

## Review Article

# Antidepressants in bipolar disorder: the case for caution

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The 2002 American Psychiatric Association (APA) guidelines for the treatment of bipolar disorder recommended more conservative use of antidepressants. This change in comparison with previous APA guidelines has been criticized, especially from some groups in Europe. The Munich group in particular has published a critique of assumptions underlying the conservative recommendations of the recent APA treatment guidelines. In this paper, we re-examine the argument put forward by the Munich group, and we demonstrate that indeed, conceptually and empirically, there is a strong rationale for a cautious approach to antidepressant use in bipolar disorder, consistent with, and perhaps even more strongly than, the APA guidelines. This rationale is based on support for the following four propositions: (i) The risk of antidepressant induced mood-cycling is high, (ii) Antidepressants have not been shown to definitively prevent completed suicides and reduce mortality, whereas lithium has, (iii) Antidepressants have not been shown to be more effective than mood stabilizers in acute bipolar depression and have been shown to be less effective than mood stabilizers in preventing depressive relapse in bipolar disorder and (iv) Mood stabilizers, especially lithium and lamotrigine, have been shown to be effective in acute and prophylactic treatment of bipolar depressive episodes. We therefore draw three conclusions from this interpretation of the evidence: (i) There are significant risks of mania and long-term worsening of bipolar illness with antidepressants, (ii) Antidepressants should generally be reserved for severe cases of acute bipolar depression and not routinely used in mild to moderate cases and (iii) Antidepressants should be discontinued after recovery from the depressive episode, and maintained only in those who repeatedly relapse after antidepressant discontinuation (a minority we judge to represent only about 15–20% of bipolar depressed patients).

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Over the last decade, reports generated in the US and Canada have pointed out the paucity of evidence on the efficacy of antidepressants in bipolar disorder (1, 2). Further, recent North American-based treatment guidelines, including those of the American Psychiatric Association, have been conservative, recommending antidepressants only for severe bipolar depression (3–8). Moreover, if antidepressants are to be used, they should be withdrawn as early as possible. This shift away from antidepressant use has engendered criticism from some groups in Europe, particularly Germany (9). In that critical

article on US and Canadian-based treatment guidelines, the authors assert that these guidelines are not balanced, and should be rewritten to remove restrictions on the use of antidepressants in the treatment of bipolar depression.

The Munich group asserts that the argument for restriction of antidepressants in US guidelines is based on four premises (9), which they state as:

- (i) The risk of switching into mania/rapid cycling induced by antidepressants is an important clinical phenomenon in bipolar depression

- (ii) The risk of suicidality, suicide attempts and suicide in bipolar depressive patients is of minor clinical relevance
- (iii) The antidepressive efficacy of antidepressants in bipolar depression is insufficiently proven
- (iv) The antidepressive efficacy of mood stabilizers in bipolar depression is sufficiently proven

This paper will re-examine these four assertions, and make the case for US-based treatment guidelines that de-emphasize the use of antidepressants in the treatment of bipolar disorder.

#### The case for caution

We agree that antidepressants may be effective in treating acute bipolar depression, as there is some evidence to that effect. While all treatment guidelines recognize this, the point of contention regarding North American-based treatment guidelines centers on how often antidepressants should be used and for how long.

We believe that the evidence of antidepressant efficacy in bipolar depression is not as definitive as many assume. Given the risks of acute mania, the routine use of antidepressants would appear to be more risky without much added benefit over the use of mood stabilizers alone for acute bipolar depression, a point which seems even more compelling with the appearance of lamotrigine. Further, available studies fail to provide any rigorous evidence of antidepressant prevention of depressive relapse. In contrast, such evidence exists with mood stabilizers. Moreover, there is likely a significant risk of more mood episodes over time and possible rapid cycling with long-term antidepressant use in bipolar disorder.

Seen this way, the research evidence appears to support US and Canadian-based treatment guidelines in which antidepressants use is restricted to cases of severe depression (or when the appropriate mood stabilizer combination has failed to prevent or reverse a depression); further the guidelines recommend antidepressant discontinuation after acute recovery.

Critics fear that, if antidepressants are used less aggressively, bipolar depression will go undertreated and the suicide risk will rise. The evidence, however, is not clear that there is anti-suicidal benefit with antidepressants, whereas lithium, among *all* psychotropic agents, has by far the most extensive evidence of an anti-suicide effect. Moreover, these treatment guidelines account for potential undertreatment of depression by supporting antidepressant use in cases of severe depression. The question is not whether or not

antidepressants should be used in bipolar disorder, but whether or not antidepressants should be *routinely* used in bipolar disorder. We argue for cautious, selected, use rather than *routine* use.

The rest of this paper will examine the evidence on which this approach is based.

#### Methodological issues

We would like to highlight some methodological differences between our approach in this review and the Munich critique. In the Munich paper, the selection of papers cited does not appear to be comprehensive. It is now an accepted axiom of scientifically valid clinical research that reviews of the literature need to be systematic and transparent in their inclusion and exclusion criteria so that their conclusions can be independently evaluated by others.

