Letters to the Editor

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[3,4]—this is a particular concern because antipsychotics are often used for the treatment of a number of mental disorders in old age.[5,6] Attempts to treat TD symptoms with neuroleptics, cholinergic drugs, benzodiazepines, and calcium channel blockers have not produced encouraging results.[7] The potential benefit of vitamin E in preventing or reducing the severity of TD has been supported by some studies[8,9] 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.[10–12] 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, lips, tongue, arms, and feet that had started sometime during the previous 2 years. At the time of assessment, she was receiving propranolol (40 mg/day), haloperidol (5 mg/day), clomipramine (75 mg/day), and chlorpropamide (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 guidelines[13]—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 parkinsonism. 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,[14] 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 would promote neuronal degeneration of nigrostriatal neurons and consequent dyskinetic movements.[15,16] 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).[4,8,9] However, Lieberman and colleagues[17] 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.[12]

The novel atypical antipsychotic olanzapine shows many pharmacologic similarities to clozapine and has the advantage of not producing agranulocytosis.[18,19] A recently published study[20] 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

1. Baldessarini RJ, Cole JO, Davis JM, et al. Tardive Dyskinesia: Task Force Report No. 18. Washington, DC: American Psychiatric Association; 1980
2. Jeste DV, Wyatt RJ. Therapeutic strategies against tardive dyskinesia: two decades of experience. Arch Gen Psychiatry 1982;39: 803–816
3. Jeste DV, Caligiuri MP, Paulsen JS, et al. Risk of tardive dyskinesia in older patients: a prospective longitudinal study of 266 outpatients. Arch Gen Psychiatry 1995;52:756–765
4. Caligiuri MP, Lacro JP, Rockwell R, et al. Incidence and risk factors for severe tardive dyskinesia in older patients. Br J Psychiatry 1997; 171:148–153
5. Borson S, Raskind MA. Clinical features and pharmacological treatment of behavioral symptoms of Alzheimer's disease. Neurology 1997;48(suppl 6):17–24
6. Häfner H, Maurer K, Löffler W, et al. The influence of age and sex on the onset and early course of schizophrenia. Br J Psychiatry 1993;162:80–86
7. Soares KVS, McGrath J, Adams C. Evidence and tardive dyskinesia. Lancet 1996;347:1696–1697
8. Lohr JB, Cadet JL, Lohr MA, et al. Vitamin E in the treatment of tardive dyskinesia: the possible involvement of free radical mechanisms. Schizophr Bull 1988;14:291–296
9. Lohr JB, Cadet JL, Wyatt RJ, et al. Partial reversal of the iminodipropionitrile-induced hyperkinetic syndrome in rats by alpha-tocopherol (vitamin E). Neuropsychopharmacology 1988;1: 305–309
10. Durif F, Vidailhet M, Assal F, et al. Low-dose clozapine improves dyskinesias in Parkinson's disease. Neurology 1997;48:658–661
11. Casey DE. Extrapyramidal syndromes and new antipsychotic drugs: findings in patients and non-human primate models. Br J Psychiatry 1996;138(suppl 29):32–39
12. Tamminga CA, Thaker GK, Moran M, et al. Clozapine in tardive dyskinesia: observations from human and animal model studies. J Clin Psychiatry 1994;55(9, suppl B):102–106
13. Psychopharmacology Research Branch, National Institute of Mental Health. Abnormal Involuntary Movement Scale (AIMS). In: Guy W, ed. ECDEU Assessment Manual for Psychopharmacology, Revised. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976: 534–537
14. Casey DE. Tardive dyskinesia: pathophysiology. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: The Fourth Generation of Progress. 4th ed. New York, NY: Raven Press; 1995:1497–1502
15. Miller R, Chouinard G. Loss of striatal cholinergic neurons as a basis for tardive and L-dopa-induced dyskinesias, neuroleptic-induced supersensitivity psychosis and refractory schizophrenia. Biol Psychiatry 1993;34:713–738
16. Szymanski S, Munne R, Gordon MF, et al. A selective review of recent advances in the management of tardive dyskinesia. Psychiatr Ann 1993;23:209–215
17. Lieberman J, Johns C, Cooper T, et al. Clozapine pharmacology and tardive dyskinesia. Psychopharmacol Bull 1989;99(suppl):54–59
18. Pilowsky LS, Busatto GF, Taylor M, et al. Dopamine D2 receptor occupancy in vivo by the novel atypical antipsychotic olanzapine: a 123I IBZM single photon emission tomography (SPET) study. Psychopharmacology (Berl) 1996;124:148–153
19. Fulton B, Goa KL. Olanzapine: a review of its pharmacological properties and therapeutic efficacy in the management of schizophrenia and related psychoses. Drugs 1997;53:281–298
20. Tollefson GD, Beasley CM Jr, Tamura RN, et al. Blind, controlled, long-term study of the comparative incidence of treatment-emergent tardive dyskinesia with olanzapine or haloperidol. Am J Psychiatry 1997;154:1248–1254
21. Lohr JB, Bracha HS. Association of psychosis and movement disorders in the elderly. Psychiatr Clin North Am 1988;11:61–81

