacy of therapies, their reductionistic approach, which involves exclusion of subjects with common comorbid conditions, limits their generalizability. As has been pointed out elsewhere,[37] generalizability is even more important when the intent of a study is to assess how often an event occurs in a population than it is in therapy studies. It may be argued, then, that our inclusion of studies with nonrandomized designs increases the generalizability and utility of this report.

Our findings have obvious implications with respect to the management of bipolar II disorder. North American treatment guidelines for bipolar I disorder[6–8] recommend that antidepressants be prescribed cautiously and for relatively brief periods to avoid precipitating manic episodes. Although close follow-up and a degree of caution are also warranted in patients with bipolar II disorder, clinicians may be reassured that the likelihood of a serious mood elevation during acute and maintenance treatment with antidepressants is relatively low in bipolar II disorder. Our findings also speak to the validity of the diagnosis of bipolar II disorder. Chun and Dunner[15] have argued that the rate of antidepressant-associated mood elevations in MDD is sufficiently low that it falls within the error rate of misdiagnosis of bipolar disorder as MDD. Mood elevations are thus unique to bipolar illness, providing evidence that it is a distinct disorder from MDD. The low rate of antidepressant-associated mood elevations we detected in MDD, even compared to bipolar II disorder, supports this hypothesis and suggests that the MDD patients in the studies we selected who experienced antidepressant-associated mood elevations were misdiagnosed and actually have bipolar illness. Similarly, as mood elevations in bipolar II disorder occur almost exclusively into hypomania, the rare occurrence of manic episodes is likely due to misdiagnosis of bipolar I disorder as bipolar II disorder, and an argument can be made that bipolar I disorder and bipolar II disorder are distinct entities.

Furthermore, the fact that bipolar II disorder has a lower rate of antidepressant-associated mood elevations than bipolar I disorder illustrates that treatment decisions derived from clinical trials in bipolar I disorder patients cannot be generalized to bipolar II disorder. This finding is in keeping with the results of numerous previous studies. For example, reports on the efficacy of lithium and carbamazepine in the maintenance treatment of bipolar disorder demonstrated a significant benefit of lithium over carbamazepine in bipolar I disorder patients but a numerical advantage for carbamazepine in those with bipolar II disorder.[11,12] A post hoc analysis of a 6-month study assessing the efficacy of lamotrigine in preventing mood episodes in rapid-cycling bipolar patients suggested an effect in bipolar II disorder but not bipolar I disorder.[38] Quetiapine had a robust effect in treating bipolar I disorder depression in 2 recent large-scale clinical trials but was superior to placebo in bipolar II disorder patients in only one trial.[13,39]

The results presented here do not, however, inform us about whether antidepressants alter the course of bipolar II disorder and, specifically, whether they cause an increased frequency of mood elevations, either in absolute terms or relative to bipolar I disorder. Bipolar II disorder is a chronic condition characterized by irregularly occurring episodes of depression and hypomania.[1] In the absence of studies comparing antidepressants to placebo in the treatment of bipolar II disorder depression, determining whether antidepressants cause an increased incidence of antidepressant-associated mood elevations in bipolar II disorder compared to no treatment is not possible. To date, only 2 placebo-controlled trials have assessed the efficacy and safety of antidepressants in bipolar II disorder. One study[34] reported that 20% (1/5) of patients taking imipramine versus 14% (1/7) of patients receiving placebo experienced mood elevations over 1 year, but this report is limited by its small sample size. A second study[29] comparing the addition of antidepressant (paroxetine or bupropion) versus placebo to mood stabilizing and other medications in patients with bipolar I disorder or bipolar II disorder did not report rates of mood elevations for the placebo arm separately for bipolar I disorder and bipolar II disorder. Given the lack of placebo-controlled data and the fact that the course of bipolar II disorder is known to be associated with greater depressive morbidity and a lower frequency and severity of mood elevations than bipolar I disorder,[1,40] the finding of a lower rate of antidepressant-associated mood elevations in bipolar II disorder during antidepressant treatment may reflect the natural history of bipolar I disorder and bipolar II disorder rather than a differential effect of antidepressants on them.

The greater rates of antidepressant-associated mood elevations we observed in bipolar I disorder versus bipolar II disorder and in bipolar II disorder versus MDD are unlikely to be due to less frequent use of mood-stabilizing medications, as more patients with bipolar I disorder than

bipolar II disorder received mood stabilizers (90.2% vs. 51.4%), and rates of usage were similar in studies that compared bipolar II disorder and MDD (4.5% vs. 4.7%). Based on the available data, it cannot be determined whether mood stabilizing medications protect against antidepressant-associated mood elevations in bipolar II disorder, as none of the studies reviewed here compared antidepressant-associated mood elevations in bipolar II disorder patients prescribed antidepressant plus mood stabilizer versus antidepressant plus placebo. However, 2 findings from our analysis are noteworthy. First, the mean rate of antidepressant-associated mood elevations in bipolar II disorder across all studies in which mood stabilizers were not employed[20,21,32,33] is very similar to the mean rate in trials in which all patients received mood stabilizers[17,19,24,26–29] (13.8% vs. 10.2%). Second, while the relative risk of antidepressant-associated mood elevations was higher in bipolar I disorder than in bipolar II disorder both in trials in which mood stabilizers were not utilized and in trials in which all patients received mood stabilizers, the magnitude of the difference was larger in trials without mood stabilizers (2.28 vs. 1.69), suggesting that a lack of mood-stabilizing treatment increases the rate of antidepressant-associated mood elevation to a greater degree in bipolar I disorder than in bipolar II disorder.