In this paper, the data we cite represent comprehensive summaries of the randomized literature on the three topics of rapid cycling and antidepressants, use of mood stabilizers in bipolar depression, and efficacy of new antidepressants for bipolar depression. These summaries are based on MEDLINE searches with the keywords 'rapid cycling', 'antidepressants', 'mood stabilizers', and 'bipolar depression', supplemented by bibliographic cross-referencing, review of abstracts of major psychiatric conferences for the past five years, as well as hand searches of major psychiatric journals for the past five years. Our discussion of the other two main topics of the use of mood stabilizers for suicide prevention and the risk of acute manic switch induced by antidepressants are based on systematic reviews with similarly transparent methodology by Tondo and colleagues (10) and by Goldberg and Ernst in this issue.

Where we cite non-randomized data, we do so only as secondary information of possible clinical relevance or where no randomized literature exists, such as in our recent clinical work on antidepressants and tolerance in bipolar disorder. The limitations of such non-randomized data are always noted.

When reviewing the literature it is important to be consistent and precise in one's use of basic epidemiological concepts such as validity and power (11). For example, it is not appropriate to draw the general conclusion that a group of small studies that agree with each other are, in the aggregate, necessarily less valid than a single study with a large sample size. Such a conclusion reflects confusion between the concepts of 'validity' and 'power'. If a study result is positive, then its occurrence in a small

sample size *per se* is irrelevant; it has sufficient power to show a statistically significant effect. While one might question the generalizability of small studies, in those instances where there have been multiple replications this reservation is less compelling. By the same token, a large sample size does not necessarily make a study more valid. For instance, a medium-sized randomized study is probably more valid than a very large non-randomized study. It is also important to be consistent in applying different weights to different levels of evidence. Widely accepted among investigators is that randomized data are more convincing than non-randomized data. Unfortunately, in the Munich paper the evidence is not evaluated for reliability (principally by distinguishing random from non-random samples). Thus, they cite non-randomized naturalistic data on antidepressant effectiveness in preventing suicide and in bipolar depression, but dismiss similarly naturalistic data that comes to different conclusions on these two issues.

We make these methodological comments to highlight the importance of objective and balanced epidemiological inference in reviews of complex clinical issues.

### **A re-examination of the premises underlying caution with antidepressants**

The four premises listed below are not our assumptions but rather the premises that the Munich group asserts underlie the North American based approach to the use of antidepressants in bipolar disorder. In the course of examining those premises we will offer our interpretation of the appropriate reasons for our approach, which are not exactly the same as the four assumptions put forward by the Munich group.

#### **Premise 1: The risk of antidepressant-induced manic switching and/or rapid cycling is high**

It is often asserted that this conclusion is based solely on anecdotal or uncontrolled evidence. In fact, there are randomized data to support caution in the use of antidepressants in bipolar disorder and very little randomized evidence to the contrary. First, we should distinguish between two issues. One is *short-term* acute manic switch following antidepressant use. As described by Goldberg elsewhere in this issue, the period of observation for a switch that might reasonably be considered as drug induced should probably be limited to the first 2 months after the initiation of the antidepressant. Manic 'switches' that occur

later are difficult to attribute to the initiation of an antidepressant as opposed to the natural history of the bipolar disorder.

The other issue is the long-term risk of antidepressant-induced *mood destabilization*, or the association of antidepressants with more and more mood episodes (both mania and depression) over time. This long-term mood destabilization risk consists of two patterns: (a) cycle acceleration defined as an increase of two or more DSM-IV affective episodes while on antidepressants when compared with a similar exposure-time immediately before such treatment and (b) induction of *de novo* rapid cycling or exacerbation of pre-existing rapid cycling, applying the DSM-IV definition of rapid cycling, i.e. four or more mood episodes in a year. These are two different issues, acute manic switch versus long-term mood destabilization, which are often mistakenly conflated. Let us discuss them separately.

#### Short-term risk of acute manic switch

First, regarding induction of acute mania/hypomania by antidepressants, critics often argue that uncontrolled data are uninterpretable and that randomized data suggest a low risk. In fact, we believe the randomized data demonstrates a causal association. While the randomized studies can establish that the association is more than a chance one, they are, out of necessity, studies of relatively small sample size and may therefore not be as useful for estimating the extent of the problem. For this, real-world non-randomized data can prove insightful.

The randomized studies of acute mania risk with antidepressants are discussed in detail elsewhere in this issue by Goldberg and Ernst (Table 1). For the purpose of this discussion, we will focus on new antidepressants [excluding tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs)], as many believe that these newer agents are particularly safe. In one study (n = 89), which the authors interpreted as evidence of low manic switch rate and increased efficacy of fluoxetine compared with imipramine, the results are in fact more complex (12). Specifically, the fluoxetine-treated group received concomitant lithium therapy twice as often as the imipramine group, thus biasing any direct comparison of efficacy. Further, these data are often used to assert that fluoxetine has a low mania switch rate due to a lower switch rate than imipramine in the initial parallel arm comparison (0%, 0 of 30 trials with fluoxetine versus 7%, two of 30 trials with imipramine). However, we re-analyzed the data to include not

Table 1. Randomized studies of acute mania induction by new antidepressants

Study	n	Treatments	Acute mania induction
Cohn et al. (1989)	89	FLX versus IMI	FLX (7% <sup>a</sup> ) = IMI (7%) > PBO
Sachs et al. (1994)	15	BUP versus DMI	DMI (50%) > BUP (11%)
Young et al. (2000)	27	PRX + MS versus MS + MS	PRX + MS (0%) = MS + MS (0%)
Nemeroff et al. (2001)	117	PRX versus IMI versus PBO	IMI (8%) > PRX (0%) = PBO (5%)
Vieta et al. (2002)	60	PRX versus VLX	VLX (12%) > PRX (2%) <sup>b</sup>
Post et al. (2003)	127 (175 trials)	BUP versus VLX versus SER	9.1% of all trials associated with acute mania induction

All patients were also taking lithium and most were diagnosed with type I bipolar disorder.