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

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, liothyronine sodium, 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 methotrimeprazine, 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[4] or spontaneous remissions. It is also unlikely that this is a case of antidepressant drug–induced cycling as suggested by Wehr.[5] There was no cycling in response to past trials of antidepressant drugs; instead, the prior 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.[6–8] 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.[9]

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

1. Entsuah AR, Rudolph RL, Chitra R. Effectiveness of venlafaxine treatment in a broad spectrum of depressed patients: a meta-analysis. Psychopharmacol Bull 1995;31:759–766
2. Addis A, Iskedjian M, Mittman N, et al. Meta-analysis of the treatment of major depressive disorders [abstract]. Can J Clin Pharmacol 1997;4:43
3. Nierenberg AA, Feighner JP, Rudolph R, et al. Venlafaxine for treatment-resistant unipolar depression. J Clin Psychopharmacol 1994;14:419–423
4. Quitkin FM, Stewart JW, McGrath PJ, et al. Further evidence that a placebo response to antidepressants can be identified. Am J Psychiatry 1993;150:566–570
5. Wehr TA. Tolerance to antidepressants [letter]. Am J Psychiatry 1985;142:1519–1520
6. Cohen BM, Baldessarini RJ. Tolerance to therapeutic effects of antidepressants. Am J Psychiatry 1985;142:489–490
7. Mann JJ. Loss of antidepressant effect with long term monoamine oxidase inhibitor treatment without loss of monoamine oxidase inhibition. J Clin Psychopharmacol 1983;3:363–366
8. Donaldson SR. Tolerance to phenelzine and subsequent refractory depression: three cases. J Clin Psychiatry 1989;50:33–35
9. Cain JW. Poor response to fluoxetine: underlying depression, serotonergic overstimulation, or a "therapeutic window"? J Clin Psychiatry 1992;53:272–277

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 articles[2] 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.[1] should be taken as justification for rapidly switching patients from phenelzine to tranylcypromine.

References

1. Szuba MP, Hornig-Rohan M, Amsterdam JD. Rapid conversion from one monoamine oxidase inhibitor to another. J Clin Psychiatry 1997; 58:307–310
2. Gelenberg AJ. Switching MAO inhibitors. Biol Ther Psychiatry 1984; 7:36
3. Gelenberg AJ. Switching MAOIs—the sequel. Biol Ther Psychiatry 1985;8:41

Jeffrey A. Mattes, 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 1 case[2] was also treated by other potentially causative agents (L-dopa and bromocriptine[4]) and the remaining 2 patients[3] 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

reinstitution. Seven months later, her depressive disorder recurred while she was compliant on the same regimen. Clomipramine was replaced—after 24 hours of withdrawal—by moclobemide 300 mg/day rapidly raised to 600 mg/day; the alprazolam dosage remained unchanged. One week after moclobemide treatment began, Ms. A returned for treatment and was mildly confused and somnolent, with mild euphoria and disinhibition. She reported that a few hours after the first dose of moclobemide she experienced mental status change with elevation of mood, nausea, shivering, and flushing. She had continued the moclobemide treatment throughout the week and had experienced sudden onsets of somnolence during the daytime, distraction, restlessness, incoordination, nighttime insomnia, and feelings of being drunk. Moclobemide was discontinued, and a marked improvement took place the next day. Eight days later, Ms. A had fully recovered from drug interaction–induced symptoms and was moderately depressed. Paroxetine was prescribed (20 mg/day) with alprazolam (0.5 mg/day), and no serotonin syndrome occurred during the next 3 months.

Ms. A fulfilled the diagnostic criteria for serotonin syndrome proposed by Sternbach.[1] Unfortunately, no plasma levels were obtained. Nevertheless, since clomipramine's half-life varies from 22 to 84 hours,[5] 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.[6] Moreover, desmethylated and hydroxylated metabolites of clomipramine have demonstrated powerful serotonin reuptake inhibition.[7] A confusional state solely due to moclobemide is possible,[8] 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[9]; although this was not the case in Ms. A, the contribution of alprazolam to the onset of the syndrome cannot be excluded.

Previous reports of a low potential for interaction between RIMAs and serotonergic antidepressants[10] are now challenged,[11,12] and serotonin syndromes can be observed at therapeutic dosages. When a RIMA is initiated after discontinuation of a serotonergic agent, length of withdrawal should be adapted to the half-life range of the latter drug to assure that serotonin syndrome will be prevented.

