Tardive Dyskinesia Associated With Olanzapine in a Neuroleptic-Naive Patient With Schizophrenia

Dear Editor:

Compared with traditional antipsychotics, olanzapine reduces psychotic symptoms without elevated risk of movement disorders (1). Cases of movement disorders have emerged following olanzapine use with previous neuroleptic exposure (2–4). We describe tardive dyskinesia (TD) occurring in a neuroleptic-naive individual following olanzapine use.

Mr A, aged 44 years, was diagnosed with untreated schizophrenia of more than 20 years’ duration according to DSM-IV-TR criteria. He also suffered from polysubstance dependence (specifically, binge pattern alcohol, cannabis, nicotine, and cocaine). No spontaneous movement disorders were elicited at his initial presentation.

The patient commenced olanzapine 20 mg daily, along with participation in an outpatient dual-diagnosis program. Three months later, paroxetine 20 mg daily was added for major depression, together with maintenance diazepam for withdrawal symptoms. The frequency of polysubstance use decreased gradually over the following year. At annual follow-up, parkinsonism (that is, postural rigidity, left upper extremity tremor, and rigidity without TD occurrence) was observed and recorded according to the Extrapyramidal Symptom Rating Scale (ESRS) (5). During the subsequent year, diazepam was tapered, and topiramate 300 mg daily was added for mood stabilization. Olanzapine was gradually increased to 40 mg daily to decrease residual psychotic symptoms. The polysubstance use became sporadic. At second-year follow-up, the ESRS elicited new jaw TD with previously stable parkinsonism. Owing to ongoing psychotic symptoms, we did not attempt any pharmacotherapy changes. Currently, the patient is not bothered by TD and continues pharmacotherapy. Illicit substance use remains a concern.

Animal studies suggest that olanzapine’s low TD potential may be owing to selectivity for basal ganglia nuclei, along with selective nuclear acid expression in the thalamic reticular nucleus (6). By contrast, typical antipsychotics appear nonselective: they broadly affect basal ganglia, causing changes in the substantia nigra and mediodorsal nucleus while also altering thalamic reticular nucleus gene expression. This nonselectivity could explain TD occurrence following chronic antipsychotic exposure (6). Apart from high dosages, alcohol abuse (4) and neurological disease (7) may be other risk factors for TD occurrence with atypical antipsychotics. Our patient was receiving high-dosage olanzapine, partly to decrease psychotic symptoms and partly because of his male sex and cigarette smoking, both of which decrease olanzapine levels (8). Vigilance for TD with atypical antipsychotics is warranted in schizophrenia patients with comorbid substance dependence.

References


Dear Editor:

Dr Ramassubu reports the case of a man aged 67 years who on 2 separate occasions 4 months apart developed anxiety, agitation, irritability, confusion, gait ataxia, and bilateral motor weakness on stopping paroxetine (1). On both occasions, symptoms remitted within 48 hours of his restarting paroxetine. The patient had multiple risk factors for multiinfarct dementia (that is, hypertension, diabetes, and coronary artery disease) and a history of memory problems. Following the first episode, magnetic resonance imaging (MRI) showed ischemic changes in the vertebrobasilar region, and angiography revealed mild occlusion or hypoplasia of part of the anterior cerebral artery. Repeat MRI after the second episode revealed no progression of the ischemic changes. Dr Ramassubu suggests that the 2 episodes of ataxia and motor weakness may reflect minor strokes caused by paroxetine discontinuation. We think this is highly improbable. The most likely explanation is that the patient experienced 2 episodes of paroxetine discontinuation syndrome and that the MRI changes are coincidental, perhaps reflecting early multiinfarct dementia for which this patient had multiple risk factors.

Selective serotonin reuptake inhibitor (SSRI) discontinuation syndrome can
account for all the patient’s symptoms. Anxiety, agitation, irritability, and unsteady gait are common features of the syndrome (2,3). It is unclear from Dr Ramassubu’s report exactly what “confusion” and “bilateral motor weakness” refer to. Confusion is a vague term, but it is a frequent complaint of patients experiencing SSRI discontinuation syndrome (2,3). Delirium has occasionally been reported with SSRI termination (4), and it is reasonable to postulate that delirium is more likely to occur in an elderly person such as this patient, in whom the central nervous system (CNS) is already compromised by cerebrovascular changes. With regard to bilateral motor weakness, the patient’s confusion and ataxia may have hindered objective assessment of motor power, particularly if fatigue and muscle aches—common SSRI discontinuation symptoms (2,3)—were present. Irrespective of this, we have observed muscular weakness in patients experiencing antidepressant discontinuation syndrome (5).

