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Review Article

Antidepressants and suicidal behavior in bipolar disorder

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Patients with bipolar disorder are at very high risk for suicidal ideation, non-fatal suicidal behaviors and suicide and are frequently treated with antidepressants. However, no prospective, randomized, controlled study specifically evaluating an antidepressant on suicidality in bipolar disorder has yet been completed. Indeed, antidepressants have not yet been shown to reduce suicide attempts or suicide in depressive disorders and may increase suicidal behavior in pediatric, and possibly adult, major depressive disorder. Available data on the effects of antidepressants on suicidality in bipolar disorder are mixed. Considerable research indicates that mixed states are associated with suicidality and that antidepressants, especially when administered as monotherapy, are associated with both suicidality and manic conversion. In contrast, growing research suggests that antidepressants administered in combination with mood stabilizers may reduce depressive symptoms in patients with bipolar depression. Further, the only prospective, long-term study evaluating antidepressant treatment and mortality in bipolar disorder, although open-label, found antidepressants and/or antipsychotics in combination with lithium, but not lithium alone, reduced suicide in bipolar and unipolar patients (Angst F, et al. J Affect Disord 2002: 68: 167–181). We conclude that antidepressants may induce suicidality in a subset of persons with depressive (and probably anxious) presentations; that this induction may represent a form of manic conversion, and hence a bipolar phenotype, and that lithium's therapeutic properties may include the ability to prevent antidepressant-induced suicidality.

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Considerable clinical and epidemiological evidence indicates that adults with bipolar disorder are at a very high risk for suicidal ideation, non-fatal suicidal behaviors and suicide (1–19). The annual average suicide rate in men and women diagnosed with bipolar disorder was recently estimated to be more than 20 times that of the general population (0.40%/year versus 0.017%/year) (11). In a large,

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observational cohort study of all prescribed lithium and recorded suicides in Denmark from 1995 to 1999, Kessing et al. (18) reported that the crude suicide rate among patients who purchased at least one lithium prescription was over 11 times higher [rate ratio 11.5, 95% confidence interval (CI), 9.4–14.1] compared with persons who did not purchase lithium. Rates of lifetime suicide attempts and suicidal ideation among patients with bipolar disorder are much higher, at 25–50% and 80%, respectively. Although less extensively studied, available research shows adolescents with bipolar disorder are similarly at very high risk for suicidal ideation and behaviors (20–22). Indeed, although much research suggests major depressive disorder is the psychiatric condition most commonly associated with suicide, recent epidemiological data suggest bipolar disorder's association with suicide ideation and attempts may be stronger (3, 4, 11, 12, 17, 23).

Considerable clinical evidence also indicates that persons with bipolar disorder who seek treatment are frequently given antidepressants (10, 24–26). Of the first 258 patients followed prospectively for 1 year in the Stanley Foundation Bipolar Network, 53% received an antidepressant (24). Of the first 955 patients enrolled in the National Institute of Health Systematic Treatment Enhancement Program for Bipolar Disorder (NIMH STEP-BD), 38% received an antidepressant (25). Indeed, in some samples, patients with bipolar disorder are more likely to have received antidepressants than mood stabilizers. Of 2,839 bipolar disorder patients enrolled in the Stanley Center Bipolar Disorder Registry, 54% reported using an antidepressant, whereas 37% reported using an antimanic agent (10). Similarly, from October 1993 to January 1999, nearly half (47%) of the 3,797 recognized bipolar disorder patients from the California Medicaid (Medi-Cal) fee-for-services program did not use a mood stabilizer at the time they initiated antidepressant therapy (26).

Despite the substantial exposure of bipolar patients to antidepressants, the role of these agents in the treatment of bipolar disorder has been and continues to be controversial (2, 27–44). Antidepressants have been vastly under-studied in the treatment of bipolar disorder compared with depressive and anxiety disorders. Different experts and authoritative guidelines provide different recommendations regarding the use of these agents in this illness (31–35, 40–49). The only antidepressant agent approved by the US Food and Drug Administration (FDA) for use in bipolar disorder, fluoxetine, is approved for use in combination with olanzapine (as Symbyax) for the acute treatment of bipolar depression. No single antidepressant agent or antidepressant class was shown to be efficacious as monotherapy in any phase of bipolar disorder (depression, mania or maintenance) in two adequately powered, randomized, placebo-controlled trials, and no antidepressant is approved as monotherapy by the FDA for the treatment of any phase of the illness. Clinical research indicates that although some patients do well with these agents (29, 33, 36, 37, 42), response rates are generally low and some patients destabilize by switching into manic, hypomanic, mixed and rapid-cycling affective states (31, 32, 34, 35, 41, 43, 44). Perhaps most importantly, whereas substantial evidence suggests that lithium may reduce various aspects of suicidality in patients with bipolar disorder (11–13, 50–53), no clear evidence indicates that antidepressants have comparable effects (51, 53).

The controversy surrounding antidepressant use in bipolar disorder takes on greater relevance with recent re-analyses of pediatric depression trials showing that antidepressants may increase suicidal behaviors (but not suicide), while having limited efficacy in children and adolescents with major depressive disorder (54–59) – a subgroup of patients that may be at increased risk for developing bipolar disorder (60–63). Thus, in October 2004, the FDA issued a public health advisory requiring a black-box warning for all antidepressants about the risk for 'clinical worsening, suicidality, and unusual changes in behavior' in pediatric patients receiving antidepressants (64). The warning was subsequently extended to adults receiving antidepressants for major depressive disorder. Of note, the warning implies but does not outrightly contend what many experts who treat bipolar disorder have been suggesting for quite some time – that antidepressants may induce mood and behavioral dysregulation, including suicidality, by inducing various aspects of mania, including mixed states, in patients with occult or misdiagnosed bipolar disorder (65–69). Thus, in a section labelled 'screening patients for bipolar disorder', the FDA warning notes that 'a major depressive episode may be the initial presentation of bipolar disorder' and recommends that patients should be 'adequately screened to determine if they are at risk for bipolar disorder' because 'it is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder' (64). The warning then states 'whether any of the symptoms described above represents such a conversion is unknown'.

Very little systematic research has prospectively examined the effects of antidepressants on suicidality in bipolar disorder. However, growing clinical evidence indicates that: (i) bipolar disorder is much more common than realized, particularly when its soft spectrum forms are considered, and is frequently misdiagnosed as unipolar depression and other conditions (e.g., anxiety disorders) for which many antidepressants have FDA indications (70–74); (ii) mixed states are much more common than once thought, in part due to more accurate conceptualizations of their boundaries with pure affective (including depressive) states (67–69, 71–78); (iii) mixed states are frequently associated with suicidality, possibly more so than pure states (66–69, 79–81), and (iv) mixed states associated with suicidality, including subthreshold mixed states – or the co-occurrences of manic and depressive symptoms that do not meet the narrow DSM-IV definition of a mixed episode – may be induced or exacerbated by antidepressants (65, 66, 68, 69, 82). In addition, preliminary data suggest there are age effects on the phenomenology of bipolar disorder as well as the rate of antidepressant-induced switch induction, with greater rates of spontaneous mixed states and antidepressant-induced manic switches seen in pediatric compared with adult forms of the illness (83–87). At the same time, emerging clinical trial data suggest that, when administered to bipolar patients with mood stabilizers (which include second-generation antipsychotics), antidepressants may reduce depressive symptoms with a lower risk of inducing manic conversion than when administered as monotherapy agents (36, 42).

In this paper, we selectively review the literature in an attempt to assess the effect, if any, of antidepressants on suicidality in bipolar disorder. Because no prospective, randomized, controlled study of an antidepressant on suicidality in bipolar disorder has yet been completed, we will approach this issue by asking three questions: (i) Can antidepressants induce suicidality by inducing mixed states, especially when administered as monotherapy? (ii) Can antidepressants reduce suicidality by treating depressive symptoms, especially when administered in combination with mood stabilizers? (iii) Does age modify the response of bipolarity to antidepressants?

In asking these questions, we performed a MEDLINE search of the English-language literature for the years 1966–2005 using the following terms: 'activation', 'akathisia', 'antidepressant', 'bipolar', 'lithium', 'mania', 'mixed', 'suicide', 'suicidality', 'suicide attempt' and 'switch'. We reviewed reference lists of published studies to extract other articles. We also searched the FDA antidepressant database. Randomized prospective trials, large epidemiological studies and comprehensive reviews were selectively reviewed when available. However, as very little empirical research has explored the issues addressed in this review, including the three specific questions asked, retrospective chart reviews and open-label studies were used when more methodologically rigorous studies were not available.

