

# Antidepressant-Associated Mania and Psychosis Resulting in Psychiatric Admissions

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**Background:** The safety and tolerability of the selective serotonin reuptake inhibitors and the newer atypical agents have led to a significant increase in antidepressant use. These changes raise concern as to the likelihood of a corresponding increase in adverse behavioral reactions attributable to these drugs.

**Method:** All admissions to a university-based general hospital psychiatric unit during a 14-month period were reviewed.

**Results:** Forty-three (8.1%) of 533 patients were found to have been admitted owing to antidepressant-associated mania or psychosis.

**Conclusion:** Despite the positive changes in the side effect profile of antidepressant drugs, the rate of admissions due to antidepressant-associated adverse behavioral effects remains significant.

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**A**ntidepressants have been recognized as potential inducers of mania and psychosis since their introduction in the 1950s. Kuhn<sup>1</sup> described psychosis as an adverse effect of imipramine, and the emergence of mania in patients being treated for tuberculosis with iproniazid prompted the original trials of monoamine oxidase inhibitors for depression. Subsequent reports suggest that all antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and the newer non-SSRI antidepressants,<sup>2,3</sup> appear capable of producing mania and psychosis in vulnerable individuals. In the Physicians' Desk Reference,<sup>4</sup> every antidepressant is listed as having this potential side effect, although the wording of the warning varies considerably from drug to drug.

Since the introduction of fluoxetine in 1988, patterns of antidepressant use in the United States have changed considerably. Antidepressants currently account for the largest proportion of psychopharmacologic drug visits in the outpatient setting, and this increase in antidepressant

use can be accounted for almost entirely by the SSRIs. As described recently by Pincus and colleagues,<sup>5</sup> the absolute number of antidepressant prescriptions by primary care physicians and psychiatrists has more than doubled since 1985.

As an assessment of the impact of possible adverse behavioral reactions associated with the use of antidepressants, we previously reported the prevalence of antidepressant-associated psychosis and mania following a review of 207 consecutive inpatient admissions over a 6-month period.<sup>6</sup> We found 23 such cases accounting for 11% of admissions. Fifteen of the 23 had recently been prescribed antidepressant medication, and 8 had a recent reduction in neuroleptic dosage in combination with continuing antidepressant treatment. We have subsequently narrowed our inclusion criteria to include only those patients who had recently been prescribed an antidepressant, and we expanded our period of review to 14 months.

## METHOD

Five hundred thirty-three consecutive admissions to the adult psychiatric inpatient service at Yale-New Haven Hospital (New Haven, Conn.) were reviewed, covering a 14-month period between January 1, 1997, and February 28, 1998. Patients admitted during this period included 307 women and 226 men. Their mean  $\pm$  SD age was  $38 \pm 8$  years, and various ethnic/minority groups were represented (white,  $N = 317$ ; African American,  $N = 150$ ; Hispanic American,  $N = 61$ ; Asian American,  $N = 5$ ). Inclusion criteria for antidepressant-associated mania or psychosis were (1) initiation or increase in psychotic and/or manic symptoms as the primary reason for hospital admission, (2) antidepressant use at the time of admission, (3) recent (within 16 weeks) initiation of antidepressant use as confirmed by chart review and contact with outpatient treaters, and (4) rapid improvement following discontinuation of antidepressants with addition of a neuroleptic or mood-stabilizing regimen when clinically indicated. In our initial report,<sup>6</sup> we also included cases in which neuroleptic treatment dose had been recently reduced while antidepressants were continued. We excluded such cases in the present study in order to provide a more rigorous review of behavioral changes due to antidepressant

treatment. Exclusion criteria were (1) stable medication regimen prior to admission, (2) severe characterological disturbance including borderline personality disorder, or (3) concurrent substance use at time of admission.

Statistical analyses included calculation of the ratio of cases meeting criteria for antidepressant exacerbation of psychosis or mania to all cases reviewed. Means and standard deviations of clinical data sets were also computed.

