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Case Report

Ziprasidone-associated mania: a case series and review of the mechanism

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Atypical antipsychotics are now commonly used in the treatment of bipolar disorder, as they have been shown to have effects on mania as well as psychosis. Shortly after the introduction of atypical antipsychotics, several cases of associated hypomania and mania were reported. Ziprasidone is an atypical antipsychotic recently approved by the Food and Drug Administration for the treatment of psychosis. Although ziprasidone has also been shown to be effective in treating mania, it may be associated with the induction of mania or hypomania. We report four cases of mania associated with initiation of ziprasidone, which, to our knowledge, are the first reported for this drug in bipolar patients. As ziprasidone has substantial serotonergic and noradrenergic action, we hypothesize, it may more likely induce mania than other atypical antipsychotics. We advocate future studies to evaluate ziprasidone's efficacy in treating bipolar disorder and caution clinicians that induction of mania or hypomania may be possible with this agent.

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Atypical antipsychotics are now commonly used in the treatment of bipolar disorder as they have been shown to have effects on mania as well as psychosis (1). Two such antipsychotics, olanzapine and risperidone, are efficacious in the treatment of acute mania (2, 3). There is also emerging evidence suggesting a possible role for these agents in treating bipolar depression (4, 5). Shortly after the introduction of atypical antipsychotics, several cases of risperidone- and olanzapine-induced hypomania and mania were reported (6–9). A MEDLINE search of the literature from 1966 to 1999 using the terms *atypical antipsychotics, risperidone, olanzapine, hypomania and mania* revealed 16 cases of mania induced by risperidone and 10 cases of mania induced by olanzapine (for review, see 10).

Ziprasidone, a novel atypical antipsychotic, was recently released as an alternative treatment for psychosis with a unique side-effect profile including minimal weight gain, low levels of sedation, and a low incidence of orthostatic hypotension (11). Like other atypical antipsychotics, ziprasidone has a high affinity for blocking 5-HT2 and D2 receptors. However, ziprasidone-like many antidepressants – is also a potent inhibitor of serotonergic and noradrenergic reuptake sites (11). Based on the evidence that antidepressants may increase the likelihood of switching from bipolar depression to mania (12, 13), we hypothesized that these additional pharmacological characteristics of ziprasidone may make it more likely, than other atypical antipsychotics, to be associated with mania. Although Davis and Risch (14) recently reported a case of mania associated with ziprasidone use in a patient with schizoaffective disorder, we present here, what we believe to be the first reported cases of mania associated with ziprasidone use in bipolar patients.

Cases

Case 1

Mr L is a 26-year-old single white male with a 7-years history of bipolar I disorder, rapid cycling (four episodes/year), who presented with a 3-week history of depressed mood, decreased sleep with difficulty falling asleep, anhedonia, diminished energy, poor concentration, and decreased appetite with a 2.27 kg weight loss. Suicidal ideation was

not present. Mr L's daily medications included carbamazepine 800 mg, clonazepam 2.0 mg and quetiapine 25 mg. Quetiapine was discontinued because of excessive sedation 1 week before the ziprasidone was started. Ziprasidone was initiated at 20 mg twice a day. After 7 days of ziprasidone treatment, Mr L reported decreased need for sleep, impulsivity, increased libido, distractibility, and inability to perform school work secondary to racing thoughts and poor concentration. He began having thoughts of having an affair, despite being engaged to be married. Mr L self-discontinued ziprasidone after 8 days of treatment. Four days later, Mr L had improved compared with 1 week prior, but still had complaints of racing thoughts and increased energy.

Case 2

Mr G is a 45-year-old divorced white male with a 30-years history of bipolar disorder, type I who was suffering from severe depression of 10-month duration prior to treatment with ziprasidone. Mr G experienced depressed mood, low energy, anhedonia, increased sleep, poor appetite, poor concentration and passive suicidal ideation. One week prior to initiation of a trial of ziprasidone, Mr G made a non-lethal suicidal attempt.

Mr G had failed prior treatment with numerous medications for this index episode including high dose selective serotonin reuptake inhibitors (SSRI's), serotonin neuroepinephrine reuptake inhibitors (SNRI's), tricyclic antidepressants, monoamine oxidase inhibitors (MAOI's), electroconvulsive therapy (ECT), quetiapine, olanzapine, risperidone, pramipexole and tolcapone. Mr G's daily medications included: lithium 1500 mg, lamotrigine 300 mg, oxcarbazepine 200 mg, clonazepam 2 mg and tolcapone 400 mg. Tolcapone was discontinued secondary to poor efficacy and ziprasidone was initiated at 20 mg twice a day. After 3 days of ziprasidone treatment, Mr G reported the following symptoms: euphoric and irritable mood, racing thoughts, decreased need for sleep, elevated energy, increased jocularity, talkativeness, and reckless driving with his children in the car. His symptoms were consistent with a manic episode. Ziprasidone was discontinued and treatment with perphenazine was initiated. Mania resolved after 4 days.

Case 3

Mr C is a 25-year-old single white male with a 8-years history of bipolar disorder, type I, who presented an euthymic state. Daily medications included lithium carbonate 1200 mg, clonazepam 2 mg, lamotrigine 250 mg and olanzapine 20 mg. Olanzapine was decreased to 10 mg a day secondary to significant weight gain and ziprasidone 20 mg twice a day was started. After 4 days of treatment, Mr C reported elevated mood, decreased need for sleep, increased energy, racing thoughts, agitation and decreased concentration. After 1 week of symptoms, ziprasidone was reduced to 20 mg once a day and olanzapine was increased to 20 mg. Mr C showed improvement in manic symptoms after 1 week.