FLX = fluoxetine; IMI = imipramine; PBO = placebo; BUP = bupropion; DMI = desipramine; PRX = paroxetine; MS = mood stabilizer (lithium or valproate); VLX = venlafaxine; SER = sertraline.

<sup>a</sup>Includes patients in open phase and double-blind phase.

<sup>b</sup>not statistically significant.

only the initial parallel arm comparison but also the second crossover phase. If both phases are included, the acute mania switch rates for fluoxetine (7%, four of 55) and imipramine (7%, two of 30) are exactly the same. While crossover data are less valid than parallel-design data, it is interesting to note that fluoxetine did poorly in the crossover phase. A second study, where either paroxetine or imipramine was added to lithium in 117 patients, reported no manic switches in the paroxetine group, compared with 7.7% with imipramine and 2.3% with placebo, with statistically significant differences (13). Another small study (n = 27) found no evidence of acute manic switch with paroxetine added to valproate or lithium (14). In a small study, bupropion has also been shown to have a lower switch rate (11%, one of nine trials) than the TCA desipramine (50%, five of 10 trials) (15). Other open randomized data suggest lower acute mania switch rates with paroxetine (2%) versus venlafaxine (12%), although not statistically significant (n = 60) (16). Further, as discussed by Post et al. in this issue, the recent Stanley Network study suggests double-blind randomized rates of about 10% acute manic switch with bupropion, sertraline, or venlafaxine. When hypomanic episodes are included, however, this rate climbs to 25%. Older RCTs with TCAs also demonstrate a manic risk greater than placebo (17). In sum, the randomized literature demonstrates a likely excess of acute mania risk with at least some antidepressants versus placebo (especially TCAs but also perhaps fluoxetine).

Another report, which is often cited as evidence of minimal risk with the newer antidepressants, is a review in which manic switch occurred more frequently with TCAs (11.2%) versus SRIs (3.7%) or placebo (4.2%), with no significant difference between serotonin reuptake inhibitors (SRIs) and placebo (18). This report, however, was a *post hoc* exploratory pooled-analysis from unipolar depression clinical trials. The data was re-analyzed

for bipolar disorder by retrieving information on study patients diagnosed with type II bipolar disorder. Furthermore, no mania rating scales were performed, likely resulting in unreliable reporting of manic symptoms. Finally, as the analysis is *post hoc*, it does not represent a hypothesis testing approach that establishes relationships, but instead represents hypothesis generation, which cannot be accepted without further prospective replication. Other recent re-analyses of unipolar clinical trials with fluoxetine and venlafaxine also share in these limitations, especially the fact that they are limited at best to type II bipolar disorder and are not generalizable to type I bipolar disorder. For instance in a re-analysis of the study by Amsterdam et al. on fluoxetine (19), we found that short-term acute manic switch episodes occur in 3.8% (n = 80) of bipolar II patients and 0.3% (n = 661) of unipolar patients. Converted to risk ratios with 95% confidence intervals [risk ratio (RR) = 12.4, 95% CI 2.1–73.1], these data strongly suggest a much higher risk of acute manic switch with fluoxetine in type II bipolar disorder than in unipolar depression. Therefore, these data suggest that fluoxetine, at least in type II bipolar patients, may have a higher risk of acute manic switch than unipolar patients. These reports of minimal risk with antidepressants, although stemming from randomized data, are methodologically flawed in serious ways such that they at best generate the hypothesis of lower risk of mania with antidepressants in type II bipolar disorder. These reports, however, do not test or prove that hypothesis (19, 20).

If we accept, based on randomized data, that there is a real causal relation between antidepressant use and induction of acute mania, the question becomes what is the extent of this relationship. Here, the randomized data are less useful than real-world data. From the randomized data, the risk rates would be less than 10% for most agents, including TCAs. A large clinical literature,

however, suggests much higher rates with TCAs (30–60%) (17). Skeptics might argue that only randomized data should be assessed for all topics, but this view would represent a misunderstanding of the principles of epidemiology. Randomized designs are ideally setup to answer a yes or no questions (does something occur?). They do so by sacrificing generalizability for validity, that is, a pure homogenous sample is selected for intensive examination. Determining how frequently something happens requires much more generalizable samples, that is, subjects who represent a broad range of patients with the disorder. In the case of antidepressant-induced mania, there likely are clinical variables that lead to exclusion of patients from clinical trials and a consequent artificially low rate of manic induction with antidepressants in randomized clinical trials (RCTs). One of these is substance abuse, which has been shown to be a major predictor of antidepressant-induced mania (21) and is a routine exclusion criteria in RCTs. Hence, well-conducted real-world samples will likely give the most accurate, generalizable rates of risk of antidepressant-induced mania. With SRIs, real-world clinical samples demonstrate rates that are not minimal, i.e. 15–27% (22–24). As a rule of thumb, we suggest that the real rates are around 40% with TCAs and 20% with newer antidepressants, which the randomized data demonstrate are drug-related rates that exceed a lower baseline spontaneous rate. There is also observational evidence that concurrent mood stabilizer use reduces these rates somewhat (23, 25).