## RESULTS

Forty-three cases of psychosis or mania (8.1%) were judged by our inclusion criteria to be related to antidepressant administration. This figure reflects a crude incidence rate of 6.8% per year. Thirty were women and 13 were men, with ages ranging from 21 to 55 years (mean  $\pm$  SD = 36  $\pm$  9 years). The mean duration of illness was 14  $\pm$  9 years, and the mean age at onset was 22  $\pm$  11 years. The majority were white (N = 35; 81%), and only 44% (N = 19) had ever been married. Diagnostic categories at admission included DSM-IV bipolar I disorder (N = 15), major depressive disorder with psychotic features (N = 9), schizoaffective disorder bipolar type (N = 8), schizophrenia (N = 7), and other Axis I disorders (autism, N = 1; generalized anxiety disorder, N = 1; dementia, N = 1; psychotic disorder not otherwise specified [NOS], N = 1). At the time of admission, 29 patients were receiving neuroleptics, and 25 were taking mood stabilizers (valproic acid, N = 14; lithium, N = 6; carbamazepine, N = 4; topiramate, N = 1). Table 1 provides data on antidepressant treatment that was started prior to admission. Of note, in the tricyclic antidepressant (TCA) subgroup, 5 patients (12%) were receiving a TCA agent as monotherapy, whereas the other 4 (9%) received a combination of an SSRI and a TCA. Venlafaxine is listed as "atypical," although it is considered to have some SSRI properties.

### Case Examples

**Case 1.** Ms. A, a 52-year-old, married, white woman with a past history of bipolar disorder, presented for admission after 2 weeks of severely decreased sleep, appetite, and concentration as well as pressured speech, racing thoughts, and command auditory hallucinations with suicidal content. At admission, she reported that her daily fluvoxamine dose had been increased from 150 to 300 mg and desipramine, 50 mg/day, was added to treat increased depressive symptoms 4 weeks preceding admission. Admission medications also included risperidone, 1 mg; zolpidem, 10 mg; and oxazepam, 10 mg (total daily doses). At admission, desipramine and fluvoxamine were discontinued. As the patient refused both divalproex sodium and lithium owing to past reported adverse effects, a gabapentin trial was initiated. The patient was discharged after 3 days of hospitalization on treatment with gabapentin, 900 mg/day; risperidone, 1 mg/day; and zolpidem, 10 mg

**Table 1. Antidepressants Prior to Admission\***

Antidepressant	N	%
SSRIs	30	70
Fluoxetine	4	9
Fluvoxamine	4	9
Paroxetine	9	21
Sertraline	13	30
Atypical antidepressants	9	21
Bupropion	4	9
Nefazodone	2	5
Venlafaxine	3	7
TCA's	9	21
Amitriptyline	2	5
Desipramine	3	7
Imipramine	3	7
Nortriptyline	1	2

\*Abbreviations: SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant. Five cases were receiving combination therapy, and each agent is noted in the table; therefore, N = 48 for drugs: bupropion and amitriptyline, N = 1; imipramine and fluoxetine, N = 1; sertraline and bupropion, N = 1; sertraline and nortriptyline, N = 1; fluvoxamine and desipramine, N = 1.

q.h.s., with no psychotic symptoms, pressured speech, or racing thoughts.

**Case 2.** Ms. B, a 42-year-old, divorced, white woman, had a 1-year history of depression treated with fluoxetine, 20 mg/day; lithium, 900 mg/day, for augmentation; and thioridazine, 75 mg/day, for sleep. Approximately 4 months prior to the present admission, her depression worsened. Fluoxetine was increased to 40 mg/day, and imipramine, 50 mg/day, was added to her regimen. The patient began to experience derogatory and then command auditory hallucinations to kill herself, which were regarded as a further aggravation of her depression, and imipramine was increased to 100 mg/day. At admission, both fluoxetine and imipramine were discontinued. Initially, lithium was maintained at 900 mg/day, thioridazine was increased to 150 mg/day, and clonazepam, 1.5 mg/day, was added. Subsequently, lithium was tapered and discontinued, and thioridazine was changed to olanzapine. Over the next 2 weeks, the patient's mood brightened, her energy level and sleep were restored, and her suicidal ideation and auditory hallucinations receded. The patient was discharged on treatment with olanzapine, 15 mg/day, and clonazepam, 1.5 mg/day, with improved mood and freedom from psychotic symptoms.