The rapid and complete resolution of symptoms on restarting paroxetine is characteristic of a discontinuation syndrome and implies a reversible neurochemical etiology (6). These features suggest that irreversible CNS ischemia (that is, stroke) is an improbable mechanism. That the 2 MRI scans showed no progression of the ischemic changes, despite the patient’s experiencing a second episode of discontinuation syndrome in the intervening period, also suggests that stroke was not the underlying mechanism and that the ischemic changes on the original MRI scan were coincidental. Dr Ramassubu suggests that the strokes may have occurred secondary to anxiety and elevated blood pressure experienced during the discontinuation syndrome (1). However, in a study specifically designed to characterize SSRI discontinuation syndrome, little variation in blood pressure was observed despite high rates of discontinuation symptoms (7). SSRI treatment may occasionally cause cerebral vasoconstriction (8), but the corollary is that, if vascular changes occurred on SSRI stoppage, one would expect to see vasodilation.

Dr Ramassubu reports an interesting case. However, the clinical features are not consistent with a stroke, and further, there is no convincing mechanism by which SSRI discontinuation syndrome could cause stroke. In our view, the importance of Dr Ramassubu’s case is that it demonstrates how antidepressant discontinuation symptoms can easily be misdiagnosed. We have encountered such symptoms misdiagnosed as adverse effects of a newly started antidepressant (9), as stroke (5), as influenza, as labyrinthitis, and as relapse and exacerbation of the underlying psychiatric illness.

References


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Re: Depression, Stroke Diagnosis, and SSRI Discontinuation Syndrome

Dear Editor:

I read with great interest Dr Ramassubu’s and Dr Patten’s article on the effects of depression on stroke morbidity and mortality (1), as well as Dr Ramassubu’s letter in the same issue about minor strokes related to paroxetine discontinuation (2). Together, these reports provoke much thought about the role of selective serotonin reuptake inhibitors (SSRIs) in preventing stroke and the complications of stroke. Dr Ramassubu reported an association between depressive symptoms and increased risk of stroke morbidity and mortality (1). Alternatively, in addition to an association with SSRI discontinuation syndrome, withdrawal of antidepressants such as paroxetine may create a clinical picture similar to a minor stroke. In their double-blind, placebo-controlled study of sertraline and the prevention of depression in stroke patients, Rasmussen and others reported that the prophylactic use of sertraline prevented the development of depression in poststroke patients (3). They also reported that patients given sertraline experienced fewer cardiovascular and noncardiovascular adverse events than patients treated with placebo. While there is room for much speculation about the mechanism by which SSRIs reduce the risk of stroke and cardiovascular events, a factor that may bear further consideration is the direct effect of SSRIs on platelets. SSRIs induce reduced platelet adhesion and activity, as has been noted by Musselman and colleagues (4). Further clinical evidence is summarized by Dalton and others (5). In a community-based study, Dalton found that SSRIs, but not non-SSRIs, were associated with significantly increased risk of gastrointestinal bleeding, particularly with the concomitant use of nonsteroidal antiinflammatory drugs.

In essence, depression, which is a well-established risk factor for the development of cardiovascular disease (6), can now be considered as a risk factor for cerebrovascular disorders. The SSRIs’ ability to inhibit platelet adhesion,
independent of their effect on mood, may be the causative agent. Whether response to depression is necessary for this added benefit has not been established.

If these observations are supported by further studies, we now also have another factor to consider in the selection of antidepressants. Patients who may be at increased risk for cardiovascular or cerebrovascular events may be better served by SSRIs as a drug of first choice. Alternatively, a non-SSRI agent may be the drug of first choice in the treatment of depression for those patients who are on nonsteroidal antiinflammatory drugs.

References


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Reply: Depression, Stroke Diagnosis, and SSRI Discontinuation Syndrome

Dear Editor:

I thank Dr Haddad and Dr Dursun for their interest in my case report (1) and for giving me an opportunity to address and discuss their concerns regarding whether physical symptoms related to paroxetine discontinuation were misdiagnosed as minor strokes. They assert that the manifested ataxia and bilateral motor weakness may have been related to the physical symptoms of selective serotonin reuptake inhibitor (SSRI) discontinuation syndrome and were unlikely to be caused by minor strokes.