Long-term risk of mood destabilization

Three RCTs suggest an increased risk of cycle acceleration with antidepressants (Table 2). In the first study, manic episodes were reported almost 2.5 times more frequently in bipolar type I patients with double-blind treatment of lithium plus imipramine (24%) compared with lithium alone (10%)

over a mean 1.6-year follow-up (n = 75) (26). These results were statistically significant in the female subgroup. Depressive relapse rates were similar for lithium alone (10%) compared with lithium plus imipramine (8%). The second study, a small placebo-controlled on-off-on study RCT, also demonstrated a pattern of increased cycling with TCAs (27). This study reported that time between affective switches was almost four times shorter with desipramine compared with lithium monotherapy. The third controlled study assessed 51 patients with rapid cycling admitted to the NIMH over a decade (28). Non-randomized assessments of treatment response history suggested antidepressants were associated with rapid cycling in 51% of patients. After prospective double-blind randomized replacement of tricyclic antidepressant with placebo, the study concluded that 33% (17 of 51) experienced rapid cycling directly related to tricyclic antidepressants. They further studied that subgroup of 17 patients more intensely, and determined, through repeated on-off-on-off design, that tricyclic antidepressant use was definitively associated with rapid cycling in 10 patients from the original sample (19.6%). Thus, this study, which probably represents the most rigorous examination of this issue, demonstrates with high likelihood a causative association between tricyclic antidepressants and rapid cycling that can be conservatively estimated at about 20%, at least in a highly refractory population such as that seen at the NIMH.

The non-randomized observational literature is mixed, but there is more suggestion of an association between antidepressant use and rapid cycling (29–34) than evidence of lack of such an association (35, 36). Nonetheless, the randomized data carry the most weight, and in the one study that actually compared non-randomized data and randomized assessments, a clear association with rapid cycling was confirmed in at least 20% of patients exposed to antidepressants (28).

Table 2. Randomized studies of antidepressant-induced long-term mood destabilization of bipolar illness

Study	n	Mean duration of follow-up (month)	Treatments	Long-term mood destabilization
Wehr et al. (1979)	5	27	Li versus Li + DMI	Li + DMI treatment resulted in four times more rapid cycling than Li treatment
Quitkin et al. (1981)	75	19	Li versus Li + IMI	2.4 times more manic episodes in Li + IMI group versus Li + PBO group
Wehr et al. (1988)	51	59	Li + PBO versus TCA + Li	33% higher rapid cycling rate with TCA + Li versus Li + PBO

Long-term mood destabilization in these studies is limited to cycle acceleration, defined as two more DSM-IV affective episodes during versus similar exposure-times immediately before antidepressant-treatment.

Li = lithium; DMI = desipramine; IMI = imipramine; TCA = tricyclics; PBO = placebo.

Frequently, natural history data are cited which found that antidepressant treatment was confounded by an underlying relationship between depression and rapid cycling (37). In other words, after controlling for the presence of depression, antidepressants use in itself was not sufficient to induce rapid cycling. This is an important observation that needs to be assessed in other studies. One methodological issue is that while the study sample consisted of ill patients with many past episodes of illness, follow-up was available only for a limited portion of the total duration of illness. In any case, these natural history data, while important, do not refute the available randomized data.

If antidepressants are associated with long-term risk of rapid cycling or worsening, then the recommendation to discontinue antidepressant treatment as soon as possible after remission of the acute episode would appear logical. Critics sometimes refer to a recent study that reported an association between antidepressant discontinuation and relapse into depression in patients with bipolar disorder ( $n = 41$ ) (38). There is a potential flaw, however, in the methodology of this non-randomized naturalistic study. More specifically, there is a possible selection bias in the composition of the two groups, one in which, by physician choice, antidepressants were discontinued ( $n = 25$ ) and continued in the other ( $n = 19$ ). Based on current guidelines, clinicians may be more likely to discontinue antidepressants in rapid cycling than non-rapid cycling patients. In rapid cycling, by definition, mood episodes occur more frequently than in non-rapid cycling. Thus, based on natural history alone rather than drug effect, one would expect to find earlier relapse in the rapid cycling group (in which antidepressants were stopped for clinical reasons) compared with the non-rapid cycling group where antidepressants were continued. As this report is non-randomized, and such potential confounding was not controlled, definitive conclusions cannot be drawn. With these methodological problems, only a randomized study can prove whether there is a relationship between antidepressant discontinuation and relapse into depression. In fact, such a randomized study has been conducted by Prien et al. in 1984. It involved 150 type I bipolar patients who had received lithium plus imipramine openly for 2 months (39). Following this 2-month period, patients were randomized under double-blind conditions to either lithium plus imipramine or to lithium plus placebo. In the ensuing 2-year follow-up, the rates of depressive relapse were virtually identical in the two groups (29% in lithium + placebo versus 22% in lithium + imipramine). In

other words, antidepressant discontinuation did not lead to any increased risk of relapse into depression. A mild benefit with imipramine plus lithium appeared possible in the first 6 months of treatment based on survival analysis, but not afterwards. This provides double-blind randomized data for the clinical recommendation of discontinuation of antidepressants after 6 months of recovery from acute major depressive episode in bipolar disorder.