Is there any evidence pharmacotherapy reduces suicidality in bipolar disorder?

As noted earlier, we found no published prospective, randomized, controlled study of an antidepressant in bipolar disorder that evaluated suicidality as a primary outcome measure. Indeed, bipolar patients with clinically significant suicidality have generally been excluded from pharmacotherapy trials. Moreover, most controlled studies of antidepressants in bipolar disorder did not use suicidality measures as secondary outcome scales or separately report changes on values of suicidality items from depressive symptom scales (29, 30, 43, 44, 88–98). Thus, very few controlled data have empirically addressed the effects of antidepressants upon suicidal ideation, suicidal behavior or suicide in persons with bipolar disorder.

One important exception is the placebo-controlled comparison of olanzapine and the combination of olanzapine and fluoxetine (OFC) in 833 patients with bipolar type I depression carried out by Tohen et al. (36). In this 8-week study, olanzapine was found to be superior to placebo and OFC superior to both olanzapine and placebo in reducing overall depressive symptoms as measured by the Montgomery Asperg Depression Rating Scale (MADRS). Although patients 'with suicidal behavior within the previous 3 months' were excluded from participation, effects on suicidality were reported. On the suicidal thoughts item of the MADRS, all three treatments showed comparable improvement (−0.9 for placebo, −1.1 for olanzapine and −1.2 for OFC), perhaps because baseline values were similarly low in all three groups. In addition, there were no reports of serious adverse events involving suicidal ideation, non-fatal suicidal behavior or suicide for any of the three treatment groups.

In contrast to the dearth of data on antidepressants in suicidality in bipolar disorder, mounting evidence has suggested that maintenance lithium treatment is effective in reducing suicidal ideation, suicide attempts and completed suicide in bipolar

patients (11–13, 18, 51–53, 99, 100). For example, in the large cohort study by Kessing et al. (18), in which patients who purchased at least one lithium prescription had a higher suicide rate than persons who never purchased lithium (crude rate ratio 11.5, 95% CI 9.4–14.1), it was also found that patients who purchased two or more lithium prescriptions had a 0.43-fold reduced suicide rate (95% CI 0.27–0.69) compared with patients who purchased lithium only once. Similarly, in a meta-analysis of 32 trials of 1,389 patients with mood disorders randomly assigned to receive lithium and 2,069 to receive other compounds, Cipriani et al. (52) reported that patients who received lithium were less likely to die by suicide [2 versus 11 suicides; odds ratio (OR) 0.26, 95% CI 0.09–0.77]. A composite measure of suicide plus deliberate self-harm was also lower in patients who received lithium (OR = 0.21, 95% CI 0.08–0.50). The authors also found 'no evidence of any difference between trials that included patients with unipolar depression and trials that included patients with bipolar disorder', suggesting that lithium's antisuicidality properties occur in unipolar as well as bipolar disorder.

Although comparable data do not yet exist for other mood stabilizers (11, 51, 53, 100, 101), it should be acknowledged that many of the lithium maintenance studies on which the above (and similar) analyses are based have methodological limitations (11–13, 51–53, 102, 103). These include the lack of study designs aimed specifically at assessing suicidal risk, lack of placebo controls, inclusion of patients with unipolar and schizoaffective as well as bipolar disorders, the administration of lithium by 'lithium clinics' (and thus by personnel who are highly skilled in providing treatment to bipolar patients), and frequent concomitant use of antipsychotics and antidepressants. These potential limitations should be kept in mind when evaluating studies of antidepressants in bipolar disorder and their effects on suicidality.

Factors associated with suicidality in bipolar disorder

Although no clinical trial of an antidepressant has specifically targeted suicidality reduction in bipolar disorder, extensive research has evaluated risk factors for suicidality in bipolar patients. Consistently identified risk factors have included: depression; mixed states; hospitalization for depression; alcohol and drug abuse; a prior suicide attempt; family history of suicidality; impulsive or aggressive traits; early age of illness onset; early physical or sexual abuse; Axis I, II and III comorbidities; greater duration of time spent affectively ill, and male gender (2, 7–9, 11–16, 22, 65–69, 79–81, 104–117).

Growing research has suggested mixed states in particular are associated with suicidality in patients with bipolar disorder (2, 22, 75, 79–81, 104, 117). Recent research using life charting of mood symptoms has shown that depressive episodes or subsyndromal depressive symptoms not only dominate the course of illness of persons seeking treatment for bipolar I and II disorders (118, 119), but also frequently co-occur or rapidly alternate with manic and hypomanic symptoms to form various types of mixed and rapid-cycling affective states (76, 78). Such states include mixed mania, mixed hypomania, mixed depression, agitated depression, ultra-rapid cycling and rapid mood switching (65–69, 75–81, 120–126). Although the precise nosological boundaries of these mood states are an active area of research, an increasing number of empirical studies have shown that these mixed states are often associated with suicidality. In addition, several studies have shown mixed mania – syndromal mania associated with prominent or syndromal depression – to be associated with greater suicidality than pure mania (79–81, 120). Perhaps more importantly, a growing number of studies have shown that depressive mixed states – syndromal major depression associated with hypomanic or manic symptoms (but not a manic syndrome) – may similarly be characterized by more suicidal thoughts or behaviors than pure or simple depressive states (i.e., major depression without hypomanic features) (69, 77, 123).

For example, Akiskal et al. (69) evaluated the relationship between intra-episode hypomanic symptoms and psychomotor agitation in 254 consecutive non-medicated unipolar patients with major depressive episodes (MDEs) with the Structured Clinical Interview for DSM-IV (SCID) and the Hypomania Interview Guide (HIGH-C). Three or more intra-MDE hypomanic symptoms were required for a diagnosis of a depressive mixed state. Agitated depression, defined as an MDE with a high psychomotor agitation score on the HIGH-C, was present in 19.7% of patients. The authors found a strong association between agitated depression and depressive mixed states (OR = 36.9); 90% of patients with agitated depression had a depressive mixed state compared with 20% of patients with non-agitated depression. Patients with agitated depression had significantly higher rates of suicidal ideation (62.0% versus 42.6%, respectively; OR = 2.1, 95% CI 1.1–4.1, $p < 0.05$). Among depressive mixed state symptoms, there was an association among suicidal ideation, psychomotor activation and racing

thoughts. Logistic regression showed that a depressive mixed state, talkativeness and suicidal ideation were the independent significant predictors of agitated depression. Akiskal et al. (69) concluded that agitated depression overlapped with the depressive mixed state and appeared to belong to the bipolar spectrum.

In a related study, Cassano et al. (127) compared the lifetime depressive and manic symptoms of 117 patients with remitted unipolar depression with those of 106 patients with bipolar I disorder (by DSM-IV and ICD-10 criteria), and found that the lifetime depressive and manic component scores were similarly correlated in both groups ($r = 0.40$, $p < 0.0001$ for unipolar patients; $r = 0.45$, $p < 0.001$ for bipolar patients). Moreover, among both groups of patients, the greater the number of manic/hypomanic items reported, the greater the likelihood of suicidal (and paranoid) ideation. For example, among the unipolar patients, for each manic/hypomanic item endorsed, the likelihood of suicidal ideation was increased by 4.2% (OR = 1.04, 95% CI 1.01–1.08, $p < 0.03$).

These findings suggest that depressive symptoms in combination with even minimal hypomanic symptoms may be more likely to be associated with suicidal ideation and attempts than pure or simple depressive symptoms (depressive symptoms without hypomanic symptoms), and raise broader questions about the relationships between mood state, mood syndromes, mood disorders and suicidality. Thus, many studies suggest depression is the most common mood state associated with suicide ideation, suicide attempts and completed suicide. The vast majority of these studies, however, did not assess for the presence of mixed states, including mixed states defined according to broader conceptualizations (2, 67–69). It is therefore unknown how many depressed patients with suicidality actually experience depressive mixed states, or even manic mixed states, as depression or dysphoria (irritability combined with depression) is often the predominant mood of a mixed state. One important question that remains unanswered therefore is how often depressive mixed states, such as agitated depression and mixed depression, are associated with suicidal ideation, suicidal behavior and/or suicide compared with pure or simple depressive states.

Is there any evidence that antidepressants increase suicidality in patients with bipolar disorder?

One potential risk factor for suicidality in bipolar disorder that received relatively little attention until recently is treatment with antidepressants. We found eight studies that addressed this question in some manner, which we describe below in chronological order (18, 26, 120, 128–132).

