

Switching, Induction of Rapid Cycling, and Increased Suicidality With Antidepressants in Bipolar Patients: *Fact or Overinterpretation?*

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ABSTRACT

Antidepressants constitute a central cornerstone in the treatment of depressive syndromes. In bipolar patients, however, there is an ongoing controversy about their usefulness for at least 3 decades. Early reports, mainly concerning tricyclic antidepressants, have repeatedly pointed toward unfavorable side effects on the course of the disorder, namely switching into (hypo)mania, induction of rapid cycling, and increased risk of suicide. Most evidence for both unfavorable and favorable effects has been deducted, thus far, from small studies with methodological flaws. More substantiated evidence only recently became available. From this it appears that, at least, the switch risk, and perhaps also the risk for rapid cycling and new-onset suicidality have been overinterpreted. At the same time, these new data raise doubt about the efficacy of antidepressants as a primary-treatment choice in bipolar depression.

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Needs Assessment

Depression constitutes a major challenge in the acute treatment of bipolar disorder. Whereas the use of mood stabilizers is a generally accepted treatment strategy, there is some controversy regarding the use of antidepressants. Clinicians should be aware of the advantages and risks of antidepressants to ensure their proper use.

Learning Objectives

At the end of this activity, the participant should be able to:

- Identify arguments in favor and against the use of antidepressants in acute bipolar depression.
- Be able to estimate their risk in continuous, long-term use.
- Discuss the pros and cons of antidepressants with respect to suicidality.

Target Audience: Neurologists and psychiatrists

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INTRODUCTION

Few issues in psychiatry are surrounded by so much controversy and uncertainty as the usefulness and associated risks of antidepressants in bipolar patients.¹⁻³ Despite the decade-long debate, surprisingly little has been done until recently to clarify these issues, namely: Are antidepressants efficacious in bipolar depression? Do they put the patient on increased risk of affective switching or rapid cycling? Do they promote suicidality in bipolar patients?

It was not until early 2008, when the first large-scale, placebo-controlled monotherapy study with an antidepressant in bipolar depression had been presented; and even this study was not designed to clarify issues on efficacy and switch risks of the antidepressant, but to support an antidepressant claim for the atypical antipsychotic quetiapine.⁴ Nevertheless, with some other recent studies (eg, results from the Systematic Treatment Enhancement Program for Bipolar Disorder [STEP-BD] program)^{5,6} we are now in a position where we can start to demystify the use of antidepressants in bipolar disorder, although more data are clearly needed. This article will attempt to tie up our assumptions and knowledge about links between the use of antidepressants in bipolar patients and affective switching, rapid cycling, and new-onset suicidality.

AFFECTIVE SWITCHING

What Has Been Reported?

Reports on mood switch in bipolar patients are numerous and virtually every available class of antidepressants has been associated with these events. In 1994, Peet⁷ published an analysis of what has been considered as treatment-emergent switches into mania, calculated from all available clinical trial data on the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, fluvoxamine, paroxetine, and sertraline, relative to comparative groups treated with tricyclic antidepressants (TCAs) or placebo. At this time, available trials were almost exclusively conducted in unipolar depressed patients; bipolarity was mostly considered as exclusion criterion. Within the few bipolar depressives, a manic switch occurred substantially more often with TCAs (11.2%) than with SSRIs (3.7%) or placebo (4.2%). This finding of an increased likelihood of switches with TCAs is predominantly in line with other reports from this time,^{8,9} but other case series^{10,11} or retrospective

chart analyses¹² could not verify increased switch risks, or a less favorable outcome even when switches occur.¹³ Within the class of newer antidepressants, the serotonin-norepinephrine reuptake inhibitor venlafaxine has been associated with a significant higher switch risk than the SSRI sertraline or the dopamine reuptake inhibitor bupropion,¹⁴ which is also consistent with the results of an earlier study by Vieta and colleagues¹⁵ comparing paroxetine and venlafaxine. For other serotonin-norepinephrine reuptake inhibitors, namely duloxetine, the switch rate is unknown, but presumably low as deduced from unipolar depression studies.¹⁶ As a consequence, most guidelines recommend the addition of a mood stabilizer or an antimanic agent to antidepressant treatment to reduce the switch risk.¹⁷ If a switch occurs, most studies also agree that bipolar I disorder patients are more at risk to switch than bipolar II disorder patients.^{18,19}

What is the Best Available Evidence?

