Olanzapine for the Treatment of Tardive Dyskinesia

Sir: Tardive dyskinesia (TD) is one of the most troublesome side effects associated with the use of antipsychotics. It is estimated that 20% to 30% of patients on long-term administration of neuroleptics will develop these abnormal involuntary movements that involve most commonly the tongue, face, fingers, arms, shoulders, and legs.1–2 Elderly patients seem to be particularly vulnerable to the development of these side effects—this is a particular concern because antipsychotics are often used for the treatment of a number of mental disorders in old age.3,4 Attempts to treat TD symptoms with neuroleptics, cholinergic drugs, benzodiazepines, and calcium channel blockers have not produced encouraging results.5 The potential benefit of vitamin E in preventing or reducing the severity of TD has been supported by some studies6,7 and is probably due to its antioxidant properties (free radical mechanisms). Recent reports have also suggested that the novel atypical antipsychotics may be beneficial in managing at least some types of dyskinesias.8–10 This report describes the case of an elderly chronic schizophrenic woman who developed moderately severe neuroleptic-induced dyskinetic movements that responded to the use of the recently introduced atypical antipsychotic olanzapine.

Case report. Ms. A, a 76-year-old single lady with a diagnosis of schizophrenia since age 24, was referred for the treatment of chronic auditory hallucinations and delusions. She also displayed signs of mild increase in muscle tone and dyskinetic movements of the face, jaw, tongue, arms, and feet that had started sometime during the previous 2 years. At the time of assessment, she was receiving propranoanol (40 mg/day), haloperidol (5 mg/day), clomipramine (75 mg/day), and chloropropamide (125 mg/day). After a 5-week period of drug adjustment, Ms. A was kept on haloperidol, 5 mg/day, biperiden, 3 mg/day, and bromazepam, 4.5 mg/day, for 7 months. Toward the end of this 7-month period, she experienced deterioration of her clinical state and of her dyskinetic movements. The dose of haloperidol was then increased to 7.5 mg/day for another 5 months, which was followed by mental state improvement but further deterioration of the extrapyramidal signs to a point that they often interfered with her eating. After 12 months of follow-up, the abnormal movements were rated according to the AIMS guidelines11—scores ranged from minimal (face, tongue, and lower limbs) to moderate (lips, jaw, and upper limbs). There was mild muscle rigidity at evaluation, but no gait problems.

Treatment alternatives were discussed with Ms. A and her main caregiver (brother). It was agreed that Ms. A would gradually discontinue the use of haloperidol and biperiden over 1 week and that olanzapine would be then introduced up to a dose of 10 mg/day over the next week. There was substantial improvement of all abnormal movements after 5 weeks of treatment with olanzapine—AIMS scores ranged from not present (face, jaw, tongue, lower limbs) to minimal (lips and upper limbs), and there were no signs of TD symptoms. After 10 weeks of treatment, Ms. A’s mental state and mood improved as well.