In the first study, a blind, retrospective chart review, Stoll et al. (128) compared the psychopathology of 49 consecutive inpatients with 'antidepressant-associated manic states' with 49 matched inpatients with spontaneous manias. Patients were included in the antidepressant-associated manic state group if they had received at least 3 days of antidepressant treatment within 2 weeks of hospital admission and were admitted with the DSM-III-R diagnoses of bipolar disorder, manic or mixed phase or schizoaffective disorder, bipolar type, manic phase. Similar proportions of patients in both groups had received mood stabilizers (70.8% in both groups) and antipsychotics (43.8% versus 45.8% in the antidepressant-associated versus spontaneous manic groups, respectively). Although antidepressant-associated manic states were statistically significantly less severe on several variables, including number of hours in seclusion/restraints, delusions, auditory hallucinations and bizarre behavior, they were associated with similar degrees of suicidal ideation.

In the second study, Goldberg et al. (120) explored correlates of suicidal ideation in 100 bipolar manic patients with mixed features, defined as at least two depressive symptoms other than suicidality during an acute manic episode. Suicidal ideation was present in 59% of mixed manic patients, and was significantly more common (nearly four times) among patients who took antidepressants in the week prior to admission than among those who did not.

In the third study, Akiskal et al. (129) compared 52 patients with major depression and antidepressant-associated-only hypomanias with 144 bipolar type II patients with spontaneous hypomanias, and found that patients with antidepressant-associated-only hypomanias were more likely to be admitted to the hospital for suicidal depression (80% versus 43%, $p = 0.002$). However, patients with antidepressant-associated-only hypomanias also had greater chronicity of depression, higher ratings on measures of depressive temperament, a significantly greater family history of suicide, and significantly less past treatment with lithium. Patients with spontaneous hypomanias had an earlier age of onset of illness, more hypomanic episodes, higher ratings on cyclothymic and hyperthymic temperaments, and higher rates of alcohol abuse. The two groups were otherwise indistinguishable regarding hypomania checklist scores and rates of familial bipolarity

In the fourth study, Shi et al. (26) compared the suicide attempt risk of antidepressant-treated

patients with recognized bipolar disorder and unrecognized bipolar disorder with that of non-bipolar patients among 24,460 adults with a new episode of antidepressant therapy in the California Medicaid fee-for-services program from 1993 to 1999. Recognized bipolar patients (n = 3,797) were defined as those who had received either a bipolar diagnosis or a mood stabilizer (lithium or valproate) on or before the initiation of antidepressant therapy; 47% received an antidepressant alone as initial therapy, 42% received two drugs and 10.5% received three or more drugs. Unrecognized bipolar patients (n = 1,582) were those who received their bipolar diagnosis or mood stabilizer therapy after antidepressant initiation; 77.5% of these patients received an antidepressant alone as initial drug therapy. Shi et al. found that unrecognized bipolar patients were significantly more likely to have attempted suicide (0.9%) than either recognized bipolar patients (0.3%) or non-bipolar patients (0.2%). Controlling for baseline health status, sex and gender, patients with recognized bipolar disorder were at no higher risk for suicide than non-bipolar patients, but were 66% less likely to attempt suicide than unrecognized bipolar patients (hazard ratio 0.32, 95% CI 0.14–0.71). Unrecognized bipolar patients were also more likely to attempt suicide than non-bipolar patients (hazard ratio 3.78, 95% CI 1.99–7.18). The authors additionally reported that the estimated difference in suicide risk between unrecognized and recognized bipolar patients increased when patients using mood stabilizers without a bipolar diagnosis were removed from the analysis (data not provided).

In the fifth study, the large cohort study by Kessing et al. (18) of all prescribed lithium users and recorded suicides in Denmark from 1995 to 1999, it was also found that purchasing antidepressant medication was associated with a substantially increased risk of suicide (risk ratio 6.07, 95% CI 5.10–7.21), regardless of whether or not lithium was purchased. The authors did not specify how many patients who purchased lithium also purchased an antidepressant, nor did they provide further comparative suicide data for patients who purchased an antidepressant only once versus two or more times. Nonetheless, they argued that the antidepressant–suicide association probably reflected the high risk of committing suicide during a depressive episode rather than a suicide-inducing effect of antidepressants. Indeed, purchasing antipsychotic and anxiolytic medication in addition to lithium was associated with a two-fold increased risk of suicide. Purchasing anticonvulsant medication, however, was not associated with an increased suicide risk.

In the sixth study, Goldberg et al. (130) used a cross-sectional design to examine patterns of psychotropic drug use relative to suicidal ideation among 1,000 bipolar patients in the NIMH STEP-BD program. Suicidal ideation was more prevalent among patients taking an antidepressant than those who were not (25% and 14%, respectively), as well as those taking a second-generation antipsychotic compared with those who were not (26% and 17%, respectively). By contrast, the presence of suicidal ideation was similar between patients taking versus not taking any lithium (22.2% and 25.8%, respectively) and between patients taking versus not taking any valproate (20.3% and 21.5%, respectively). Moreover, after controlling for other variables, lithium prescriptions were significantly more common among patients with suicidal ideation. The authors concluded that, for bipolar patients with suicidal ideation, community practitioners prescribed antidepressants and second-generation antipsychotics more often than other medications and reserved lithium for patients with more severe illness.

To investigate the hypothesis that new-onset suicidality was associated with increased antidepressant exposure, Bauer et al. (131) evaluated the first 425 participants in the NIMH STEP-BD program (out of the first 2,000 followed for 18 months) to experience a prospectively observed new-onset MDE without suicidal ideation. About half (52%) of the patients were receiving mood stabilizers (lithium, anticonvulsants or second-generation antipsychotics). Increased antidepressant exposure was defined as antidepressant initiation or dose increase. A total of 24 of these participants (5.6%) developed new-onset suicidality at follow-up, including two suicide attempts. There was no association between new-onset suicidality and increased antidepressant exposure or change in antidepressant exposure, and no association between new-onset suicidality and initiation of antidepressant treatment.

Most recently, in the seventh study, Aizenberg et al. (132) conducted a retrospective, matched, case-controlled study of the association between psychotropic exposure and suicide attempts in a cohort of elderly patients hospitalized with bipolar disorder over a 10-year period. All records of bipolar patients aged 65 years or more admitted to the Abarbanel Mental Health Centre, Bat-Yam, Israel from January 1995 to December 2004 were evaluated. The index group (n = 16, mean age 75 years) consisted of those patients who had attempted suicide in the month prior to admission. The control group (n = 16, mean age = 74 years)

consisted of the next admission of an elderly bipolar patient, matched for sex and age, who had not attempted suicide in the month prior to admission. Not surprisingly, the number of patients who had past suicide attempts was significantly greater in the index group [seven (43.8%) versus two (12.5%) patients, $p = 0.039$]. Among the treated subjects (13 in each group), the distribution of psychotropic medications, including antidepressants, did not differ significantly between the two groups, except that the index group was less likely to have received antidepressants and mood stabilizers in combination [two (12.5%) versus seven patients (43.8%), $p = 0.047$].

Although naturalistic and thus methodologically limited, five of the eight studies found a positive relationship between antidepressant treatment and increased suicidality in patients with definite or probable bipolarity (18, 26, 120, 129, 130). In four of these studies, the association could be explained by 'confounding by indication', in which the higher rate of suicidality among antidepressant-treated patients may have led to their higher rate of antidepressant exposure (18, 120, 129, 130). If valid, it would be important to document the occurrence of such a phenomenon because the effects of antidepressants on suicidality in bipolar disorder are unknown.

The one study to find a possible relationship between antidepressant exposure and suicidality that could not be attributed to confounding by indication did so by comparing unrecognized bipolar patients receiving primarily antidepressant monotherapy with recognized bipolar patients receiving roughly equal proportions of antidepressant mood stabilizer combination therapy and antidepressant monotherapy (26). The two studies that did not find a positive relationship between antidepressant exposure and suicidality found either no relationship in recognized bipolar patients with new-onset, non-suicidal MDEs receiving antidepressants in combination with mood stabilizers about half the time (131), or no relationship between suicide attempt rate and antidepressant exposure in general but a decrease in suicide attempt rate with increased exposure to antidepressant-mood stabilizer combination treatment, also in recognized bipolar patients (132). Taken together, these three studies suggest that antidepressants might increase suicidality in unrecognized bipolar patients when administered as monotherapy (26), but not when administered with mood stabilizers in bipolar patients with recognized illness (131, 132). In light of the methodological limitations of these studies, however, further research into this issue is greatly needed.

Can antidepressants induce suicidality by inducing the switch process?