**Case 3.** Ms. C, a 49-year-old, widowed, African American woman, presented for her first psychiatric admission with anxious mood, decreased sleep, and frank paranoid delusions. Her past psychiatric history was negative until 3 months prior to admission, when she was started on venlafaxine, 75 mg/day, for "low mood and anxiety." One week prior to admission, the patient began to feel unsafe unless surrounded by family members, started to think that television messages were directed to her, and reported having overwhelming feelings of doom, as if her family members and she might die. At admission, venlafaxine was discontinued, and olanzapine, 10 mg/day, and clonazepam,

1.5 mg/day, were started. The patient's symptoms remitted rapidly, and she was discharged to home 3 days after admission.

## DISCUSSION

Our retrospective analysis of 533 consecutive inpatient admissions over a 14-month period yielded an 8.1% prevalence of apparent antidepressant-induced psychosis or mania. This rate of decompensation associated with antidepressants in susceptible individuals raises the concern that as the amount of antidepressant prescriptions has increased over the past 10 years, so has the rate of significant adverse events. These findings suggest the need for increased vigilance in prescribing practices for this commonly used pharmacotherapy.

Psychiatric history was highlighted in this study as an important indicator of potential susceptibility to antidepressants. Most cases meeting inclusion criteria were known to have a psychotic/ manic diathesis by history. A past history of psychosis was found in 61% ( $N = 26$ ) of our group and seems to represent a strong risk factor for adverse behavioral change associated with antidepressant treatment. Most patients had been ill for a long time (mean duration of illness = 14 years). Although many patients with a history of psychosis or mania may require an antidepressant trial, close monitoring for adverse effects of the antidepressant is warranted, and early detection of adverse behavioral change should be a hallmark of treatment. Twelve of our cases represented new-onset mania or psychosis. Such cases are not the focus of this report, but based on our clinical experience, they are not rare. We do not think that our data should be interpreted as showing that SSRIs are more likely than other antidepressants to be associated with mania or psychosis in susceptible individuals. Rather, the number of cases of mania or psychosis during SSRI treatment very likely reflects the increased use of these drugs generally.

The capacity of antidepressants to exacerbate psychosis and mania has long been known. In addition to Kuhn's early observations,<sup>1</sup> Klein and Fink<sup>7</sup> called attention to psychotic and manic responses to imipramine in 1962, and Baldessarini and Willmuth<sup>8</sup> reported psychotic reactions during amitriptyline therapy in 1968. With the advent of the newer antidepressants, a number of studies reported a decreased risk for inducing mania/psychosis as part of a generally improved side effect profile.<sup>9,10</sup> There has been some disagreement as to whether antidepressant-associated mania is related to course of illness or antidepressant use.<sup>2</sup> The question of which antidepressants are more likely to facilitate a switch to mania has received considerable attention in clinical trials. Cohn and colleagues<sup>11</sup> compared fluoxetine and imipramine in a placebo-controlled, double-blind treatment of bipolar depression. The results did not favor either drug as less

likely to induce mania. In a double-blind study, Young and associates<sup>12</sup> compared the addition of paroxetine or a second mood stabilizer with a mood-stabilizer regimen for bipolar depression. Although the numbers were small (11 received paroxetine), no manic exacerbations were recorded. Amsterdam and associates<sup>13</sup> reported a low mania switch rate in a double-blind study of fluoxetine monotherapy in bipolar II disorder. However, there are case series reporting manic reactions in association with other SSRIs and with bupropion.<sup>14,15</sup> Overall, the available data may suggest less risk of manic switch with paroxetine and bupropion, but the differences are likely relative rather than absolute. Ghaemi and associates<sup>16</sup> have highlighted concerns regarding possible underdiagnosis of bipolar disorder and overutilization of antidepressants.

