

# Persistent akathisia masquerading as agitated depression after use of ziprasidone in the treatment of bipolar depression

Thomas M Penders<sup>1</sup>

Salina Agarwal<sup>2</sup>

Rachel Rohaidy<sup>1</sup>

<sup>1</sup>Department of Psychiatric Medicine, Brody School of Medicine, East Carolina University, Greenville, NC, USA; <sup>2</sup>Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX, USA

**Abstract:** There has been increasing recognition that the second-generation antipsychotic drugs can produce extrapyramidal side effects. This case reports the development of severe akathisia in a patient being treated with ziprasidone for bipolar depression. The case illustrates that this symptom can be easily mistaken for worsening agitated depression. Akathisia may produce considerable distress and elevate suicide risk. Such symptoms may persist for weeks and be refractory to discontinuation of the offending agent or to pharmacological interventions commonly used to mitigate this reaction.

**Keywords:** extrapyramidal, second-generation, affective, antipsychotic, suicide, mood disorder

## Introduction

The efficacy of psychotropic drugs is frequently limited by lack of adherence to their use. Adherence rates decline in direct proportion to side effects experienced. Lack of adherence to antipsychotic treatment regimens has been identified as an unmet need of many with severe mental illness.<sup>1</sup> A reduced risk of extrapyramidal side effects is often cited as an advantage of second-generation antipsychotics over the “typicals.” Compliance with first-generation antipsychotic drugs is frequently limited by the appearance of dystonias, drug induced Parkinsonism, and akathisia.<sup>2,3</sup>

Recent observations have shown that atypical agents may also produce troubling extrapyramidal side effects.<sup>4</sup> We report a case of akathisia persisting for weeks following dosage increases of ziprasidone used to treat bipolar depression.

While there have been several reports of akathisia associated with onset of use or with tapering of ziprasidone, this is the first case known to the authors of persistence of akathisia for an extended period after discontinuation of the drug.<sup>5,6</sup>

This case illustrates the dilemma of differentiating akathisia from psychomotor agitation. The case also demonstrates that akathisia can be quite refractory to common interventions such as discontinuation or addition of pharmacological interventions commonly used to treat this condition. Importantly, the case also shows how akathisia may persist for several weeks causing such distress that the symptom itself may lead to development of a sense of hopelessness, elevating suicide risk.<sup>7</sup>

## Case report

A 67-year-old female was diagnosed with bipolar II disorder after presentation at age 64 with symptoms of subjective depression, lethargy, anhedonia, insomnia with mid-cycle awakening, and irritability. By the patient's self-report, she had suffered prior episodes

Correspondence: Thomas M Penders  
Department of Psychiatric Medicine,  
Brody School of Medicine, 600 Moye  
Blvd, Suite 400-E, Greenville,  
NC 27834, USA  
Tel +1 252 744 2660  
Fax +1 252 744 3815  
Email penderst@ecu.edu

of hypomania occurring in spring and depression occurring frequently in early fall. She first sought treatment for depression at age 40 when she reported improvement with an unknown antidepressant drug. She discontinued this agent several months later and had not come again to psychiatric treatment until age 64. At the time of this presentation a Quick Inventory of Depression Symptoms (QIDS) score of 17 was noted. A trial of sertraline, increased over 6 weeks to 200 mg, resulted in moderate improvement but with continued depressive symptoms, and a QIDS score of 9. After a switch in the antidepressant to venlafaxine at 150 mg she developed an episode of hyperactivity, pressured speech, and grandiosity, for which she was hospitalized. Quetiapine at 300 mg per day resulted in return to a euthymic state. After experiencing daytime sedation with reduced dosage, quetiapine was discontinued. One year later she presented again for a routine office visit in mid-autumn, complaining of a sudden onset of depressive symptoms.

She had left her job from which she had previously gained a good deal of gratification, became socially withdrawn, and noted increased anxiety, diminished appetite, reduced levels of energy, and anhedonia. Three separate trials of lithium at 600 mg per day at different times over several months were terminated after she experienced increased subjective dysphoria. A trial of valproate resulted in subjective cognitive dulling and motor incoordination.