Pathophysiologic theories of TD suggest that these abnormal movements result from excessive dopaminergic activity in the striatum induced by chronic neuroleptic use,12 although the poor efficacy of antidopaminergic drugs in managing TD does not fully support this hypothesis. Others suggest that chronic neuroleptic use stimulates the production of free radicals, which in turn promote neuronal degeneration of nigrostriatal neurons and consequent dyskinetic movements.13,14 If that is indeed the case, an effective drug treatment for TD would be almost unattainable, and our efforts should be mostly based on strategies to prevent its development (e.g., decrease in dose and time of neuroleptic exposure, use of vitamin E).15,16 However, Lieberman and colleagues17 showed that some of their 37 chronic schizophrenics taking clozapine displayed a significant improvement of their dyskinetic movements after several weeks of treatment. Moreover, a recent report indicated that clozapine can effectively treat TD symptoms both in animals and humans and that dyskinetic patients lose their TD symptoms with long-term (12 months) clozapine treatment.18 The novel atypical antipsychotic olanzapine shows many pharmacologic similarities to clozapine and has the advantage of not producing agranulocytosis.19 A recently published study20 comparing 707 patients taking olanzapine with 197 patients taking haloperidol showed that the incidence of TD at follow-up was significantly lower among subjects treated with olanzapine. The outcome of the case reported here suggests that olanzapine may also be useful in the treatment of patients with abnormal dyskinetic movements induced by neuroleptics. However, other factors may also have contributed to improve TD in this particular case. Dyskinetic movements can be superimposed with other extrapyramidal signs (e.g., parkinsonian tremor) that may increase the severity of abnormal movements. In such cases, the reduction or discontinuation of typical antipsychotics is associated with improvement of motor functioning. Although this possibility cannot be totally dismissed, this is unlikely to have been the case in this particular instance, as the patient showed only very mild signs of parkinsonism before the discontinuation of haloperidol and biperiden. A second possibility is that it was not so much the introduction of olanzapine but the discontinuation of haloperidol and biperiden that was associated with the improvement of the patient’s abnormal movements. It is accepted that the discontinuation of anticholinergic drugs may mitigate the signs of TD to some extent, although the interruption of typical antipsychotics seems to be more often associated with an exacerbation of TD movements.21 A washout...
period would have been necessary to clarify whether the motor improvement observed in this case was associated with the introduction of olanzapine or the discontinuation of haloperidol and biperiden.

Single case studies present obvious methodological limitations, and the generalization of their findings can often be misleading. However, the failure to provide effective treatment for a debilitating condition such as TD should encourage the search for new forms of treatment. This case suggests that the efficacy of olanzapine for the treatment of TD merits further evaluation in systematic clinical trials.

REFERENCES

15. Miller R, Chouinard G. Loss of striatal cholinergic neurons as a basis for tardive and t-dopa-induced dyskinesias, neuroleptic-induced supersensitivity psychosis and refractory schizophrenia. Biol Psychiatry 1993;34:713–738

Oswaldo P. Almeida, M.D., Ph.D.
São Paulo, Brazil

Letters to the Editor

Venlafaxine: Loss of Antidepressant Effect and Its Management

Sir: The antidepressant profile of venlafaxine includes a broad range of clinical activity, as its effect is not influenced by factors such as the presence of melancholic features, age, gender, severity, or duration of depression.¹ A recent analysis of the treatments of major depression revealed that venlafaxine had the highest efficacy rates and lowest dropout rates when compared with tricyclics and serotonin reuptake inhibitors.² Up to one third of patients with rigorously defined treatment-resistant depression show a favorable response to venlafaxine, but nearly half of these patients are unable to sustain the antidepressant effect during the first 3 months of treatment.³ I present the case of a woman who was unable to sustain antidepressant response for more than 4 months following 2 separate trials of venlafaxine, but showed, on both occasions, an excellent response when rechallenged with venlafaxine after a 2-week washout period.

Case report. Ms. A, a 28-year-old married woman, had a 9-year history of major depression with underlying dysthymia, and panic disorder with phobic avoidance behavior. Before initiation of venlafaxine, she had failed to respond to adequate trials of imipramine, clomipramine, amitriptyline, phenelzine, isocarboxazid, fluoxetine, sertraline, and nefazodone. Augmentation strategies with the addition of lithium, lithium carbonate, and the combination of sertraline and amitriptyline were also unsuccessful. Similarly, she did not show a favorable response to a course of bilateral electroconvulsive therapy. Despite receiving trials of benzodiazepines, such as alprazolam in a daily dose of 1.5 mg, and valproic acid, Ms. A continued to experience rather frequent and severe panic attacks, which resulted in a marked reduction in her activities outside the home. Ms. A self-medicated with alcohol during the early part of the illness, but had been abstinent for several years before the initial trial of venlafaxine. In spite of requiring at least a dozen hospitalizations and complying regularly with the prescribed medications, Ms. A had remained highly symptomatic. The family history was positive for major depression and panic disorder in first-degree relatives, and a distant relative on her mother’s side of the family had committed suicide. There was no personal or family history of bipolar illness.