When it comes to methodologically more sound evidence, a meta-analysis of Gijsman and colleagues²⁰ identified five placebo-controlled, but mostly small studies with antidepressants in bipolar depression until 2003. They found that the data "do not suggest that switching is a common early complication with antidepressants." However, with a 10% switch rate with TCA, they also concluded that "It may be prudent to use an SSRI or a monoamine oxidase inhibitor rather than a TCA as a first-line treatment." The largest study included into this meta-analysis was, in fact, a study using a fixed combination of an atypical antipsychotic (olanzapine) with an antidepressant (fluoxetine).²¹ Thus, making it difficult to separate the contribution of each agent to efficacy and switch risk. More conclusive evidence can be derived from two recent, large controlled studies, one being a monotherapy study,⁴ the other a study investigating the combination of a mood stabilizer and the choice of two antidepressants.⁶

The monotherapy study⁴ compared quetiapine with placebo, including paroxetine 20 mg/day as an internal comparator. Paroxetine treatment was ineffective for bipolar depression, but was not associated with an increased switch risk compared to placebo. The second study,⁶ part of the STEP-BD program, compared the effectiveness of a mood stabilizer (lithium or valproate) alone against the combination of mood stabilizer, either with bupropion or paroxetine. The

antidepressants could not add greater benefit to mood-stabilizer monotherapy, but were also not associated with an increased switch risk during up to 26 weeks of treatment.⁶

Methodological Issues, Challenges, and Perspectives

As it stands, there exists not one sufficiently powered and placebo-controlled study with antidepressants in bipolar depression that supports an increased switch risk with antidepressants. However, it must be noted that the same is true for unambiguous proof of efficacy of antidepressants in bipolar patients. The assumption that antidepressants cause clinically meaningful switch rates may partially be also a consequence of several methodological problems as outlined by Angst (oral communication, November 2005). For example, only switch events are reported but not the fact that patients do not switch, which leads to a publication bias. In addition, all studies reporting on switches have no uniform definition of a switch and calculate switch rates on an intent-to-treat basis. Assuming that antidepressants are efficacious at least in a subgroup of patients, this would clearly favor fewer switch events in placebo-treated patients. Only patients who respond can switch but not those who remain depressed. In addition, placebo-treated patients may drop-out of trials earlier due to inefficacy and thus have a shorter observational period and smaller chance to develop a switch as part of the natural course of bipolar disorder.

A central problem when discussing antidepressant induced switches, however, is the absence of a uniform definition of a switch. Recently, a task force of the International Society of Bipolar Disorder²² began to develop definitions of outcome and course specifiers in bipolar disorder. They concluded that due to the irregular course of acute symptoms, the problems of definition and attribution of "affective switch" present inter-related challenges and is at best operational and still leaves room for considerable error. They prefer to refer to these events as a "treatment emergent affective switch" (TEAS) because it does not attribute causality. Terms such as "antidepressant-induced switch" or "antipsychotic-induced switch" are, in the opinion of the task force, error prone and hazardous. They recommend not only consideration for the term TEAS but also the development of operational definitions that consider causality, amplitude duration, and window

of intervention that need to be examined for their reliability and practicality in future trials.

Although the evidence for increased full switching to (hypo)mania with antidepressants is not convincing and prone to methodological errors, it cannot be denied that antidepressants, as part of their action, induce changes in symptomatology. The previously stable depressive syndrome becomes unstable, and symptoms such as dysphoria, increased irritability, and agitation may evolve. These changes may precede recovery, following the arguments of Angst (oral communication, November 2005), as previously outlined, but may also give rise to worries (eg, increased danger of suicide attempts). El-Mallakh and colleagues²³ described this mood destabilization as a syndrome they called "antidepressant-associated chronic irritable dysphoria" (ACID) in a reasonable number of antidepressant-treated patients within the STEP-BD program. However, they also noted that almost exclusively those patients who had a history of TEAS were prone to ACID. Clearly, it needs more prospective research on whether ACID constitutes a risk for prospective switching and whether it is an enduring or a transient state on the way to recovery. Data of the Stanley Foundation Bipolar Network²⁴ suggest that higher Young Mania Rating Scale scores while depressed correlate not only with a past history of switching, but also with prospective TEAS.

RAPID CYCLING

Whereas the literature about TEAS, due or not due to antidepressants, is quite extensive, reports about long-term consequences of the use of antidepressants in bipolar patients are scarce and rarely conclusive.