No randomized, controlled studies have been conducted, to our knowledge, with the explicit aim of determining whether antidepressants can induce hypomania, mania, mixed mania or other mixed states in persons with or without bipolar disorder (also referred to as 'switch induction' or 'manic conversion'). Moreover, whether or not antidepressants can induce the switch process depends in part on how hypomania, mania, mixed states and bipolar disorder itself are defined (43, 44). As discussed by many authorities, the DSM-IV definitions of bipolar disorder in general and of individual mood episodes in particular (especially of hypomania and mixed episodes) need modification if they are to accurately represent the disease (67–69, 71–78, 127). Nonetheless, even with DSM or ICD definitions, considerable clinical evidence suggests that antidepressants as a class do induce hypomanic, manic and mixed episodes in some persons with bipolar disorder (reviewed in 34, 35). This has been reported for all antidepressants, all aspects of the switch process (induction of hypomanic symptoms; hypomanic, manic and mixed episodes; and increased rates of mood cycling) and in persons of all ages from all aspects of the bipolar spectrum (from recurrent unipolar depression to subthreshold bipolar II disorder to bipolar II disorder to bipolar I disorder).

Several lines of evidence in particular provide support for antidepressant-induced manic conversion. First, the two randomized, placebo-controlled studies of antidepressant monotherapy in phases of bipolar disorder other than depression that we are aware of as having been published to date suggest that these agents worsen acute manic symptoms and increase the frequency of manic episodes (133, 134). In the only placebo-controlled monotherapy study of an antidepressant in acute mania, Klein, in 1961, randomized 13 inpatients in the manic phase of manic-depressive illness to imipramine, chlorpromazine or placebo for 6 weeks (133). Imipramine was titrated to 300 mg/day; chlorpromazine was titrated to 1200 mg/day. A global outcome rating showed that, compared with placebo, patients significantly improved with chlorpromazine, but non-significantly worsened on imipramine. In the only placebo-controlled antidepressant monotherapy maintenance trial in bipolar disorder, Prien et al. (134) in 1973, randomized 35 bipolar patients to 20 months of treatment with lithium ($n = 17$), imipramine ($n = 9$) or placebo ($n = 9$); 67% of the imipramine group had a manic episode,

compared with 12% of the lithium group and 33% of the placebo group. (By contrast, depression occurred in none of the imipramine group, 12% of the lithium group and 55% of the placebo group.) Taken together, these data suggest that imipramine monotherapy may increase both acute manic symptoms and the frequency of manic episodes; however, the data are limited by their small numbers.

A second line of evidence supporting the ability of antidepressants to induce manic conversion are randomized trial data showing that switch rates increase with the duration of antidepressant treatment. In the imipramine trial described above, the risk for manic conversion increased over time and was not limited to the period right after antidepressant initiation (134). This has also been reported when antidepressants are given adjunctively with mood stabilizers. During 288 10-week trials and 87 continuation trials in 184 depressed bipolar patients in which bupropion, sertraline, or venlafaxine were added to ongoing mood stabilizers, the switch rate was nearly doubled for continuation treatment trials (22% full hypomanias and 15% manias) compared with acute treatment (11% and 8%, respectively) (43).

The third line of evidence supporting antidepressant-induced switch induction concerns controlled clinical trial and pharmacoepidemiological data suggesting antidepressants from different classes, and hence with different putative mechanisms of action, may differentially affect manic conversion rates. Thus, antidepressants with 'broader' or 'dual' spectrums of action or that potently block norepinephrine uptake [i.e., tricyclic antidepressants (TCAs) and venlafaxine (135, 136)] appear to be more likely to induce manic conversion than those with 'narrower' modes of action or less potent noradrenergic effects [i.e., serotonin selective reuptake inhibitors (SSRIs) and bupropion] (43, 44, 96, 98). A meta-analysis conducted by Peet in 1994 comparing the liability of different antidepressant drug classes to induce mania among bipolar depressed patients found that TCAs were associated with a significantly higher rate (11.2%) than SSRIs (3.7%), the rate of which was comparable with that of placebo (137). A more recent meta-analysis conducted by Gijsman et al. (42) of 12 randomized trials of antidepressants in the short-term treatment of bipolar depression in a total of 1,088 patients (75% of whom were receiving a concurrent mood stabilizer) found that the overall switch rate for antidepressants (3.8%) was comparable with that for placebo (4.7%) (difference = 0.9%, 95% CI −2.0–3.8), but that the switch rate for TCAs (10%) was higher than that for all other antidepressants combined (3.2%) (risk ratio 2.92, 95% CI 1.28–6.72; absolute risk difference 6.8%, 95% CI 1.7–11.9). In a 6-week comparison of venlafaxine and paroxetine in bipolar I depression, Vieta et al. (98) reported that patients treated with venlafaxine (n = 30) showed similar response rates (48%) but higher rates of manic switch (13%) than those treated with paroxetine (n = 30; 43% and 3%, respectively). The switch rates, however, were not statistically significantly different (analytic data not provided). In a 10-week comparison of sertraline, bupropion and venlafaxine in 174 patients with bipolar I, II or not otherwise specified (NOS) depression, response rates were similar for the three drugs (49.0–53.4%), but there was a statistically significantly increased risk for hypomanic/manic switches (defined as ≥ 2-point increase on the Clinical Global Impression Modified for Bipolar Disorder Mania Severity Rating) on venlafaxine (29.2%) compared with bupropion (9.8%) and sertraline (8.6%) ($\chi^2 = 12.45$, df = 2, p = 0.002) (44).

Pharmacoepidemiological data are consistent with the above clinical trial data. Martin et al. (86) evaluated the risk of conversion to mania by antidepressant class (and age; see below) in a national database involving 87,920 mental health users aged 5–29 years receiving antidepressants for anxiety or non-bipolar depressive disorders during a median follow-up of 41 weeks (range 8–251). Manic conversion, defined as a new diagnosis of bipolar disorder, occurred in 5.4% of patients, or 6.0%/year. The conversion rate among antidepressant-treated patients (7.7%/year) was three-fold that among patients unexposed to antidepressants (2.5%/year; rate ratio 3.1, 95% CI 3.0–3.2). Importantly, conversion rates differed by medication type: they were higher for TCAs (9.3%/year) and other antidepressants (8.7%/year) and lower for SSRIs (7.5%/year).

A fourth line of evidence supporting antidepressant-induced manic conversion concerns data showing that age may affect this phenomenon. In the above noted pharmacoepidemiological study, Martin et al. (86) found that children aged 5–14 years were at significantly higher risk of manic conversion (conversion rate ratio 2.9, 95% CI 2.8–3.1) than persons aged 15–25 years (rate ratio 1.4, 95% CI 1.3–1.5, p < 0.001). Further analyses revealed significant negative interactions for age on conversion hazards for the pooled antidepressant, SSRI and other antidepressant groups, but not the TCA group. Among the former groups, age was inversely related to conversion hazards, reaching maximum values in 10–14-year-old children.

These data are consistent with preliminary clinical observations that the earlier and more extensive use of antidepressants (and possibly stimulants) in younger populations may lead to an earlier expression of bipolar disorder (87, 138, 139). Cicero et al. (138) evaluated all consecutive admissions with a diagnosis of bipolar disorder to a university-affiliated children's hospital regarding age of onset of illness and previous exposure to antidepressants and stimulants. Children who had received prior antidepressants or stimulants had an earlier diagnosis of bipolar disorder (10.7 years) than non-exposed children (12.7 years). Stimulants were tolerated for a longer duration than antidepressants (5.5 months versus 6.7 months). Indeed, Reichart and Nolen suggested that prepubertal bipolar disorder is more prevalent in the USA than the Netherlands due to the greater use of antidepressants and stimulants for depression and attention-deficit hyperactivity disorder by US children and the subsequent induction of manic conversion by these drugs (139).

Yet another line of evidence supporting antidepressant-induced manic conversion is that polymorphisms of the serotonin transporter gene have been associated with antidepressant-associated mania, rapid-cycling and agitation (140–142). Thus, a genetic factor has linked antidepressant exposure with manic conversion. Genetic variation might further explain the individual heterogeneity clinically observed with this phenomenon.

In short, although some authorities continue to doubt the ability of antidepressants to induce the switch process, growing evidence suggests that a subset of bipolar patients may develop new or worsening manic symptoms with antidepressant exposure (34, 35). Importantly, this worsening may be expressed as increased hypomanic, manic, mixed, cycling and/or depressive symptoms, and thus, as various admixtures and combinations of manic and depressive, inducing suicidal, symptoms. How small or large this subgroup of patients is remains unknown. Moreover, the phenomenology of antidepressant-induced manic conversion has received only limited study in adults (128) and virtually no systematic study in children. Thus, how often antidepressant-induced manic conversions are associated with suicidality or other depressive symptoms is not definitely known at this time.