Ms. A showed a rather robust response to the addition of venlafaxine, up to 262.5 mg/day, to lithium, 750 mg/day, diazepam, 15 mg/day, and mexitolimprazepine, 25 mg/day. Not only did she experience a complete resolution of symptoms after 1 month of treatment, but there was also a marked improvement in her level of functioning. She was able to return to school after a hiatus of several years and was extremely pleased with her academic performance. The improvement was sustained for only 4 months, however, and over the next few months, Ms. A...
experienced a relapse of depression that included intense thoughts of suicide. She failed to respond to a higher daily dose (300 mg) of venlafaxine. Following a 2-week washout period during a hospitalization, venlafaxine was recommenced. Once again, she showed an excellent response to a daily dose of 262.5 mg, but unfortunately the symptoms of depression and anxiety reappeared after 4 to 5 months of treatment. She had no response when the venlafaxine dose was increased to 375 mg. Her condition continued to deteriorate, and she required rehospitalization. The doses of other psychotropic medications were kept the same, and the lithium level was in the therapeutic range. Venlafaxine was once again discontinued and then restarted after a 2-week washout period, this time titrated to a daily dose of 187.5 mg. Ms. A has been symptom free for 9 months but remains highly apprehensive about experiencing yet another relapse.

This patient suffered from a long history of treatment-resistant depression with nonresponse to adequate trials of various antidepressant drugs from different classes and electroconvulsive therapy as well as augmentation strategies. This makes it unlikely that the periods of improvement following trials of venlafaxine were related to placebo effect, or spontaneous remissions. It is also unlikely that this is a case of antidepressant drug–induced cycling as suggested by Wehr. There was no cycling in response to past trials of antidepressant drugs; instead, the course of the illness was marked by pervasive treatment-resistant depression.

Loss of antidepressant response has been described in relation to various antidepressant drugs, including monoamine oxidase inhibitors and tricyclics. Various strategies, including increasing the dose to the level of tolerability, substitution with another antidepressant drug, and decreasing the dosage of drug, have been suggested. Several hypotheses have been put forward to explain this apparent loss of antidepressant efficacy.

Given the clinical and heuristic implications of this observation, systematic studies are needed to further our understanding of loss of response to antidepressant drugs in certain patients.

References

Verinder Sharma, M.B., B.S., F.R.C.P.C.
London, Ontario, Canada

Stroke Resulting From a Rapid Switch From Phenelzine to Tranylcypromine

Sir: The article by Szuba et al.1 was brought to my attention by a patient (a social worker) who had a hemorrhagic stroke after being switched from phenelzine to tranylcypromine. This patient remains significantly disabled from the sequelae of her stroke; she was previously described in one of the articles2 3 cited by Szuba et al. and was further described in a subsequent article by Gelenberg.3

As indicated by Szuba et al.,1 some patients apparently can be switched abruptly from phenelzine to tranylcypromine without difficulty. However, other patients can have severe sequelae, and there is no way to predict which patients will have difficulty. The monitoring suggested by Szuba et al. would not have prevented my patient’s stroke, since it occurred precipitously. Of note, this patient sued her treating psychiatrist and won a fairly large settlement.

Also of note is that Szuba et al. did not state how long patients had been taking their initial monoamine oxidase inhibitor (MAOI) before the switch. They also did not indicate the dose of the initial MAOI. Both of these factors are crucial in evaluating the safety of rapidly switching from one MAOI to another.

My patient asked me to write this letter. She has residual hemiparesis, walks with a limp, and may also have cognitive changes as a sequelae to her cerebrovascular accident. I do not believe that the article by Szuba et al. should be taken as justification for rapidly switching patients from phenelzine to tranylcypromine.