Since Dunner and Fieve²⁵ coined the term "rapid cycling," it has been the subject of intensive research, more recently also of controlled treatment studies. However, careful prospective investigation reveals that rapid cycling is not only a transitory phenomenon²⁵ but also an arbitrarily defined cut-off at four episodes per year on the continuum of episode frequency seen in naturalistic-treated outpatients with bipolar disorder.^{26,27} Thus, it may be more adequate to ask whether antidepressants induce increased cycling frequency instead of rapid cycling. But as much of the research specifically uses development of rapid cycling as outcome, we will use to this phrase.

Wehr and Goodwin²⁸ first raised the issue of

antidepressant-induced rapid cycling. Further observational reports, mainly from the TCA era, appeared supportive for such a link,²⁹⁻³² but have also recently been questioned.³³ The causality of a rapid cycling course to any treatment is less than clear as treatment modality is only one factor in which rapid cycling and nonrapid cycling patients do separate. In a large prospective study by the Stanley Foundation Bipolar Network,²⁷ it was found that rapid cycling patients (N=206, 38.2%) differed from nonrapid cycling (N=333, 71.8%) with respect to the following: lifetime history of rapid cycling; more lifetime episodes; presence of bipolar I subtype; history of childhood physical and/or sexual abuse; earlier age of onset; longer duration of illness; longer delay until first treatment; lifetime histories of dysphoric mania/hypomania, drug abuse, and anxiety disorders; parental history of drug abuse; and, finally, among others, exposure to antidepressants. All associations increased progressively with episode frequency, not with a "magical" cut-off at four episode per year. But was exposure to antidepressants causative for rapid cycling? Probably not, as it was also found that time spent in depression was greater in rapid cycling patients (39.5% vs 33.2% in nonrapid cycling patients), which, by itself, may bring on a more frequent use of antidepressant.

A similar interaction has also been demonstrated in a large naturalistic study by Coryell and colleagues.³⁴ Higher depressive morbidity predicts rapid cycling courses and leads to a greater likelihood that antidepressants are introduced as part of the treatment regimen. No interaction between introduction or cessation of antidepressants and changes of cycling frequency could be observed in this large study.

A recent article based on prospective data from 1,742 participants in the STEP-BD study²⁶ seems, at first glance, favorable for the notion that antidepressants induce rapid cycling. However, at a closer look, it contains a clear methodological flaw, as also acknowledged by the authors, and a self-fulfilling prophecy. Methodologically, it is always questionable to compare retrospective versus prospective data, as this makes conclusions vulnerable to bias. The main finding supports what has been previously demonstrated also by other investigators: The more severely ill someone is at study entry, the more likely it is that he has frequent episodes in the prospective follow-up year. But the finding that antidepressant

exposure was about three times more likely in patients developing rapid cycling can be regarded as a self-fulfilling prophecy. The authors stated "The pharmacotherapy procedures were based on expert consensus guidelines, such as those published by American Psychiatric Association and others.⁶ The treatment choices were presented in tiers, corresponding to treatments considered 'first line' in one or more published guidelines, 'second line,' etc." The mentioned guidelines consider the use of antidepressants either only in severe depression or after failure of mood-stabilizer monotherapy. This must lead to the conclusion that patients on antidepressants are likely more severely ill at treatment initiation (not necessarily at baseline Montgomery-Åsberg Depression Rating Scale interview, for which the authors controlled) and/or have failed on first-line mood-stabilizer treatment. Having a less favorable outcome is then a self-fulfilling prophecy, and to deduce causality to antidepressant use may be misleading.

Thus, in summary, it is premature to generally associate antidepressant use with rapid cycling as it has been done in a recent editorial.³⁵ There are likely subgroups of instable patients who get further destabilized by any powerful pharmacologic intervention, including antidepressants. On the other hand, there is now some controlled evidence³⁶ that long-term treatment with antidepressants may stabilize acute antidepressant responders.

SUICIDALITY

Induction of mood swings and suicidality may appear, at first glance, not necessarily linked to each other. But there might be a connection: if antidepressants induce mixed states and agitation in depressed patients, or ACIDs, as described by El-Mallakh and colleagues²³ it is reasonable to assume that this might also increase suicidality/suicide attempts. Dealing with suicidality is probably the greatest challenge in the treatment of depression, both for the psychiatrist and the patient (and, of course, his family). Perhaps the most accurate prospective long-term, large-cohort study on suicide risk in affective disorders was conducted by Angst and colleagues³⁷ who followed 406 patients with unipolar depression or bipolar disorder from 1963–2003. By 2003, 11.1% of these patients had committed suicide. This figure underlines the prominent role of early diagnosis and treatment of depression for suicide preven-

tion. But could treatment, namely antidepressants, inherit additional risks of suicide attempts?