Nonetheless, numerous clinicians with expertise in bipolar disorder have reported the induction of mixed states with suicidality by antidepressants for at least 15 years (65, 66, 143, 144). In 1987, for example, Akiskal and Mallya described 25 young and middle-aged adults referred to their mood disorder clinic for depressions 'resistant' to TCAs (65). Rather, patients had mixed states characterized by 'unrelenting dysphoria, severe agitation, refractory anxiety, unendurable sexual excitement, intractable insomnia, and suicidal obsessions and impulses'. Patients responded to reduction or elimination of TCAs and institution of lithium or carbamazepine with or without low-dose, short-term neuroleptics. Koukopoulos et al. (66) similarly reported 45 patients with bipolar disorder who experienced a 'mixed depressive syndrome' with depressive and manic symptoms that met DSM-III-R criteria for major depression but not for mania. Patients deteriorated when treated with antidepressants – displaying increased agitation, insomnia and, in some cases, suicidal impulses – and responded to low-dose antipsychotics, lithium, antiepileptic drugs and electroconvulsive therapy. Importantly, similar suicidal mixed states coincident with antidepressant treatment have also been described in children and adolescents. Faedda et al. (144) reported 82 children (mean age 10.2 years) with 'modified' bipolar disorder, 33 (40.2%) of whom met criteria for treatment-emergent mania upon exposure to antidepressants or stimulants. Some of these children also displayed 'prominent suicidal, homicidal, or psychotic behavior'.

Despite the frequent reports of suicidality co-occurring with mixed depressive states and the not uncommon reports of suicidal mixed states occurring in the context of antidepressant use, modern studies of antidepressants in mood disorder patients have not routinely used systematic measures of manic symptoms to assess whether and how often antidepressant-associated suicidality represents mixed states. Moreover, if a patient displays suicidal ideation or behavior in a study of an antidepressant agent, it is usually not customary that the patient be evaluated – either clinically or systemically with structured interviews or scales – for hypomanic or manic symptoms, and thus, for hypomanic, manic and mixed syndromes. Thus, it is presently unknown from clinical trials of antidepressants in bipolar or major depressive disorders how often the development of suicidality with antidepressant treatment represents the development of a mixed state.

Nonetheless, several investigators have observed that the phenomenologies of both spontaneous and antidepressant-associated mixed states (68, 69) are similar to that of the activation syndromes with suicidality occurring with antidepressant treatment in apparently unipolar patients (145–148). In addition to having new onset or exacerbated

suicidality, the latter patients are often described as being dysphoric, energized and/or fatigued, restless, and as having insomnia and/or hypersomnia. Thus, in an attempt to determine whether antidepressants might induce suicidality by causing an 'activation syndrome', the FDA analysis of suicidal events in the pediatric depression trials also evaluated 'treatment emergent agitation or hostility' (54). Although none of the individual trials had a statistically significant result, the overall risk ratios for all antidepressants (risk ratio 1.79, 95% CI 1.16–2.76), all SSRIs (risk ratio 2.34, 95% CI 1.24–4.41) and for paroxetine (risk ratio 7.69, 95% CI 1.80–32.99) were statistically significant (Table 1). The relationship between suicidality and agitation/hostility could not be evaluated because information on the timing of the latter events was not available. However, the association of antidepressants with both suicidality and agitation/hostility in pediatric depression is important in the light of growing research that suggests that irritability is more common than euphoria as the mood disturbance in mania (2), and that behavioral activation, rather than euphoria, may be the core feature of mania (149).

By contrast, the relationships among antidepressant treatment, suicidality and akathisia – another activation syndrome often implicated as a cause of antidepressant-induced suicidality – remains unclear, especially in bipolar disorder (150–152). Indeed, the relationship between akathisia and suicidality is controversial (150, 152). Although suicidality has been reported to be associated with akathisia caused by both antipsychotics and antidepressants, a 2001 review of 83 references could not unequivocally link suicidal behavior to akathisia (150). Similarly, although authorities have noted the phenomenological overlap between akathisia and mixed states, no empirical studies have systematically compared the phenomenology or evaluated the co-occurrence of the two states. Moreover, no studies have evaluated whether there are differences in the suicidality associated with akathisia apparently induced by antidepressants versus that induced by traditional antipsychotics versus that induced by second-generation antipsychotics, or in akathisia-induced suicidality occurring in patients with bipolar versus depressive versus other disorders. The FDA analyses of the pediatric depression trials, to our knowledge, have not yet carried out analyses for mania or akathisia comparable with those for suicidality or agitation/hostility (54). In addition, we found no reports of antidepressant-induced akathisia associated with suicidality in patients with bipolar disorder (153), including in the study by Tohen et al. (36) of olanzapine and fluoxetine in bipolar depression (in which movement disorder scales were used). However, Scholten and Setlen recently reported a series of five patients developing suicide attempts (n = 3) or ideation (n = 2), along with 'akathisia, agitation, insomnia, and dysphoria', shortly after beginning aripiprazole (154), an atypical antipsychotic with antimanic properties that has been hypothesized to also have antidepressant properties (155). In short, greater empirical attention should be devoted to the relationship between psychotropically induced akathisia, mixed states and suicidality.

Is there any evidence that antidepressants reduce suicidality in bipolar disorder?

Several lines of indirect evidence might be taken to suggest that antidepressants may reduce some aspects of suicidality in bipolar disorder. First, a number of epidemiological studies that have analyzed general population trends in suicide rates coincident with antidepressant use have found that suicide rates decline as antidepressant use increases

Table 1. Overall risk estimates of 'definitive suicidal behavior/ideation' and 'treatment-emergent agitation or hostility' and whether familial bipolar disorder was excluded in pediatric major depressive disorder trials by antidepressant[a]

Drug	Suicidality relative risk (95% CI)	Agitation/hostility relative risk (95% CI)	Familial bipolar disorder excluded in no. of trials
Fluoxetine	0.89 (0.36, 2.19)	1.01 (0.40, 2.55)	2 of 3 (Yes)
Paroxetine	2.15 (0.71, 6.52)	7.69 (1.80, 32.99)	2 of 2 (Yes)
Sertraline	2.16 (0.48, 9.62)	2.92 (0.31, 27.83)	2 of 2 (No)
Citalopram	1.37 (0.53, 3.50)	1.87 (0.34, 10.13)	2 of 2 (No)
Venlafaxine	8.84 (1.12, 69.51)	2.86 (0.78, 10.44)	2 of 2 (Yes)
Mirtazapine	1.58 (0.06, 38.37)	0.52 (0.03, 8.27)	1 of 1 (Yes)
Nefazodone[b]		1.09 (0.53, 2.25)	2 of 2 (Yes)

[a]From refs 54, 187.
[b]Value not reported, presumably because trials did not evaluate 'definitive suicidal behavior/ideation'.

– in adults as well as in adolescents and elderly people (156–163). Some authorities have argued that such data suggest that antidepressants may have antisuicide properties, at least in unipolar depression. Although none of these studies assessed psychiatric diagnoses or whether antidepressants were taken in conjunction with mood stabilizers or antipsychotics, it is possible that many of the persons in these studies who took antidepressants and did not commit suicide had bipolar disorder, thereby supporting the possibility that these drugs also have antisuicide properties in bipolar disorder. Conversely, it is also possible that the individuals who committed suicide and were taking antidepressants had elevated rates of bipolarity. It is therefore intriguing to note that several studies comparing suicide rates across different antidepressant classes found similar or higher suicide rates among persons receiving TCAs than among those receiving SSRIs (164–166), paralleling clinical trial data showing TCAs to have higher switch rates than SSRIs (42, 137). For example, Isacsson et al. (166) evaluated different antidepressants in the toxicological screenings of 14,857 suicides compared with 26,422 cases of death by accident or natural causes in Sweden from 1992 to 2000 and found that SSRIs had lower odds ratios than the other antidepressants. In the 52 suicides under 15 years of age, no SSRIs were detected. In the 15–19-year-old age group, SSRIs had a lower relative risk of suicides compared with non-SSRIs. Explanations provided for this finding included the possibility that persons receiving SSRIs obtained more sophisticated treatment, the suicide attempts with SSRIs were less likely to be lethal because of their lower toxicity and that TCAs were prescribed to more severe or treatment-resistant cases of depression. One possibility that was not considered is that SSRIs may have a lower rate of switching into mixed states.