Our review has several limitations. Among these is the retrospective design of the study. As a function of this design, it is difficult to ensure that the emergence of psychotic or manic symptoms was due to the initiation of antidepressant treatment and not intrinsic to the disease course. In addition, we used an arbitrary cutoff of 4 months as maximal latency to symptom onset from antidepressant start date. In the future, a shorter latency period would minimize the risk for false-positive cases. However, the apparent correlation of prompt symptom remission with antidepressant withdrawal strengthens the argument that manic and psychotic symptoms are secondary effects of the drug. Owing largely to the ongoing pressures of managed care to shorten the length of inpatient hospitalization, the majority of patients had an initiation or increase in neuroleptic shortly after antidepressant discontinuation. In some cases, the severity of the patient's symptoms mandated this aggressive treatment strategy. In less severe cases, however, the argument for an antidepressant as the etiology for psychiatric decompensation would be strengthened if stopping the drug alone, in the supervised inpatient setting, were evaluated as a sufficient first step in treatment. Finally, we consider this report primarily a case series highlighting the issue of antidepressant-induced mania and psychosis, not a study of incidence or prevalence of this phenomenon. A control group was therefore not included.

The neurobiological mechanism responsible for antidepressant exacerbation of manic and psychotic symptoms is unknown. There has been some preclinical research that may be relevant, however. For example, Tanda and coworkers<sup>17</sup> have shown that administration of desipramine or fluoxetine (10 mg/kg i.p. once a day for 2 weeks) differentially affected monoamine efflux in rat prefrontal cortex as measured by transcerebral microdialysis. The authors conclude that chronic fluoxetine is associated with normal presynaptic dopamine transmission in the prefrontal cortex as a result of tolerance to a fluoxetine-induced early increase in extracellular dopamine. In contrast, chronic desipramine is associated with an in-

crease in presynaptic dopamine transmission in the prefrontal cortex. In other studies, Tanda and coworkers<sup>18</sup> have shown that these changes in dopamine efflux did not occur in the nucleus accumbens. However, Ichikawa and colleagues<sup>19</sup> reported that basal dopamine efflux was increased in the nucleus accumbens after chronic imipramine pretreatment but not after chronic fluoxetine. These authors use their results to support an alleged greater risk of manic or psychotic exacerbations with TCAs compared with SSRIs.

Another area of research that may be relevant to this issue is the work of Winter and colleagues<sup>20</sup> showing that fluoxetine and other SSRIs can simulate the effects of lysergic acid diethylamide (LSD) and phenethylamine hallucinogens in an operant discriminative stimulus paradigm. These investigators have shown that this effect is quite likely mediated by serotonin-2 receptors. To the extent that LSD and phenethylamine hallucinogens are seen as psychotogenic in humans, then SSRIs may facilitate the emergence of some forms of psychosis.

In summary, a significant proportion of psychiatric hospitalizations reviewed (8.1%) was judged to be due to antidepressant-associated psychotic or manic symptoms. As the uses of antidepressants continue to increase, vigilance is warranted in prescribing these medications to individuals who may be susceptible to this form of behavioral change.

*Drug names:* amitriptyline (Elavil and others), bupropion (Wellbutrin), carbamazepine (Tegretol and others), clonazepam (Klonopin and others), desipramine (Norpramin and others), divalproex sodium (Depakote), fluoxetine (Prozac), fluvoxamine (Luvox), gabapentin (Neurontin), nefazodone (Serzone), nortriptyline (Pamelor and others), olanzapine (Zyprexa), oxazepam (Serax and others), paroxetine (Paxil), risperidone (Risperdal), thioridazine (Mellaril and others), topiramate (Topamax), sertraline (Zoloft), valproic acid (Depakene), venlafaxine (Effexor), zolpidem (Ambien).

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