References

1. Sternbach H. The serotonin syndrome. Am J Psychiatry 1991;148: 705–713
2. Spigset O, Mjörndal T, Lovheim O. Serotonin syndrome caused by a moclobemide-clomipramine interaction [letter]. BMJ 1993;306:248
3. Neuvonen PJ, Pohjola-Sintonen S, Tacke U, et al. Five fatal cases of serotonin syndrome after moclobemide-citalopram or moclobemide-clomipramine overdoses [letter]. Lancet 1993;342:1419
4. Sandyk R. L-Dopa induced "serotonin syndrome" in a parkinsonian patient on bromocriptine. J Clin Psychopharmacol 1986;6:194–195
5. Balant-Gorgia AE, Gex-Fabry M, Balant LP. Clinical pharmacokinetics of clomipramine. Clin Pharmacokinet 1991;20:447–462
6. Schatzberg AF, chair, for the Discontinuation Consensus Panel. Serotonin reuptake inhibitor discontinuation syndrome: a hypothetical definition. J Clin Psychiatry 1997;58(suppl 7):5–10
7. Linnoila M, Insel T, Kilts C, et al. Plasma steady-state concentrations of hydroxylated metabolites of clomipramine. Clin Pharmacol Ther 1982;32:208–211
8. Freeman H. Moclobemide. Lancet 1993;342:1528–1532
9. Cano-Muñoz JL, Montejo-Iglesias ML, Yañez-Saez RM, et al. Possible serotonin syndrome following the combined administration of clomipramine and alprazolam [letter]. J Clin Psychiatry 1995;56:122
10. Joffe RT, Bakish D. Combined SSRI-moclobemide treatment of psychiatric illness. J Clin Psychiatry 1994;55:24–25
11. Brodribb TR, Downey M, Gilbar PJ. Efficacy and adverse effects of moclobemide [letter]. Lancet 1994;343:475
12. Lane R, Baldwin D. Selective serotonin reuptake inhibitor-induced serotonin syndrome: review. J Clin Psychopharmacol 1997;17: 208–221

Roland M. Dardennes, M.D.
Christian Even, M.D.
Nicolas Ballon, M.D.
François Bange, M.D.
Paris, France

Bipolar Depression Associated With Fenfluramine and Phentermine

Sir: Fenfluramine and phentermine have often been used in combination for the treatment of obesity. Although the *Physicians' Desk Reference*[1] lists depression as a potential adverse effect of fenfluramine, it is not contraindicated in the treatment of patients with comorbid mood disorders. We present the case of 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, ruminations of worthlessness, and recurrent suicide ideation. She was under no major stressors at the time. 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 phentermine and/or fenfluramine. Cleare[2] 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[3] described restlessness, racing thoughts, and altered mentation induced by a combination of phentermine and fluoxetine in a patient with major depression. Raison and Klein[4] 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.[5] 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

the only patient who had been maintained on treatment with a mood stabilizer prior to starting diet pills.

A common thread in the case reports is that phentermine, fenfluramine, or dexfenfluramine, either as single agents or in combination, may have destabilizing effects on mood in predisposed individuals. Although fenfluramine has been temporarily removed from the market because of concerns of pulmonary hypertension,[6] these reports may indicate that these agents should be avoided in patients with current depression, a history of bipolar disorder, or a strong family history of bipolar disorder.

References

1. Physicians' Desk Reference. Montvale, NJ: Medical Economics; 1997
2. Cleare AJ. Phentermine, psychosis, and family history. J Clin Psychopharmacol 1996;16:471–472
3. Bostwick JM, Brown TM. A toxic reaction from combining fluoxetine and phentermine [letter]. J Clin Psychopharmacol 1996;16: 189–190
4. Raison CL, Klein HM. Psychotic mania associated with fenfluramine and phentermine use [letter]. Am J Psychiatry 1997;154:711
5. Preval H, Pakyurek AM. Psychotic episode associated with dexfenfluramine [letter]. Am J Psychiatry 1997;154:1624–1625
6. Mark EJ, Patalas ED, Chang HT, et al. Fatal pulmonary hypertension associated with short-term use of fenfluramine and phentermine. New Engl J Med 1997;337:602–606

Jennifer E. Zimmer
Robert J. Gregory, M.D.
Syracuse, New York

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 chlorhydrate, 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 from 20 mg/day to 25 mg/day, Mr. A presented with a severe torticollis, relieved within an hour with benztropine, 2 mg, intramuscularly. Olanzapine was replaced by flupenthixol, 18 mg/day, and procyclidine chlorhydrate, 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 chlorhydrate, 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.[1,2] 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 an exacerbation, rather than a decrease, of the acute dystonic reaction was observed when olanzapine was increased.[3]

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.[4]

References

1. Tran PV, Dellva MA, Tollefson GD, et al. Extrapyramidal symptoms and tolerability of olanzapine versus haloperidol in the acute treatment of schizophrenia. J Clin Psychiatry 1997;58:205–211
2. Tollefson GD, Beasley CM, Tran PV, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective disorders: results of an international collaborative trial. Am J Psychiatry 1997;154:457–465
3. Kang UJ, Burke RE, Fahn S. Natural history and treatment of tardive dystonia. Mov Disord 1986;1:193–208
4. Keepers GA, Clappison VJ, Casey DE. Initial anticholinergic prophylaxis for neuroleptic-induced extrapyramidal syndromes. Arch Gen Psychiatry 1983;40:1113–1117

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