Case 4

Ms D is a 29-year-old married white female with an 11-years history of bipolar disorder, type II and post-traumatic stress disorder who presented with a 7-week history of depressed mood, anhedonia, low energy, hypersomnolence, decreased libido, poor concentration and passive suicidal ideation. Her daily medications included olanzapine 15 mg, sertraline 200 mg, valproic acid (extended release formulation) 1000 mg and venlafaxine 25 mg. Olanzapine was discontinued secondary to chest pain and quetiapine 25 mg was started. Ms D experienced extreme sedation with quetiapine, and after 7 days was switched from quetiapine to ziprasidone 20 mg twice a day. The dose of ziprasidone was titrated to a total daily dose of 100 mg over a period of 5 days. On the fifth day of treatment, Ms D reported elevated mood, irritability, agitation, racing thoughts, decreased need for sleep, increased energy and hypersexuality. Of note, a previous trial of quetiapine that was abruptly stopped did not induce mania in Ms D. Ziprasidone was decreased to 40 mg twice a day with resolution of manic symptoms 3 days later.

Discussion

In these four cases, ziprasidone administration was temporally related to an induction of mania. The symptoms of mania occurred within 7 days of ziprasidone initiation. In all these cases, symptoms resolved or improved after either lowering the dose or discontinuing ziprasidone. It must be noted that the doses employed in these cases were very low compared with a recent multicentered acute mania trial (15). Keck and colleagues (15) found ziprasidone 80–160 mg/day an effective treatment for bipolar mania in a 3-week double-blind randomized trial. Therefore, if ziprasidone was the causative agent in inducing mania, we may ask what pharmacological activity accounts for this phenomenon.

Ziprasidone resembles the other atypical antipsychotics in having 5-HT2A, 5-HT2C, D2 and D3 receptor antagonism. Of these agents, it has the strongest relative ratio of 5-HT2 to D2 binding (11). Lane and colleagues (16) have proposed that mood states may be a function of this ratio. Additionally, ziprasidone has modest affinity for H1 and α1 receptors, low affinity for D1 and α2 receptors, and minimal affinity for M1 receptors. Unlike the other atypical antipsychotics, ziprasidone is also an antagonist at both pre- and postsynaptic 5-HT1D receptors, an agonist at 5-HT1A receptors, and an inhibitor of presynaptic uptake of serotonin and noradrenaline (11). These latter mechanisms of action are similar to those observed with many antidepressants. In fact, ziprasidone had virtually identical serotonin reuptake potencies and similar noradrenaline reuptake potencies to imipramine and amitryptiline in *in vitro* studies (17). Therefore, the unique pharmacological profile of ziprasidone combines features of both atypical antipsychotic agents and antidepressants. This mechanism of action, although, is unlikely to be the entire explanation, given that the other atypical antipsychotic agents that do not possess this mechanism have also been associated with mania. However, ziprasidone's similarity to imipramine may be particularly important. If the antidepressant pharmacology of ziprasidone is most similar to the tricyclics (and not SSRIs) then it lends further support to ziprasidone's possible propensity to induce mania in susceptible individuals, as it is observed that tricyclics almost double the rate of mania in bipolar patients (18). Whether or not this is because of noradrenaline reuptake inhibition alone, the combination of serotonin and noradrenaline reuptake inhibition, or some other as yet undetected process is not known.

A confounding variable in each of the current cases is that another psychotropic medication was discontinued at the same time ziprasidone was started. Although there are reports in the literature of antidepressant withdrawal-induced mania (19), there are no reports of induction of mania with discontinuation of atypical antipsychotics or tolcapone. However, it may simply be that these agents were treating or preventing a mania which broke-through when the agents were stopped. Of note, in the fourth case, quetiapine was previously abruptly discontinued without induction of mania. Furthermore, in all these cases, manic symptoms resolved or diminished shortly after ziprasidone was discontinued. In case 3, however, the increased dose of olanzapine may have contributed to rapid mood stabilization. In case 1, it is possible that the patient, a rapid cycler, became manic unrelated to medications, however, his course of illness suggested longer cycles.

Psychomotor activation and akathisia are side-effects of ziprasidone (20) which could be misinterpreted as mania. In each of these cases, mania was diagnosed based on a semistructured instrument based on DSM-IV criteria utilized by one of the authors (CFB) and not merely based on observation or the unitary symptoms of psychomotor activation or akathisia.

There are several additional caveats of the current study. For one, the data are from a series of cases and might not be applicable to other patients, especially those who do not have bipolar disorder. It may be that patients with schizophrenia or schizoaffective disorder who do not have a tendency towards mania will not be induced into a manic episode on this medication. Secondly, all the patients in this study were on multiple medications at the time of initiation of treatment with ziprasidone. It is therefore possible that the effects we observed were the result of multiple drug interactions or changes in the metabolism of the agents. Thirdly, it is possible that all these patients were progressing towards a manic episode prior to starting ziprasidone. Given, however, the rapidity with which symptoms abated after discontinuation or reduction of the dose of ziprasidone, it is less likely that the observed manic episodes were because of the natural course of the illness in these patients.

Of considerable importance is the question of what to do if a mania occurs during ziprasidone treatment. It has been our own observation as well as validated in a recent acute mania trial that higher doses of ziprasidone may be necessary to treat exacerbations of psychosis and mania. All the above cases involved manias associated with 20 mg b.i.d. doses; it is plausible that increasing the ziprasidone dose would have treated the emerging mania.

In conclusion, while ziprasidone, like other atypical antipsychotics, has been shown to be effective in treating mania (15), it may occasionally be associated with the induction of mania. The contribution of the antidepressant-like effects of ziprasidone to its induction of mania remains to be elucidated. Further prospective studies could determine if ziprasidone is more likely than other atypical antipsychotics to cause this effect.

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