Over 2 decades, there has been a controversial discussion whether antidepressant treatment may put unipolar depressed patients on an increased risk of suicide. Different claims about the use of antidepressants, especially SSRIs, and suicidality have been proposed: Antidepressants may decrease suicide rates on a population basis,³⁸ but at the same time they may increase suicidality (or even suicide events) in some individuals early in treatment.³⁹ As recently reviewed by Hall and Lucke⁴⁰ and Möller,⁴¹ there is some supportive evidence for both views. Clarification of this controversy in a controlled study would not only be unethical in every respect, but methodologically impossible. Fortunately, suicide is still such a rare event that it cannot serve as a primary outcome criterion. To improve the number of subjects and statistical power, suicidality instead of committed suicide became the focus of interest and, as still rare, pooled data subjected to meta-analysis has been used. The broader concept of "suicidality" may, depending on the study, include suicidal ideation, preparation for suicide, suicide attempts, but sometimes just the wish to be dead (which is a common symptom and indicative for the severity of depression). But still, the statistical power of studies assessing suicidality is even low. Most studies exclude at least patients with serious suicidal thoughts. The consequence of this is that any indication of increased or decreased suicidality by antidepressants does not reach statistical significance and, in addition, is far removed from the actual efficacy of antidepressants in real-life conditions.⁴⁰

Meta-analyses have given conflicting results.^{42,43} So far, the largest database from randomized controlled trials (RCTs) was assessed by Hammad and colleagues.⁴⁴ They evaluated the rate of suicide in placebo- and active-drug-treated groups of patients with major depression and various anxiety disorders participating in short-term RCTs. Data were available for 207 trials conducted in patients with major depressive disorder, including 40,028 patients and 44 trials conducted in patients with various anxiety disorders, including a total of 10,972 patients. Neither the use of placebo nor of antidepressants in short-term RCTs was associated with an increased risk of completed suicide among patients with MDD or various anxiety disorders. More recently, it has been reported that suicide rates in United States

adolescents are again on the rise as a possible consequence of a less liberal use of antidepressant,⁴⁵ but not in the United Kingdom.⁴⁶ But what are the data for bipolar patients?

In general, the evidence is scarce both in favor of a suicide promoting or preventing effect of antidepressants. Analyzing the Zurich cohort study data,³⁷ which included both unipolar and bipolar patients, long-term medication treatment with antidepressants alone or with a neuroleptic, or with lithium in combination with antidepressants and/or neuroleptics, significantly lowered suicide rates even though the treated were more severely ill than those without medication. In contrast, Yerevanian and colleagues⁴⁷ reported increased suicidal behaviors in patients on antidepressants compared with mood-stabilizer monotherapy or mood stabilizer/antidepressant combination. This observation was based on retrospective chart reviews of 405 bipolar patients. The interpretation remains problematic, as we do not know how many patients would have displayed suicidal behaviors when untreated—it may be far more than with any of these treatments—and whether these findings may be confounded by a selection bias: Those who displayed suicidal thoughts or behaviors may be more likely to receive antidepressant treatment than those who do not. The best evidence thus far originates from the STEP-BD study.⁵ Four hundred twenty-five new-onset major depressive episodes without initial suicidal ideation were observed in this study and analysed to investigate the hypothesis that new-onset suicidality was associated with increased antidepressant exposure (either antidepressant initiation or dose increase). New-onset suicidality was associated with neuroticism, prior suicide attempt, and higher depressive or manic symptom ratings at index episode, but there was no association of new-onset suicidality with increased antidepressant exposure or any change in antidepressant exposure, and no association with initiation of antidepressant treatment.

In summary, the overall data from larger cohorts thus far do not support increased suicidality in bipolar patients exposed to antidepressants. However, this does not exempt clinicians from careful monitoring of suicidality. There are possible constellations thinkable where activating antidepressant may put an individual on risk (eg, mixed depressive states, cyclothymic temperament,⁴⁸ and personality issues with risk-taking

or self-harming behaviors).

CONCLUSION

This article will not put an end to the discussion on the usefulness and risks of antidepressants in bipolar patients. Besides establishing or rejecting the claim that antidepressants are efficacious, we still need to further investigate their risks. Although at least modern antidepressants seem not to be associated with increased TEAS, increased cycling frequency and suicidality at large, we still need to identify predictors of those patients who either do well or worse on antidepressants. **CNS**

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