References
3. Gelenberg AJ. Switching MAOIs—the sequel. Biol Ther Psychiatry 1985;5:41

Jeffrey A. Matte, M.D.
Princeton, New Jersey

Serotonin Syndrome Caused by a Clomipramine-Moclobemide Interaction

Sir: The serotonin syndrome is a toxic reaction attributed to excess brain serotonin.1 Such a syndrome may be induced by a single serotonergic agent, but most cases involve the combination of 2 agents, either coadministered or successively instituted. The combination of reversible monoamine oxidase inhibitors (RIMAs) and serotonergic agents has been reported to cause a serotonin syndrome,2 3 but the patient in case4 was also treated by other potentially causative agents (L-dopa and bromocriptine) and the remaining 2 patients3 had ingested massive doses of both moclobemide and clomipramine. We present a case of a serotonin syndrome induced by the succession of clomipramine and moclobemide, both at therapeutic dosages.

Case report. Ms. A, a 25-year-old woman with a recurrent depressive disorder, recovered with clomipramine 150 mg/day and alprazolam 1.5 to 3 mg/day. After 4 months, she stopped her treatment, relapsed, and recovered again after treatment
Ms. A fulfilled the diagnostic criteria for serotonin syndrome proposed by Sterbech. Unfortunately, no plasma levels were obtained. Nevertheless, since clomipramine’s half-life varies from 22 to 84 hours, significant amounts of this drug may have been present for 5 days to 2 weeks after withdrawal. The close temporal relationship between symptoms and both the institution and the removal of moclobemide, the clinical picture, and prompt reversal of symptoms when all antidepressants were interrupted support a diagnosis of a serotonin syndrome rather than a clomipramine discontinuation syndrome. Moreover, desmethylated and hydroxylated metabolites of clomipramine have demonstrated powerful serotonin reuptake inhibition. A confusional state solely due to moclobemide is possible, which would make the association between a clomipramine-moclobemide interaction and the toxic reaction a pure coincidence; however, symptomatology and clustering of signs highly suggested a serotonin syndrome. Finally, adding alprazolam to clomipramine may cause a serotonin syndrome; although this was not evident from previous cases in that Ms. A developed depression instead of mania or psychosis. This is probably because Ms. A is a woman with a history of bipolar disorder who developed a major depressive episode following administration of fenfluramine and phentermine.

**Case report.** Ms. A, a 42-year-old obese white woman with a history of bipolar I disorder, had experienced recurring depressive episodes since the age of 13 and had her first and only manic episode when she was 20 years old. She was thereafter maintained on treatment with lithium carbonate, but nevertheless suffered from 5 subsequent episodes of major depression, spaced at 3- to 5-year intervals. Eight months after recovering from her fifth episode of depression, Ms. A was started on treatment with fenfluramine, 20 mg t.i.d., and phentermine, 30 mg q.d., by her family physician for the treatment of obesity. Four days after treatment was started, she began to experience a depressed mood, poor concentration, anhedonia, fatigue, insomnia, poor appetite, rumination, and recurrent suicide ideation. Her serum lithium level was 1.36 mg/L. The diet medications were discontinued, and a trial of tranylcypromine was initiated at 10 mg t.i.d. and increased to 50 mg/day over a 6-week period. The patient’s depression started to lift 6 weeks after discontinuing the fen-phen combination.

In addition to this case, there have been other reports of mental disturbances due to fenfluramine and/or phentermine. Cleare reported that phentermine induced a manic episode with psychosis in a patient who had no previous psychiatric diagnosis, but who did have a family history of bipolar disorder. Another case report described restlessness, racing thoughts, and altered mentation induced by a combination of phentermine and fluoxetine in a patient with major depression. Raison and Klein reported that fen-phen induced psychotic mania in a patient with severe anergic depression. Most recently, the active metabolite of fenfluramine, dexfenfluramine, was reported to trigger paranoid and grandiose delusions, agitation, and pressured speech in a patient with major depression. Our report is different from previous cases in that Ms. A developed depression instead of mania or psychosis. This is probably because Ms. A is a woman with a history of bipolar disorder who developed a major depressive episode following administration of fenfluramine and phentermine.
Acute Dystonia With Olanzapine

Sir: Olanzapine is an atypical antipsychotic recently approved for the treatment of schizophrenia.1,2 We wish to report 2 cases in which dystonia was attributed to olanzapine use.