The issue of whether mood stabilizers protect against mood elevations in bipolar II disorder has been addressed in a small number of previous reports. To our knowledge, only 1 placebo-controlled trial has measured rates of antidepressant-associated mood elevation in bipolar II disorder patients prescribed an antidepressant plus a mood stabilizer versus those prescribed an antidepressant plus placebo.[34] This 1-year maintenance study had, in fact, 4 treatment arms and reported no mood elevations in patients taking lithium or lithium plus imipramine, while 20% (1/5) of patients receiving imipramine and 14% (1/7) of patients receiving placebo experienced mania or hypomania. The small sample size (N = 27 across 4 treatment arms) makes it difficult to draw firm conclusions from these data. A placebo-controlled crossover study of escitalopram,[41] open-label trials of bupropion[42] and velafaxine,[43] and post hoc analyses of RCTs in which data regarding antidepressant-associated mood elevations were apparently generated retrospectively from chart review[36] have also reported low rates of antidepressant-associated mood elevations in bipolar II disorder. One post hoc analysis,[36] however, reported that the rate of mood elevations in bipolar II patients receiving antidepressant monotherapy, although low, was over 12 times that in patients with MDD (3.8% vs. 0.3%, respectively, over 12 weeks). Well-designed RCTs comparing mood stabilizers, antidepressants, and the combination of the 2 to placebo are required to determine whether antidepressant monotherapy is appropriate for some patients with bipolar II disorder.

The conclusions we have drawn from our analysis must be viewed in light of the limitations of our report. The limitations and advantages of including studies with nonrandomized designs were reviewed above. When possible, we have provided information regarding possible confounding variables, such as rates of use of different antidepressants in trials in which more than 1 was assessed, and rates of use of concomitant mood stabilizers, in non-RCT studies (see Tables 1 and 2). However, we cannot exclude the possibility that factors other than bipolar subtype affected the rates of antidepressant-associated mood elevations in these studies. In assessing the degree to which this limitation affected our findings, however, it is noteworthy that, when a sensitivity analysis including only RCTs was carried out, the relative risk of mood elevation in bipolar II disorder versus bipolar I disorder remained very similar to the overall results and also that a post hoc assessment of heterogeneity in rates of antidepressant-associated mood elevations between all studies was non-significant ($I^2 = 0\%$; $\chi^2 = 2.18$, df = 9, p = .99; see Figure 1).

Regarding other limitations, the analysis of antidepressant-associated mood elevations in bipolar II disorder versus MDD is less robust than that comparing bipolar I disorder versus bipolar II disorder, as noted above. As well, the studies we reviewed employed a variety of definitions of antidepressant-associated mood elevations, and in this, they are reflective of the fact that there is no standard, accepted definition of the term. While some reports utilized scores on mania rating scales to capture mood elevations, others relied on the clinical judgment of investigators and may have thus run the risk of missing mild mood elevations. This limitation might have the effect of diminishing detection of hypomania and lowering the apparent rate of antidepressant-associated mood elevations in bipolar II disorder. However, studies that closely monitored for symptoms of hypomania using rating scales[19,20,25,26,30] produced results similar to that of the overall meta-analysis. Three studies predated the DSM-IV definition of bipolar II disorder,[20,21,34] although they employed definitions very similar to the currently used one. In addition, sample sizes in some reports were small, and most studies enrolled unequal numbers of patients with bipolar I disorder and bipolar II disorder or bipolar II disorder and MDD.

Notwithstanding these limitations, our report contains several notable findings. It is the first systematic review utilizing only prospective studies to examine the rate of antidepressant-associated mood elevations in bipolar II disorder relative to bipolar I disorder and MDD. While previous studies have assessed the effect of treatment variables such as antidepressant class[27,44] on the risk of mood elevations, illness factors, particularly bipolar subtype, have been relatively ignored. Our main findings, that bipolar II disorder is associated with a

risk of antidepressant-associated mood elevations substantially lower than that of bipolar I disorder but greater than MDD and that antidepressant-associated mood elevations in bipolar II disorder generally occur into hypomania, are of immediate relevance to clinicians given the frequency of antidepressant prescription in patients with bipolar II disorder. Further research is needed to clarify the risk of antidepressant-associated mood elevations in bipolar II disorder patients prescribed antidepressants versus placebo, whether concomitant mood-stabilizing medications offer protection against antidepressant-associated mood elevations in bipolar II disorder, the relative risks with different antidepressant classes; clinical risk factors, and the neurobiological mechanisms involved.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), buspirone (BuSpar and others), carbamazepine (Carbatrol, Equetro, and others), citalopram (Celexa and others), desipramine (Norpramin and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), gabapentin (Neurontin and others), imipramine (Tofranil and others), lamotrigine (Lamictal and others), lithium (Lithobid, Eskalith, and others), lorazepam (Ativan and others), mirtazapine (Remeron and others), nortriptyline (Pamelor and others), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), quetiapine (Seroquel), risperidone (Risperidal), sertraline (Zoloft and others), topiramate (Topomax), tranylcypromine (Parnate and others), venlafaxine (Effexor and others), zopiclone (Lunesta).

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