In our observational experience, we find that withdrawal depression following discontinuation of antidepressants is infrequent and less of a problem in bipolar disorder (17.6%, six of 34) than unipolar depression (83.3%, five of six;  $p = 0.004$ ) (33). Further, we find more evidence of another problem, i.e. tolerance, with relapse into major depressive episodes despite continuation of antidepressants, which occurs in most patients with bipolar disorder (57.5%, 23 of 40) versus a minority of patients with unipolar depression (18.4%, seven of 38;  $p < 0.0001$ ). Indeed, this tolerance may represent induction of cycling with onset of the next depression coming earlier, and thus is consistent with the evidence suggestive of antidepressant-associated rapid cycling.

It is worth noting that in the only study to assess concurrent mood stabilizer use, we found that mood stabilizers were not protective against antidepressant-induced cycle acceleration (about 50% with or without mood stabilizers). Further, in a comparison of new versus old antidepressants on this issue, we found no evidence that TCA rates (9%, one of 11 trials) are higher than SRI rates (14%, eight of 56 trials,  $RR = 0.64$ , 95% CI 0.09–4.59), although the bupropion rate (4%, one of 23 trials,  $RR = 2.09$ , 95% CI 0.14–30.4) was slightly lower than TCA rates. Given the small sample sizes, these negative findings need to be replicated (25). Further, these data are observational (non-randomized), but are reported here because of the absence of other studies on this topic.

In summary, the preponderance of the evidence supports an association between antidepressants and long-term mood destabilization of bipolar disorder, especially cycle acceleration. The assertion that there is an important and relatively common risk of acute manic switch and long-term mood destabilization due to antidepressants appears valid.

#### **Premise 2: The risk of suicide in bipolar depressed patients is not a serious concern**

This assumption is not in fact part of our argument for caution with antidepressant use in

bipolar disorder. Quite the contrary, we agree that the risk of suicide in bipolar disorder is high, in the 5–20% range, depending on history of hospitalization (40). The key point of debate is an even more basic assumption underlying the Munich group's stated assumption, i.e. do antidepressants reduce suicide risk in bipolar disorder. And, conversely, do mood stabilizers reduce suicide risk in bipolar disorder?

Data on suicide prevention and pharmacologic interventions most often are derived from reports focusing on efficacy in treating bipolar disorder. Contrary to the Munich group's assertion that there is a large body of evidence supporting the use of antidepressants in reducing suicidality, in actuality the evidence of antidepressant benefit in suicide prevention is substantially less convincing than the evidence supporting lithium's benefit for suicide prevention. Furthermore, what data they cite regarding the effectiveness of antidepressants in reducing suicide risk has been derived from studies of unipolar, not bipolar, depression.

In unipolar depression, an analysis of SRI and other novel antidepressants (fluoxetine, sertraline, paroxetine, venlafaxine, nefazodone, mirtazapine, and bupropion) using the Food and Drug Administration (FDA) database ( $n = 19,639$ ) reported no significant difference in completed suicides ( $p = 0.46$ ) or attempted suicides ( $p = 0.64$ ) between antidepressant and placebo-treated groups (41). A similar study assessing venlafaxine and citalopram also reported no significant differences in completed or attempted suicides between investigational antidepressants ( $n = 1172$ ), active comparators ( $n = 161$ ), and placebo ( $n = 606$ ) (42). In other words, antidepressants could not be shown to reduce the risk of suicide compared with placebo. This lack of a difference cannot be attributed to low statistical power, especially in the large FDA database analysis with about 20 000 patients.

It is possible that anti-suicide benefits with specific antidepressants might not be detectable when all new agents are pooled as in the above FDA analysis. For instance, a pooled analysis in 1995 of only paroxetine clinical trials in unipolar depression ( $n = 2852$  for paroxetine,  $n = 554$  for placebo, and  $n = 1101$  for control antidepressants) found that, when calculated per patient year of exposure, there were 2.8 times fewer suicides with paroxetine compared with other antidepressants and 5.6 times fewer suicides compared with placebo (43). Further, in a three decade follow-up of 406 affectively ill patients in the Zurich cohort, treatment with antidepressants reduced suicide rates compared with lack of treatment (44).

However, even if such benefits with specific antidepressants are confirmed, antidepressants *as a group*, as the Munich group argues, still have not been shown to reduce suicide rates.

A major assumption that the Munich group makes is that as there is an association between bipolar depression and suicide risk; treating the former with antidepressants will reduce the latter. Regardless of whether the cited evidence supports this assumption, it is important to note the basic epidemiologic and even logical principle that 'association is not causation'. In other words, one cannot assume, *sic et simpliciter*, that bipolar depression is a 'surrogate endpoint' for suicide risk. Moreover, it is important to recognize that suicide is an outcome in a relatively small fraction of bipolar depressed patients; the question is what features of some bipolar depressed patients put them at greater risk, and which drugs might differentially impact these risk factors (such as comorbid substance abuse, mixed states, cycling within an episode, aggressive behaviors, global insomnia, and impulsivity), some of which are discussed by Goldberg (45). When antidepressants induce mania, they frequently lead to mixed states or cycling (46–49). Thus, patients who experience antidepressant-induced acute mixed episodes or cycling will actually be at higher risk of suicide.