However, factors other than changes in antidepressant treatment have been hypothesized to account for falling suicide rates. Furthermore, some epidemiological datasets have suggested suicide rates were either decreasing before antidepressant use increased (167) or were unrelated to antidepressant use patterns (163, 168, 169). In short, epidemiological studies showing associations between increases in antidepressant use and decreases in suicide rates probably should not be taken as direct evidence of the antisuicidal properties of antidepressants in bipolar disorder.

A second line of indirect evidence suggesting that antidepressants might reduce suicidality in bipolar disorder is that several double-blind, placebo-control trials of antidepressants in adult patients with presumptive major depressive disorder showed active drug was superior to placebo in reducing suicidal ideation (51). In addition, two large studies assessing the relationship between antidepressant use and suicidality during clinical use in patients with depressive disorders concluded that antidepressants might confer protective effects against suicide attempts (170) or suicide (171). Based on recent studies suggesting that 25–50% of patients with depressive episodes may have hypomanic symptoms at some time in their lives (70, 73, 127), it is possible that some of the apparently unipolar patients in these studies in fact had occult or unrecognized bipolar disorder. It might therefore be argued that antidepressant monotherapy may reduce suicidal ideation, at least in the short-term, in some patients with 'ultra soft-spectrum' bipolar disorder. As noted earlier, some authorities have argued that antidepressant monotherapy is effective for bipolar disorder II (33).

However, a growing number of analyses of antidepressant clinical trial data suggest these agents do not reduce suicide or suicide attempts in adult patients with major depressive or anxiety disorders enrolled in registration trials (51, 53, 172–175) or, as in children and adolescents, may even increase these events (176–179). In the largest of these analyses conducted to date, a meta-analysis of 702 randomized, controlled trials of SSRIs in 87,650 adults with any non-bipolar condition (414 of the trials were conducted in disorders other then major depressive conditions), Fergusson et al. (179) found a significant increase in the odds of suicide attempts for patients receiving SSRIs (OR = 2.28, 95% CI 1.14–4.55) than for those receiving placebo, but no difference in the odds ratio of suicide attempts between SSRI-treated patients versus TCA-treated patients (OR = 0.88, 95% CI 0.54–1.42). There was no difference between SSRIs and placebo in the odds ratio for suicide (OR = 0.95, 95% CI 0.24–3.78). The odds ratio for suicide for SSRIs compared with TCAs was 1.08 (95% CI 0.28–4.09).

Even those analyses that found a greater, and statistically significant, reduction in depressive symptoms with antidepressant than placebo, and statistically significant similar rates of suicide and/or suicide attempts, often found numerically greater rates of suicides and/or suicide attempts with antidepressants compared with placebo. Thus, Khan et al. (172), in 2000, used the FDA database to assess suicides, suicide attempts and depressive symptom reduction of the seven antidepressants approved by the FDA from 1 January 1987 to 13 December 1997. Although the reduction in depressive symptoms was 40.7% with investigational

drugs, 41.7% with active comparators and 30.9% with placebo, and rates of suicide ($\chi^2 = 1.53$, p = 0.46) and attempted suicide ($\chi^2 = 0.90$, p = 0.64) did not differ significantly among the placebo- and drug-treated groups, rates of suicide and attempted suicide were numerically lower with placebo than with antidepressants: 0.4% and 2.7% with placebo, 0.7% and 3.4% with active comparators, and 0.8% and 2.8% with investigational antidepressants, respectively. In a subsequent replication analysis using comparable data for citalopram and venlafaxine, Khan et al. (173) again found that both investigational and comparator antidepressants reduced depressive symptoms compared with placebo, but that there were no significant differences in rates of suicide ($\chi^2 = 0.41$, p = NS) or attempted suicide ($\chi^2 = 0.05$, p = NS). However, the rate of suicide was again numerically lower with placebo (0.5%) than with active comparators (0.9%) and investigational antidepressants (0.6%).

Taken together, analyses of registration trials in adults with depressive disorders suggest antidepressants decrease depressive symptoms without decreasing suicide risk. Analyses of trials in patients with depressive and other (i.e., anxiety) disorders suggest antidepressants may increase suicide risk. Importantly, how much antidepressant-associated suicidality is due to the inclusion of apparently unipolar patients with occult or unrecognized bipolar disorder who became suicidal by experiencing antidepressant-induced switches into unrecognized mixed states is unknown. Nonetheless, in the light of possibly higher than realized rates of occult bipolarity in these trials, these data suggest that antidepressant monotherapy in soft-spectrum bipolar patients either has no effect upon suicidal behavior or may increase it.

A third line of indirect evidence suggesting that antidepressants might reduce suicidality in bipolar disorder is that, when given in combination with mood stabilizers, they can further reduce depressive symptoms without increasing the risk of manic conversion. In Gijsman et al.'s (42) recent meta-analysis of 12 controlled antidepressant trials in the short-term treatment of bipolar depression, in which 75% of 1,088 patients were given a concomitant mood stabilizer or atypical antipsychotic, antidepressants were more effective than placebo without inducing more switching into mania [the switch rate was 3.8% for antidepressants and 4.7% for placebo (difference = 0.9%, 95% CI −2.0–3.8)]. In one of the few controlled studies to use an a priori definition of manic conversion, Tohen et al. randomized patients with bipolar type I depression to olanzapine, placebo and olanzapine in combination with fluoxetine (OFC) (36). As noted earlier, olanzapine was more effective than placebo and OFC was more effective than both olanzapine alone and placebo in decreasing depressive symptoms. Treatment emergent mania [defined as a Young Mania Rating Scale (YMRS) score < 15 at baseline and ≥ 15 subsequently] did not differ among the three groups (placebo 6.7%, olanzapine 5.7%, OFC 6.4%) and suicidality measures decreased similarly in all three treatment groups. Changes in depressive symptoms and suicidality in patients experiencing switches, however, were not reported.

In the largest controlled maintenance study of an antidepressant in combination with a mood stabilizer conducted to date, Prien et al. (91) randomized 117 bipolar patients to 2 years of treatment with lithium (n = 45), imipramine (n = 35) or the combination (n = 37). In the initial analysis, which compared the proportions of patients experiencing mood recurrences and did not account for the length of time until a recurrence or premature termination not due to recurrence, the major finding was an interaction between treatment and type of index episode. Specifically, lithium and the combination were superior to imipramine in preventing relapse in patients with index manic episodes, whereas all three treatments were equally effective in preventing relapse in patients with index depressive episodes (91). In a subsequent reanalysis using survival analytic techniques, which accounted for these limitations, lithium and the combination were again found to be superior to imipramine in patients with index manic episodes (92). The estimated median remission time for patients on imipramine was 3.1 months compared with >12.6 months on lithium and 14.8 months on the combination. However, in patients with index depressive episodes, the combination was found to be superior to imipramine, and lithium was indistinguishable from imipramine (92). The estimated median remission time for the combination was 7.6 months, compared with 4.8 months for imipramine and 3.4 months for lithium. Neither analysis reported suicidality measures or adverse events related to self-harm, but the authors of the re-analysis concluded that the 'combination appeared to be particularly effective in patients with a depressive index episode' (92).

We found only one study that addressed the effect of long-term antidepressant-mood stabilizer combined therapy on suicide mortality. Angst et al. (9, 19) assessed standardized mortality ratios in a 34–38-year follow-up of 220 bipolar patients and 186 unipolar patients who had been hospitalized for a mood episode. Nearly two-thirds of the bipolar patients were receiving medication

(62%), compared with a little over a third of unipolar patients (38%). Of the bipolar patients receiving medication, 45% received lithium plus an antipsychotic and/or antidepressant, 16% received lithium alone, 15% an antidepressant alone, 13% an antipsychotic and an antidepressant, and 11% an antipsychotic alone. Medication treatment was associated with reduced suicide rates for both bipolar and unipolar patients. Moreover, all drug-treated subgroups showed a significant reduction of suicides, with a very strong effect in patients treated with antidepressants, antidepressants plus antipsychotics, or lithium plus antidepressants and/or antipsychotics. A regression analysis found a strong reduction in completed suicides for combination therapy but not for lithium alone. (The effect to which antidepressants may have exerted an antisuicide effect independent of lithium or antipsychotics could not be estimated.)