As pointed out in the discussion, brain ischemia (that is, minor strokes) could better account for the neurological symptoms than could coexisting discontinuation syndrome, for several reasons. First, apart from 2 ischemic events following paroxetine discontinuation, the patient had presented to the emergency department with numerous episodes of transient ischemic attacks (TIA) involving vertebrobasilar territory. But on only 2 occasions were the motor weakness and ataxia that occurred following discontinuation of paroxetine considered serious enough to warrant admission to the hospital. Given the evidence of cerebrovascular disease with recurrent TIA’s, cardiovascular risk factors, and magnetic resonance imaging (MRI) findings, the neurological symptoms were clinically judged to be directly related to brain ischemia. Moreover, it is necessary to rule out a primary neurological condition such as stroke prior to considering neurological symptoms as physical symptoms of discontinuation syndrome (2). I admit that the objective assessment of motor power can be clinically challenging when the patient is agitated and tired. However, on repeat evaluations after the admission, the determination and documentation of motor weakness, pyramidal signs, and ataxia were consistent. Although “confusion” is a vague term, it is still frequently used in emergency to describe disorientation and muddled thinking. It is possible that both brain ischemia and discontinuation syndrome could have contributed to delirium.

The time course of symptom resolution for both discontinuation syndrome and minor strokes certainly overlapped in this patient. As with discontinuation syndrome, minor strokes are time-limited and reversible. The lack of progression in MRI findings was cited as the evidence against minor strokes. However, the patient’s clinical chart indicated that, during the second episode, cognitive symptoms as well as neurological symptoms definitely worsened and that recovery was incomplete, with residual deficits (This was not discussed in my case report, owing to lack of space.) Possibly overlapping symptoms (for example, delirium, weakness, and ataxia) and time course for symptom resolution between SSRI discontinuation syndrome and minor strokes may have complicated the identification of cooccurring stroke in SSRI discontinuation syndrome. Ruling out minor strokes in this patient with severe cerebrovascular disease remains virtually impossible.

The cooccurrence of SSRI discontinuation and minor strokes does not necessarily imply a causal relation and may be coincidental. The biological mechanisms suggesting a cause–effect relation between SSRI discontinuation and stroke remain largely speculative. Catecholamine activation and the related increase in blood pressure and decrease in cerebrovascular reserve have been postulated as possible mechanisms (1). Although blood pressure variation is seldom reported in SSRI discontinuation syndrome in healthy patients, this observation can not be generalized to an elderly patient with hypertension and cerebrovascular disease. Further, stimulation of the catecholamine system seems to induce platelet activation (4). Platelet activation may lead to platelet adhesion, aggregate formation, microembolization, release of granular constituents, thromboxane A2 formation, and vascular occlusion (5). Hence, platelet activation may play an important role in acute cerebrovascular events. Further, recent evidence suggests that paroxetine may have a protective effect against thrombotic vascular events, attributable to the inhibitory effect of SSRIs on serotonin-mediated platelet activation (6). More studies are required to examine the time course for the reversibility of the antiplatelet effect after acute discontinuation and the role of platelet activation on stroke-like symptoms in SSRI discontinuation syndrome.

Dr McNevin’s views about the role of depression in the development of ischemic stroke and the effect of SSRI treatment in preventing stroke are consistent with emerging literature on this subject (7,8). He rightly points out that SSRIs may play a role in preventing ischemic vascular events such as myocardial infarction (MI) and stroke (8). Taking into account that depression may increase the risk for ischemic stroke (7) and that platelet activation is associated with depression and stroke (9,10), it is...
conceivable that SSRIs may confer a protective effect against ischemic events, through their antiplatelet and antidepressant effects.

The depression recovery and inhibition of platelet activation associated with SSRI treatment may have additive protective effects against ischemic vascular events. Future studies should examine the differences in risk for MI or stroke in clinically recovered and nonrecovered depression patients treated with SSRIs. I agree with Dr McNevin’s opinion that SSRIs can be considered as a treatment of choice for patients with MI and ischemic stroke, owing to their efficacy, safety, and antiplatelet properties. Although 2 case–control studies failed to show association between SSRI use and intracranial bleeding (ICB) (11,12), caution should be exercised in using SSRIs at higher therapeutic dosages in patients with ICB and bleeding diathesis. Certainly, close monitoring is required when combining SSRIs with anticoagulants and nonsteroidal antiinflammatory drugs in these patients.

References


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