In contrast to the inconclusive state of the antidepressant literature, there is substantial and unchallenged evidence as to the effectiveness of lithium in lowering suicide risk, which has been reviewed elsewhere (50). We were somewhat surprised that our Munich colleagues underestimated this literature.

In conclusion, the evidence of benefit with antidepressants for suicide prevention is much less compelling as compared with lithium. If anything, concern about suicide should represent an additional reason to emphasize mood stabilizer use (especially lithium) for bipolar depression over antidepressants.

### **Premise 3: The evidence of efficacy in treating bipolar depression with antidepressants is minimal**

In the Munich group's critique of North American-based treatment guidelines, literature purporting to show the efficacy of antidepressants in bipolar depression is reviewed. While these authors focus on their own careful but retrospective and uncontrolled chart review, we believe it is best to start with whatever randomized data are available, turning to observational data and clinical experience only where randomized data are not available.

## Antidepressants in acute bipolar depression

As mentioned previously, TCAs have not been proven to be more effective for bipolar depression than therapeutic levels of lithium in a recent well-designed RCT (13). Furthermore, four older crossover RCTs did not clearly demonstrate better efficacy with TCAs over lithium (51–54). In addition Goodwin and Jamison review five additional studies involving almost 700 bipolar and unipolar patients in which tricyclic antidepressant response in bipolar disorder was 'relatively poor' compared with unipolar depression or in which bipolarity or a history of mania was associated with a 'poor response' to tricyclics ( $p < 0.02$ ) (17).

Concerning SRIs, the largest and best-designed study is the one mentioned above (13), which failed to find added benefit with paroxetine above lithium alone at therapeutic serum levels. In this study, which is the largest acute study of antidepressant efficacy in bipolar depression, the difference between antidepressant (either paroxetine or imipramine) versus placebo was about two points on the Hamilton Depression Rating Scale. This small effect size argues against any significant likelihood of type II error, even if a larger sample size had been used to make the difference statistically significant. Another frequently cited study, as discussed previously, has been reported to show fluoxetine to be superior to placebo, but more patients in the fluoxetine group were treated with lithium than the placebo group (12). Lithium augmentation of antidepressants is well known to

lead to enhanced efficacy which may explain this finding.

We conclude that the acute efficacy of antidepressants has not been shown to be better than lithium at full therapeutic levels. Furthermore, there is some evidence that the antidepressant efficacy of the new mood stabilizer lamotrigine may be superior to lithium without evidence (in over 1200 bipolar patients) that it is associated with a high mania/hypomania induction or cycle acceleration (55). These data are subject to interpretation because there also has been at least one unpublished negative study with lamotrigine in bipolar depression (GlaxoSmithKline, data on file).

## Antidepressants in prophylaxis

As reviewed by one of us previously, TCAs have not been shown to be effective in preventing depressive episodes in bipolar disorder in any long-term, double-blind studies ( $n = 263$ ) (56). Here we update that review by identifying seven published, controlled, long-term double-blind studies of antidepressants in bipolar disorder (mostly type I). Five studies were with TCAs, one with fluoxetine and one with bupropion (Table 3). It is important to recall a point we noted earlier, which was that all of the studies with lithium comparison arms (all involving TCAs) showed antidepressants equal or less effective compared with lithium alone (26, 27, 39, 57, 58). Moreover, one of these studies ( $n = 75$ ) (26) reported a long-term deterioration with antidepressants with

Table 3. Randomized clinical trials of long-term antidepressant treatment in bipolar disorders

Study name	n	Treatments	Findings
Prien et al. (1973)	44	Li versus IMI versus PBO	With outcome measured as hospitalization or switch to new treatment, after 24 months lithium was more effective than imipramine which was equal in efficacy to placebo
Wehr et al. (1979)	5	Li versus Li + DMI	With outcome measured by nurse ratings, efficacy (mean 19 month duration) of lithium plus DMI was greater than lithium alone, but the switch and cycling rate with lithium plus DMI was also much higher
Quitkin et al. (1981)	75	Li versus Li + IMI	After a mean of 19 month treatment, with the outcome measured with Research Diagnostic Criteria episodes (84), lithium was equal in efficacy to IMI
Kane et al. (1982)	27	Li versus IMI versus Li + IMI versus PBO	Efficacy of lithium (mean duration 11 months) greater than IMI which was equal in efficacy to placebo
Prien et al. (1984)	117	Li versus Li + IMI versus IMI	With outcome measured as RDC episodes (duration up to 24 months), efficacy of lithium was equal to lithium plus imipramine
Sachs et al. (1994)	15	BUP versus DMI	Li plus BUP was equal in efficacy to lithium plus DMI (duration up to 12 months) with outcome measured as DSM-III-R episodes
Amsterdam et al. (1998)	80	FLX versus PBO in BP II and UP	With outcome measured as DSM-III-R episodes, FLX efficacy was similar in BP II and UP, with the switch rate higher in BP II (duration up to 14 months)

Li = lithium; IMI = imipramine; PBO = placebo; DMI = desipramine; BUP = bupropion; FLX = fluoxetine.



increasing frequency of manic episodes (24% with imipramine plus lithium versus 10.5% with lithium alone) with no reduction in depressive episodes compared with lithium monotherapy (8 versus 10.5%). The lack of efficacy with TCAs bodes ill for SRIs and other novel antidepressants, which have never been proven more effective than TCAs in any mood disorder. We conclude that tricyclic antidepressants appear to have relatively low efficacy in the prevention of depression in bipolar disorder, and further one cannot assume that SRIs have any better efficacy.