Ziprasidone was then begun and increased to 80 mg over the next 5 days. One week later the patient returned and reported that her depression, withdrawal, and anergy were unimproved (QIDS score 15) and that levels of anxiety had increased, causing considerable distress. Ziprasidone was increased from 80 mg to 120 mg over the next week and clonazepam 0.5 mg twice a day was begun, to address increasing anxiety and agitation. Again, after 5 days, she reported that she felt restless and was unable to sit for long periods. Suffering increasing discomfort, she was brought to the emergency department with symptoms of agitation, anxiety, and hopelessness. She was admitted to the inpatient psychiatric program for treatment of worsening depression failing outpatient intervention. After admission, she described her symptoms as being unable to bear sitting down, a continuous feeling of anxiety, and pervasive insomnia. She also described a rather profound subjective despondency and developed passive suicidal ideation, expressing that she did not believe she could tolerate feeling as she did for very long. She was frequently observed standing in one place and shuffling her feet. Akathisia was recognized at this time, and ziprasidone was discontinued. Amantadine 100 mg twice a day was begun, but the patient was unimproved 4 days later. Light therapy

of 10,000 lux was started each early morning for 30 minutes predawn. Quetiapine 25 mg at night was added.

After 1 week, the symptom profile remained unchanged. Amantadine was discontinued and the patient was started on propranolol 10 mg three times a day, titrated up to 60 mg per day. Also, lorazepam 0.5 twice a day was begun. By day 5 of inpatient hospitalization, there was no improvement. Cogentin 1 mg twice a day was added. One week later, with no improvement in her movements or feelings of anxiety, propranolol was discontinued after the patient was noted to have symptoms and findings consistent with orthostatic hypotension. Carbidopa/levodopa was added after observation of continued shuffling gait, masked facies, and mild pill-rolling movement. Consultation with the hospital's neurology department led to discontinuation of anti-Parkinson agents and confirmed the impression that akathisia was responsible for the majority of the patient's distress. Nebivolol 5 mg was started and titrated to 10.5 mg once a day for several days without improvement. After 15 days of inpatient treatment there was little change. There were occasions of mild improvement of akathisia symptoms subjectively, but the distressing shuffling of her feet and inability to sit remained a constant. After discussion with family members and daily completion of structured suicide assessments providing assurance of nonsuicidality, she was discharged to close outpatient follow-up with persistent symptoms of akathisia (QIDS score 12). After discharge, the patient's akathisia resolved slowly over a period of 3 weeks and depressive symptoms were noted to improve.

## Discussion

It is now established that akathisia may occur following use of second-generation or atypical antipsychotic agents, including clozapine.<sup>8,9</sup> The incidence of these reactions appears to vary with the agent used, with risperidone producing more reports than ziprasidone.<sup>10</sup> Rates of akathisia with ziprasidone are estimated to occur in 14% of patients at 80 mg and 13% at 160 mg compared with a 7% rate for placebo in one series of patients with schizophrenia and schizoaffective disorder.<sup>11</sup>

Akathisia is characterized by a persistent sense of discomfort remaining at rest accompanied by motor restlessness causing considerable distress. The presence of akathisia can be confused by patients and physicians with worsening of the underlying psychiatric disorder. Akathisia has been associated with elevated risk of suicide.<sup>12</sup> In a group of schizophrenic patients, one study suggested that increased rates on the suicide subscale of the Hamilton Depression Inventory (HAMD) were double for those experiencing akathisia, compared with those without this adverse reaction.<sup>13</sup>

Second-generation antipsychotics have had expanding indications and are increasingly being recommended for use in the treatment of bipolar depression.<sup>14,15</sup> Increased risk of akathisia with second-generation antipsychotic agents has been associated with their use in management of affective disorders.<sup>16</sup>

## Conclusion

Clinicians should be aware of the potential for second-generation antipsychotic drugs to produce akathisia, complicating treatment. This distressing symptom may persist for weeks and confound diagnostic assessment. Despite discontinuation, akathisia may be relatively refractory to standard interventions and confound evaluation of underlying mood disorder.