The above findings regarding combination antidepressant-mood stabilizer therapy are important in view of the recent identification of a subgroup of bipolar patients who appear to need such therapy as maintenance treatment in order to prevent depressive relapse (37, 180). Altshuler et al. (37) followed 84 bipolar patients who achieved remission from a depressive episode with the addition of an antidepressant to an ongoing mood stabilizer regimen prospectively for 1 year; 43 patients stopped antidepressant treatment within 6 months of remission and 41 continued antidepressant treatment beyond 6 months. Shorter antidepressant exposure following successful treatment was associated with a significantly shorter time to depressive relapse. One year after successful antidepressant treatment, 70% of the group that stopped antidepressants had experienced a depressive relapse, compared with 30% of the group that continued antidepressant treatment. Moreover, the continuing use of antidepressants was not associated with a higher risk of manic relapse. These data suggest that there may be a subgroup of bipolar patients who need long-term treatment with antidepressants in combination with mood stabilizers and/or antipsychotics to reduce depressive relapses and, taken together with Angst et al.'s (9, 19) long-term observations, possibly to reduce suicide rates.

Two important and related issues in the treatment of bipolar disorder that have not yet been addressed by combination studies are (i) the completeness of mood stabilization (i.e., the degree of absence of manic symptoms) that should be achieved before antidepressant addition, and (ii) the temporal relationship between exposure to antidepressants and mood stabilizers. Thus, in the Tohen et al. (36, 181) OFC study, although rates of treatment-emergent mania were the same for patients receiving olanzapine, placebo and OFC, several features were found to be associated with manic switch. These were baseline YMRS scores ≥12, female gender and the presence of psychotic features. Because patients with a baseline YMRS score ≥12 had a 4.5-times increased risk of treatment-emergent mania compared with those with a YMRS score <12, the authors concluded that depressed patients with 'mixed features' should be closely monitored for treatment-emergent mania during pharmacotherapy (181). Regarding the temporal relationship, Winsberg et al. (182) showed that prior antidepressant (or stimulant) monotherapy might adversely affect subsequent mood stabilizer response. They treated 19 patients with bipolar II depression with valproate and found that medication-naïve patients tended to have a higher response rate (82%) than patients naïve to mood stabilizers (38%), who had experienced prior trials of antidepressants and/or stimulants. Winsberg et al.'s observations raise the question of whether antidepressant monotherapy could have subsequent adverse effects on mood stability and treatment responsiveness, and hence suicidality, in persons with bipolar disorder, including those who eventually receive mood stabilizer monotherapy as well as combination therapy.

Could antidepressant-induced suicidality in pediatric major depression represent prodromal bipolar disorder?

In a recent meta-analysis of published and unpublished data from randomized controlled trials that evaluated a serotonin reuptake inhibitor versus placebo in children aged 5–18 years, Whittington et al. (56) concluded that only two studies of fluoxetine conducted by Emslie et al. (183, 184) were found to be both efficacious in reducing depressive symptoms and safe in being associated with fewer serious adverse events. The authors argued that the other studies showed weak, equivocal or no separation between drug and placebo on primary outcome measures, along with increased rates of serious adverse events, including suicidal ideation and attempts. [In addition to the two fluoxetine studies (183, 184), one of two escitalopram studies (185) and two sertraline studies when combined for analysis (as planned *a priori*; 186) were positive; all other studies were failed or negative, including the two sertraline studies when analyzed on their own (57, 58).] The FDA meta-analysis of suicide ideation and behavior in the pediatric antidepressant trials showed a small but

significant class effect with more such events occurring in youths on antidepressants than placebo (for all indications: risk ratio 1.78, 95% CI 1.14–2.77) (54). The lowest risk was for fluoxetine (risk ratio 0.92, 95% CI 0.39–29) and the highest was for venlafaxine (risk ratio 4.97, 95% CI 1.09–22.72). Moreover, venlafaxine was the only drug that did not include 1 in the 95% CI of its risk estimate. Similar risk ratios were seen when only the major depressive disorder trials were analyzed (Table 1).

The more positive antidepressant response seen in the fluoxetine studies, in combination with the lower rate of suicidality, has been hypothesized to be due to a variety of variables, including methodological differences among the trials (reviewed in 57–59). One important methodological difference concerns subject selection. In the Emslie et al. (183, 184) studies, extra steps were taken to reduce the chances that subjects did not have prodromal or early onset occult bipolar disorder. These included extensive diagnostic evaluations and the exclusion of children with a family history of bipolar disorder in at least one first-degree relative. According to the FDA database, none of the other SSRI antidepressant studies required the latter exclusion (187). Thus, they may have included higher rates of youths with early onset bipolar disorder who switched upon antidepressant exposure, but whose switching manifested as suicidality.

By contrast, the venlafaxine, nefazodone and mirtazapine trials also excluded patients with family histories of bipolar disorder (187). As noted earlier, venlafaxine has dual uptake blocking properties and has been associated with numerically or statistically significantly higher rates of manic conversion than paroxetine, sertraline and bupropion in clinical trials of bipolar patients (43, 44, 98). Being a dual uptake inhibitor, venlafaxine's greater likelihood to induce the switch process compared with 'single' action agents may have overcome the incompletely reduced risk of exclusion of familial bipolar disorder in the pediatric depression trials. Indeed, some authorities have argued that paroxetine and mirtazapine also have dual action pharmacological profiles [serotonin-norepinephrine reuptake inhibition for paroxetine and serotonin receptor antagonism with norepinephrine agonism (via α_2 antagonism) for mirtazapine (136, 188)], possibly explaining in part the higher suicidality and/or agitation/hostility rates for these drugs (Table 1).

It is thus noteworthy that Geller et al. (62) hypothesized that one reason prepubertal depression was unresponsive to TCAs was that it often represented early onset bipolar disorder. In a follow-up of 72 children who had participated in the negative trial of nortriptyline and who had a prepubertal diagnosis of major depressive disorder, 33.3% displayed a bipolar spectrum disorder at 9.9 years follow-up (62). Subjects who had prepubertal diagnoses of major depressive disorder also had significantly higher rates of any bipolar disorder and suicidality than normal subjects. In addition, a history of parental and grandparental mania predicted bipolar I disorder.

Although pharmacoepidemiological data suggest children and adolescents are more likely to develop manic conversion upon antidepressant exposure than adults (86), it is presently unknown if the same is true for the development of suicidality. In their computerized study of 82,285 episodes of antidepressant treatment among 65,103 outpatients with depressive disorders and suicidality, Simon et al. (170) found that suicide attempts, but not suicides, were more common in children and adolescents than adults. Specifically, the probability of suicide was significantly higher in male patients (OR = 6.6, 95% CI 2.9–14.7) but did not vary across age categories, whereas the probability of suicide attempts did not vary with gender but was strongly related to young age ($Z = 3.18$, $p < 0.001$) (170). There were 314 serious suicide attempts per 100,000 in children and adolescents (95% CI 160–468), compared with 78 per 100,000 in adults (95% CI 58–98). It is also unknown whether antidepressant-associated suicidality in a child is more or less likely to represent bipolarity than it is in an adult. Considerable clinical research, however, suggests childhood and possibly adolescent forms of bipolarity may be more likely to present with mixed features than adult forms (22, 83–85, 117). Based on extensive research showing that bipolar disorder often presents with depression (2, 189) and that early onset depression is a risk factor for bipolarity (60–62), it would seem that patients of any age who develop antidepressant-associated suicidality should be carefully evaluated for bipolarity, and that this should be especially true of children and adolescents. Moreover, because large meta-analyses have shown that lithium's antisuicide properties occur in unipolar as well as bipolar disorder (11–13, 50, 52), it could be argued that such patients should be considered for lithium treatment, even if they are unipolar or their bipolarity does not meet DSM-IV criteria. Growing research has shown that the nosologic boundary between bipolar disorders and depressive disorders is unclear, leading some authorities to argue that both conditions might better be viewed as related disorders that belong to the larger family of manic-depressive illness rather than separate, discrete conditions (2, 127). Indeed, the fact that

the addition of lithium to antidepressants remains the best-documented augmentation therapy for treatment-resistant unipolar depression lends support to this view (189).

Bipolar spectrum disorder versus unipolar depression versus manic-depressive illness: where does antidepressant-associated suicidality belong?

Until the boundary between bipolar and unipolar disorders is better delineated, it might be useful to view unipolar depression as consisting of two potentially overlapping subgroups: true unipolar (or non-bipolar) depression and possible bipolar depression. Regarding the clinical response to antidepressants of patients with DSM-IV diagnoses of depressive disorders, some clearly do well regarding both depressive symptoms and suicidality, whereas a subset appear to do poorly, developing new onset or worsening suicidality, increased depressive symptoms, or both. Some of the latter patients, upon closer inspection, have hypomanic symptoms and respond to mood stabilizers (65, 66, 190). One possibility therefore is that true unipolar patients may be those who respond well to antidepressant monotherapy, with reduction of depressive and suicidality symptoms, whereas patients with any degree of bipolarity may need treatment based on mood stabilizers, with or without adjunctive antidepressant therapy, for optimal management of both symptom domains. Because of these potential treatment differences, and because depression is often the presenting symptom or syndrome of bipolar disorder, it appears crucial to attempt to distinguish bipolar depressive states from those due to depressive disorders.