In these prophylaxis studies of antidepressants in bipolar disorder, re-analysis with the use of confidence intervals fails to provide evidence of likelihood of type II error. For instance, in the study mentioned above (26), where depressive relapse was 8% with imipramine plus lithium versus 10.5% with lithium alone, the risk ratio is 0.77 with very wide confidence intervals (0.18–3.21) extending in both directions around the null (1.0), thus suggesting no likely real effect. In another prophylaxis study (39), remission rates were exactly the same (33%) with lithium plus imipramine versus lithium alone, resulting in a risk ratio of 1.0 and again very wide confidence intervals (0.53–1.88). This re-analysis indicates that the absence of added benefit with antidepressant is unlikely to be because of low statistical power.

#### **Premise 4: The evidence of efficacy in treating bipolar depression with mood stabilizers is high**

In fact, there is substantial evidence supporting the efficacy of some mood stabilizers in bipolar depression, and this evidence is at least equal to, if not better, than the available evidence for antidepressants.

##### Acute bipolar depression

Eight of nine early randomized, double-blind placebo-controlled studies ( $n = 163$ ) for acute bipolar depression reported efficacy with lithium (59). While many of these studies utilized a crossover design, it was possible to obtain 'unequivocal response,' defined as good response with lithium and relapse with placebo, from five studies (51, 60–63). While some methodological limitations can reasonably be noted in individual studies, taken together these older studies indicate at least a modest antidepressant effect of lithium in acute bipolar depression. Better still, as noted above, more recent controlled studies have also supported lithium efficacy in bipolar depression. In a large study of bipolar type I patients ( $n = 117$ ), the

addition of antidepressants (paroxetine or imipramine) to lithium was not more effective than lithium plus placebo in patients with therapeutic lithium serum levels ( $\geq 0.8$  ng/dL) (13). In another recent double-blind randomized study ( $n = 27$ ), the addition of paroxetine to mood stabilizer (lithium or valproate) was not more effective than the continuation of two mood stabilizers (14). Although the two mood stabilizer group experienced more side effects (because full monotherapy doses of each stabilizer were used), the antidepressant efficacy of the adjunctive paroxetine was not better. It should be acknowledged, however, that in the latter study, there is the potential for a false negative error because of the small sample size.

Most clinicians and researchers believe that valproate is largely ineffective in bipolar depression, primarily because of negative results from a few small studies. For instance, one study ( $n = 45$ ) reported a 43% response rate to valproate as compared with 27% with placebo (64). Although not statistically significant ( $p > 0.05$ ), the use of confidence intervals demonstrates a greater likelihood of benefit than not with valproate (RR = 1.50, 95% CI 0.64–3.50). Given that the confidence intervals suggest benefit with valproate, it is important to note the high risk of type II error inherent in small, negative studies such as this. As noted previously, the data with antidepressants do not indicate a high likelihood of type II error when re-analyzed with risk ratios and confidence intervals. This is not the case with the negative results from the small study of valproate in bipolar depression. While not yet published, preliminary analysis of data from a second double-blind randomized valproate study reports a greater decrease over time in Hamilton Depression Rating Scale scores with valproate versus placebo (5.5 versus 2.6 points per unit time,  $p = 0.02$ ) (65). A third study, as mentioned previously, suggested acute antidepressant efficacy combined lithium plus valproate (14). Observational data from our group also support acute and long-term antidepressant efficacy with valproate (66).

There are three randomized studies of carbamazepine treatment of acute bipolar depression, with two studies reporting it more effective than placebo (combined  $n = 19$ ) (67, 68) and one reporting carbamazepine plus lithium more effective than carbamazepine plus placebo ( $n = 15$ ) (69).

Lamotrigine has demonstrated some efficacy compared with placebo for acute bipolar depression (combined  $n = 226$ ) (70, 71), as well as for prevention of depressive episodes in bipolar disorder (see below).

In summary, the evidence from a large number of studies supports the efficacy of lithium and lamotrigine in the treatment of acute bipolar depression. The evidence for antidepressive efficacy of other mood stabilizers (valproate and carbamazepine) is less consistent. Direct head to head comparisons between traditional antidepressants and mood stabilizers have so far been limited to studies in which therapeutic levels of lithium, or combined lithium plus valproate, were equivalent to paroxetine.

#### Prophylaxis

There is substantial evidence, namely 12 randomized double-blind parallel group placebo-controlled studies, demonstrating efficacy of lithium in preventing depressive relapse in bipolar disorder as reviewed by Goodwin and Jamison (17). Further, a Cochrane Collaboration meta-analysis of these studies found an overall 376% reduction of risk of relapse (RR 4.76) (72). It has been suggested that some of the earlier lithium studies may have overestimated the benefit of lithium because some of the patients randomized to placebo were on lithium at that time and the sudden discontinuation may have increased the relapse rate on placebo (73). A recent meta-analysis by Baldessarini, however, found that when the 50% of studies involving prior lithium treatment were compared with the half not involving prior withdrawal, the size of the lithium effect was the same (74). Consistent with this are recent studies of lithium versus placebo (combined  $n = 1010$ ) which have controlled for this effect by either gradual discontinuation or avoiding lithium treatment in the acute treatment phase prior to randomization for prophylaxis. In these studies, lithium was again shown to be significantly better than placebo for prevention of relapse (75–77).