**Case 1.** Mr. A, a 50-year-old man who has had paranoid schizophrenia since the age of 35, previously presented with acute dystonia in the form of a torticollis after taking pimozide, 10 mg/day; risperidone, 6 mg/day; and haloperidol, 25 mg/day, in addition to an anticholinergic agent. He did not develop either dystonia or extrapyramidal symptoms during a subsequent trial of clozapine, 900 mg/day. Because of persistent positive and negative symptoms, Mr. A was switched to olanzapine, and the dosage was increased to 25 mg h.s. over 14 weeks. Procyclidine chloride, 5 mg b.i.d., was added to olanzapine, 15 mg/day, after he experienced stiffness in his neck muscles and facial tics. Two weeks after olanzapine was increased to 20 mg/day to 25 mg/day, Mr. A presented with a severe torticollis, relieved within an hour with benztrapine, 2 mg, intramuscularly. Olanzapine was replaced by fluphenazine, 18 mg/day, and procyclidine chloride, 7.5 mg b.i.d., with no recurrence of dystonia.

**Case 2.** Ms. B, a 68-year-old woman who has had a schizoaffective disorder since the age of 23, previously presented with akathisia and severe parkinsonism after taking haloperidol, 10 mg/day. Many trials of antipsychotics in combination with different mood stabilizers did not effect recovery. Recently, she was treated with risperidone, 4 mg b.i.d.; valproic acid, 875 mg/day; and procyclidine chloride, 2.5 mg h.s. Because of persistent psychotic symptoms, risperidone was replaced by olanzapine, 10 mg h.s., while the other medications were continued at the same dosages. Two days later, Ms. B presented with an acute lingual dystonia with dysarthria, relieved within an hour by diphenhydramine, 25 mg p.o. When olanzapine was increased to 15 mg h.s., she experienced a recurrence of the lingual dystonia, again alleviated first with diphenhydramine, 25 mg orally, and completely relieved thereafter with procyclidine, 5 mg b.i.d. She had no recurrence of dystonia, and psychotic symptoms were attenuated.

Acute dystonia occurs in 1.4% of patients who take olanzapine compared with 5.3% to 6.3% who take haloperidol.3,4 However, our 2 case reports suggest that patients with previous dystonia or severe parkinsonism related to antipsychotic treatment may be at higher risk to develop dystonia with olanzapine. In the first case, the dystonic reaction was observed while Mr. A was treated with olanzapine in excess of the recommended dosage. Nevertheless, significant neck muscle spasms were noticed in association with olanzapine, 15 mg/day, and probably represented a milder form of dystonia. In the second case, a withdrawal or tardive dystonia caused by risperidone discontinuation cannot be ruled out, although this appears less likely because of an exacerbation, rather than a decrease, of the acute dystonic reaction was observed when olanzapine was increased.5

Therefore, patients known for their propensity to manifest extrapyramidal side effects or dystonia during treatment with antipsychotics should be carefully monitored when treated with olanzapine. Olanzapine should be started at a low dose and increased slowly. Prophylaxis with an anticholinergic medication is advised with these patients, although this medication may be progressively discontinued in the absence of extrapyramidal side effects once the therapeutic dosage of olanzapine has been reached.6

References


Pierre Landry, M.D., Ph.D., F.R.C.C.P.  
Jocelyne Cournoyer, M.D., F.R.C.C.P.  
Montreal, Quebec, Canada