Indeed, mounting research indicates bipolar depression has phenomenological, course, comorbidity, family history and treatment response features that distinguish it from unipolar depression. Regarding phenomenology, studies have found bipolar depression is more likely to be characterized by lability, irritability, melancholic features, atypical features, mixed (hypomanic) symptoms and psychosis (2, 191–195). Goldberg et al. (191) found that up to 50% of patients hospitalized for unipolar depression and followed for 15 years eventually developed a manic or hypomanic episode, suggesting severity might also be a marker for bipolarity. Regarding course, bipolar disorder has been consistently shown to have an earlier age of onset, a postpartum onset and a greater number of recurrences (2, 193). Bipolar disorder is more likely to co-occur with other Axis I psychiatric disorders, particularly anxiety and substance use disorders. The family histories of persons with bipolar disorder have higher rates of bipolar disorders and higher overall rates of all mood disorders (2).

Finally, as noted in the introduction, recent epidemiological studies suggest bipolar disorder may be more likely to be associated with suicide attempts than is major depressive disorder. In the Epidemiologic Catchment Area (ECA) Study, the lifetime rates of one or more suicide attempts in persons with bipolar disorder, unipolar disorder, or any other evaluated DSM-III-defined disorder Axis I disorder were 29.2%, 15.9% and 4.2%, respectively (4). The odds ratio of subjects with bipolar disorder having a history of a suicide attempt relative to unipolar subjects was 2.0 ($p < 0.0001$). Moreover, in a reanalysis of the ECA database, persons with subsyndromal symptoms of mania (two or more lifetime manic symptoms without meeting the full criteria for a hypomanic or manic episode), like those with a lifetime history of mania or hypomania, were significantly more likely than those with no lifetime mental disorder or no manic symptoms to have lifetime suicidal behavior, including thoughts of death, thoughts of committing suicide and attempted suicide (74). In the National Comorbidity Survey (NCS), although every DSM-III-R disorder assessed was a significant risk factor for a lifetime suicide attempt, the odds ratios for mood disorders (7.8–29.7) were higher than those for any other disorder (2.1–5.6); within mood disorders, the odds ratio for mania (29.7) was substantially higher than for major depressive episode (11.0), dysthymia (7.8) and any mood disorder (12.9) (23). More recently, in the Australian National Survey, subjects with bipolar disorder were similarly found to have significantly higher odds of having a lifetime suicide attempt than those with major depressive disorder (2.1) as well as the rest of the sample (7.8) (17). Although not as extreme, similar findings occurred for suicidal ideation. Thus, suicidality, or at least making a suicide attempt, could be a potential marker for bipolarity (107). One important question therefore is whether antidepressant-associated suicidality (and other forms of behavioral dysregulation) should also be considered a marker for bipolarity.

As noted earlier, Akiskal et al. (129) has argued that hypomania associated only with antidepressant use may represent a distinct phenotype within the bipolar spectrum. Thus, suicidality associated with antidepressant treatment, especially if associated with any hypomanic or mixed affective symptoms – as well as a hypomanic, manic or a mixed syndrome – might also be a marker or endophenotype for bipolarity.

At present, the bipolar spectrum disorder is generally viewed as a group of neurobiological genetic illnesses of unknown etiology responsive to an array of structurally dissimilar medications with uncertain mechanisms of action, for which there are no diagnostic tests or pathognomonic biological markers (2, 196). A specific psychological and behavioral response of a person with a mood syndrome to an antidepressant may provide, at this rudimentary stage in our knowledge, important preliminary clinical information about that person's neurobiology and responsitivity to other mood-active compounds. Thus, many expert clinicians who specialize in bipolar disorder view antidepressant-induced mood or behavioral dysregulation in an initially depressed or anxious patient as a 'diagnostic test' that is highly suggestive that the patient has occult or prodomal bipolar disorder and may be more responsive to mood stabilizers (including lamotrigine and second-generation antipsychotics) – either alone or in combination with an antidepressant – than to antidepressant monotherapy. In other words, although it is presently unknown how much bipolarity contributes to antidepressant-associated suicidality, in our opinion, it is unlikely to be minimal, at least to be significant, and possibly to be substantial. Moreover, it is possible that lithium's antisuicide properties may include the ability to prevent antidepressant-induced suicidality. Thus, in the patient who develops antidepressant-associated suicidality, it is also our opinion that it is the clinician's responsibility to do his or her best to determine whether or not bipolarity exists.

Conclusions

At this time, there are no prospective, controlled clinical trial data that definitively indicate whether antidepressants decrease or increase suicidal ideation or behavior, either acutely or in the longterm, in patients with bipolar disorder. On the one hand, growing clinical evidence indicates that mixed states are often characterized by suicidal ideation and behavior (2, 22, 75, 79–81, 104, 117) and that antidepressants, especially when given as monotherapy, may induce both suicidality (26, 54, 176–179) and manic conversion (34, 35, 86). Indeed, the latter is further supported by data showing that antidepressant mechanism of action (42–44, 137), age (86, 87) and genetic factors (140–142) may differentially affect manic conversion rates. In addition, there are numerous descriptions of patients with various mixed depressive states who worsen with antidepressant monotherapy, but who improve with treatment with mood stabilizers, antipsychotics or electroconvulsive therapy. On the other hand, a meta-analysis of 12 short-term trials (42) and one medium-sized, long-term (2-year) study (91, 92) suggests antidepressants in combination with mood stabilizers and/or antipsychotics may reduce depressive symptoms without increasing manic conversion. One long-term, open-label, prospective trial suggested that lithium in combination with antidepressant and/or antipsychotics, but not alone, reduced suicide in bipolar patients (9, 19). Moreover, it is presently unknown whether patients who develop suicidal mixed states with antidepressant exposure overlap with those patients who require antidepressants in combination with mood stabilizers and/or antipsychotics for adequate treatment of depression (and possibly suicidality) or whether these represent distinct patient subtypes (e.g., antidepressant-sensitive versus antidepressant-responsive).

The finding that antidepressants may induce suicidality in a subset of persons with depressive (and probably anxious) presentations, and the possibility that this induction may represent a form of manic conversion, and hence a bipolar phenotype, has important clinical and theoretical implications. The first is that our modern nosologic system should move away from the dichotomous views of Leonhard and DSM-IV that bipolar disorder and major depressive disorder (or at least certain forms of major depressive disorder) are distinct conditions back to the Kraepelinian, dimensional view that mania and depression may be related conditions that belong to the larger family of manic-depressive illnesses, or, in modern terms, bipolar spectrum disorder (2, 127). In other words, the importance of the co-occurrence of manic and depressive symptoms in both threshold and subthreshold forms will need to be appreciated in order for future mood disorder research to be meaningful (127). Thus, a depressive syndrome with just one or two hypomanic symptoms might be pathophysiologically different from one without any hypomania; while the latter may represent a true unipolar (or non-bipolar) depressive state responsive to antidepressant monotherapy, the former may represent a bipolar mixed state that responds best to a mood stabilizer but will progress to a mixed depression or mixed mania with suicidal ideation upon exposure to antidepressant monotherapy. The presence of minimal hypomanic symptoms, including those occurring concurrently with depressive symptoms, would appear to be clinically significant – even if the patient does not meet the full DSM-IV criteria for hypomania.

Since hypomanic and mixed states have been relatively understudied compared with syndromal

mania, depression and mixed mania, it is currently unknown how best to operationally define such states (78). Until the relationships among mixed states, suicidality and antidepressant use are fully understood, definitions must be broad. Any patient presenting with any type of depressive symptom, including suicidality, must be carefully evaluated for current and past manic and hypomanic symptoms, including those co-occurring with depressive symptoms and those possibly induced by antidepressants. Moreover, future clinical trials in mood disorder patients with potential mood altering drugs and future studies of suicidality should include dimensional measures of manic, depressive and suicidality signs and symptoms so that relationships among pharmacotherapy, mixed states and suicidality can be better elucidated. Such trials should also contain measures of other causes of activation, including non-specific agitation and akathisia, so that relationships among these phenomena, mixed states and suicidality can be better appreciated.

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