The efficacy of valproate in preventing relapse has been examined in one randomized study (75), with no overall benefit found with valproate compared with placebo. Two open-randomized studies, however, report equal or better efficacy with valproate compared with lithium (78, 79). Randomized studies of carbamazepine also report better efficacy compared with placebo (combined  $n = 32$ ) (67, 80) and equal efficacy compared with lithium (combined  $n = 64$ ) (81, 82). The quality and extent of these data are better than with antidepressants but less definitive than with lithium.

Lamotrigine has also been shown to be effective in preventing depressive relapse in bipolar disorder. Two recent studies (combined  $n = 1315$ ) have demonstrated that lamotrigine is more effective

than placebo in preventing depressive episodes, without increasing the risk of manic/hypomanic switch (76, 77). Further, lamotrigine was somewhat more effective than lithium in prevention/delay of depressive relapse in a pooled analysis of both studies (55). From the evidence outlined above, we conclude that lithium and lamotrigine are both effective in preventing bipolar depressive episodes, with lamotrigine showing the most robust effect.

In summary, although they may sometimes be effective acutely, the evidence of long term efficacy with antidepressants is quite weak, whereas the evidence of long term efficacy with lithium or lamotrigine is much stronger. Further, major doubt exists as to whether antidepressants have preventative efficacy for depression in bipolar disorder, unlike lithium and lamotrigine, which have been proven effective in the prevention of depression in bipolar disorder. As a result, we think the research evidence supports the third and fourth assumptions that were challenged by the Munich group, which we might restate as follows: acutely, antidepressants and mood stabilizers – especially lamotrigine – appear equally effective for bipolar depression, and long-term, mood stabilizers appear more effective than antidepressants in the prevention of depression in bipolar disorder.

#### Summary

In asserting that antidepressants should play a bigger role in the treatment of bipolar depression, the Munich critique advocates a position contrary to that taken by current US and Canadian-based treatment guidelines (Table 4). They challenge what they believe to be four premises underlying the North American approach: antidepressants increase rapid cycling, suicide is not a serious risk in bipolar disorder, the evidence for antidepressant treatment of bipolar depression is insufficient, and that the evidence of mood stabilizer treatment for bipolar depression is sufficient. We have sought to demonstrate that the evidence in fact supports caution with antidepressants, although not exactly because of these assumptions. Specifically, randomized data provide some evidence of increased risk of cycling with antidepressants. Further, the risk of suicide in bipolar depression can be taken as supportive of the use of lithium rather than antidepressants. In addition there appears to be little evidence of antidepressants being more effective than lithium or lamotrigine in the treatment of acute bipolar depression and even less evidence as to antidepressant efficacy in longer-term treatment in prevention of depressive relapse. Finally, the evidence reviewed leads us to the conclusion that

## Antidepressants in bipolar disorder: the case for caution

Table 4. The case for caution with antidepressants in bipolar disorder

Con (Möller and Grunze, 2000)	Pro (Ghaemi et al., 2003)
1. The risk of antidepressant induced cycling is not high	1. The risk of antidepressant induced cycling is high
2. Antidepressants reduce the risk of suicidality	2. Antidepressants have not been shown to definitively prevent completed suicides and reduce mortality, whereas lithium has
3. Antidepressants are effective in treating bipolar depression	3. Antidepressants have not been shown to be more effective than mood stabilizers in acute bipolar depression and have been shown to be less effective than mood stabilizers in preventing depressive relapse in bipolar disorder
4. Mood stabilizers have not been shown to be effective in bipolar depression	4. Mood stabilizers, especially lithium and lamotrigine, have been shown to be effective in acute and prophylactic treatment of bipolar depressive episodes.
Conclusions and recommendations	Conclusions and recommendations
<ul style="list-style-type: none"> <li>• Antidepressant associated risks are exaggerated</li> <li>• Antidepressants should be used frequently along with mood stabilizers</li> <li>• Antidepressant treatment should be continued long-term (ideally 12 months) to avoid depressive relapse</li> </ul>	<ul style="list-style-type: none"> <li>• There are significant risks of mania and long-term worsening of illness with antidepressants</li> <li>• Antidepressants should generally be reserved for severe cases of acute bipolar depression and not routinely used in mild to moderate cases</li> <li>• Antidepressants should be discontinued after recovery from the depressive episode and maintained only in those who repeatedly relapse soon after antidepressant discontinuation</li> </ul>

mood stabilizers, particularly lithium and lamotrigine, are effective both in the treatment of acute bipolar depression and in the prevention of future depressive relapse episodes.

Ultimately, the controversy over antidepressant use is not that antidepressants should never be used or that they should always be used; rather the issue is how frequently and for what duration should antidepressants be used in treating bipolar disorder. In practice, both in the US (despite North American guidelines) and in Europe, the majority of patients with bipolar disorder regularly receive antidepressants (50–80%), usually long-term (2, 83). We advocate a reversal of prescription patterns such that antidepressants would be used mostly short-term and in a minority of patients (perhaps 20–40%). Clearly, further research is urgently needed to clarify these controversies, especially as to the long-term risks of mood destabilization with new antidepressants, as well as the relative risks versus benefits of antidepressants in bipolar II disorder.

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