## Disclosure

The authors report no conflicts of interest in this work.

## References

1. Pompili M, Gianluca S, Marco I, et al. Unmet treatment needs in schizophrenic patients: is asenapine a potential therapeutic option? *Expert Rev Neurother*. 2011;11(7):989–1006.
2. Glazer WM. Extrapyramidal side effects, tardive dyskinesia, and the concept of atypicality. *J Clin Psychiatry*. 2000;61 Suppl 3:16–21.
3. Hirose S. The causes of under diagnosing akathisia. *Schizophr Bull*. 2003;29:547–558.
4. Kumar R, Sachem PS. Akathisia and second-generation antipsychotic drugs. *Curr Opin Psychiatry*. 2009;22:293–299.
5. Oral ET, Altinbas K, Demirkiran S. Sudden akathisia after a ziprasidone dose reduction. *Am J Psychiatry*. 2006;163:546.
6. Gao K, Kemp DE, Ganocy J et al. Antipsychotic-induced extrapyramidal side effects in bipolar disorder and schizophrenia: a systematic review. *J Clin Psychopharmacol*. 2008;28:2039.
7. Seemüller F, Shennach AM, Mayr A, et al; German Study Group on First-Episode Schizophrenia. Akathisia and suicidal ideation in first-episode schizophrenia. *J Clin Psychopharmacol*. 2012;32:694–698.
8. Kane JM, Fleischhacker WW, Hansen L, Perlis R, Pikelov A 3rd, Assunção-Talbott S. Akathisia: an updated review focusing on second-generation antipsychotics. *J Clin Psychiatry*. 2009;70:627–643.
9. Cohen BM, Keck PE, Satlin A, Cole JO. Prevalence and severity of akathisia in patients on clozapine. *Biol Psychiatry*. 1991;29:1215–1219.
10. Rummel-Kluge, Kamossa K, Schwartz S, et al. Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head to head comparisons. *Schizophr Bull*. 2010;38:167–177.
11. David DG, Zimbroff DL, Potkin SG, Reeves KR, Harrigan EP, Lakshminarayanan M. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. *Neuropsychopharmacology*. 1999;20:491–505.
12. Drake RE, Ehrlich J. Suicide attempts associated with akathisia. *Am J Psychiatry*. 1985;142:499–450.
13. Cem Atbaşoglu EC, Schultz SK, Andreasen NC. The relationship of akathisia with suicidality and depersonalization among patients with schizophrenia. *J Neuropsychiatry Clin Neurosci*. 2001;13:336–341.
14. Young AH, McElroy SL, Bauer M, et al; EMBOLDEN I (Trial 001) Investigators. A double blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in acute phase of bipolar depression (EMBOLDEN I). *J Clin Psychiatry*. 2010;71:150–162.
15. DeFruyl J, Deschepper E, Audenaert K, et al. Second generation antipsychotics in the treatment of bipolar depression: a systematic review and meta-analysis. *J Psychopharmacol*. 2012;26:603–617.
16. Moteshaifi H, Stip E. Comparing tolerability profile of quetiapine, risperidone, aripiprazole and ziprasidone in schizophrenia and affective disorders: a meta-analysis. *Expert Opin Drug Saf*. 2012;11:713–732.

### Neuropsychiatric Disease and Treatment

### Publish your work in this journal

Neuropsychiatric Disease and Treatment is an international, peer-reviewed journal of clinical therapeutics and pharmacology focusing on concise rapid reporting of clinical or pre-clinical studies on a range of neuropsychiatric and neurological disorders. This journal is indexed on PubMed Central, the 'PsycINFO' database and CAS.

Submit your manuscript here: <http://www.dovepress.com/neuropsychiatric-disease-and-treatment-journal>

Dovepress

The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.