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LETTER TO THE EDITOR

Serotonin Syndrome Following the Administration of Tramadol with Paroxetine

Dear Editor

Serotonin syndrome, a clinical state resulting from central serotonergic hyperstimulation, presents with a variety of features including mental status changes, autonomic instability, fever, gross motor abnormalities and tremor (Brown *et al*., 1996; Martin, 1996). The serotonin syndrome is associated with high morbidity due to the involvement of the central and autonomic nervous systems, is occasionally fatal, and the symptoms may often go unrecognized or attributed to other psychiatric pathology such as anxiety, mood lability or confusion. Vulnerable patients, such as the elderly or those on multiple medications, are at greater risk for complications, including delirium, cardiovascular instability, myoclonus and even suicide (Reynolds, 1994; Sarfaty *et al*., 1995). While typically associated with the use of monoamine oxidase inhibitors, the increasing availability of antidepressant agents with serotonergic reuptake properties has increased the number of reports of this syndrome in recent years (Lane and Baldwin, 1997; Sporer, 1995).

Many recent case reports involve the use of antidepressant drug combinations, including venlafaxine and tranylcypromine (Brubacher *et al*., 1996; Hodgman *et al*., 1997), venlafaxine and phenelzine (Heisler *et al*., 1996) and trazodone with fluoxetine (George and Godleski, 1996). Fluvoxamine therapy resulted in a serotonergic reaction in a patient previously treated with paroxetine (Bastani *et al*., 1996). Concurrent administration of fluoxetine and buspirone has been reported to result in serotonergic symptoms in several recent case reports (Nijhawan *et al*., 1996; Baetz and Malcolm, 1995). The concurrent administration of selegeline with antidepressants may produce a profound serotonergic syndrome in vulnerable patients (Richard *et al*., 1997). A recent case report describes the possible emergence of serotonin syndrome in a patient taking multiple medications, including sertraline and tramadol (Mason and Blackburn, 1997). Another implicates paroxetine in combination with multiple medications in a patient compromised by severe vascular disease (Harvey and Burke, 1995).

Tramadol, a synthetic centrally acting analgesic which effects opiod mu receptors, also acts as an inhibitor of serotonin and norepinephrine reuptake (Raffa *et al*., 1992). The potential for interaction with other serotonergic agents exists, particularly when used by the frail elderly (Lee *et al*., 1993).

We report on two cases where symptoms of central serotonergic hyperactivity developed shortly after the addition of tramadol to a stable antidepressant regime of paroxetine.

CASE 1

A 78-year-old white female with a long history of recurrent major depression, osteoporosis and macular degeneration was taking paroxetine 20 mg daily with stable mood and relative remission of her depressive symptoms. Other medications included one multivitamin with iron daily and vitamin E 400 IU twice daily. She was started on tramadol 50 mg three times per day for chronic pain secondary to vertebral compression fractures. Within 3 days she began experiencing nausea, diaphoresis and irritability. On the fourth day she developed muscle weakness and confusion. She was evaluated in the emergency department with temperature of 100.8 F, pulse 110, and was noted to be agitated, restless and mildly confused. Laboratory evaluation, including CBC, chemistry panel and urinalysis, were all within normal limits. EKG showed sinus tachycardia. She was given a diagnosis of 'viral syndrome' and was advised to rest and drink fluids. She then sought psychiatric evaluation and was advised to stop both paroxetine and tramadol, due to concerns of a clinical presentation of a serotonin syndrome. Home care

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was provided and her symptoms gradually resolved over a 4–5-day period. She was able to resume the paroxetine 2 weeks later and has maintained stable remission of her depressive symptoms. She has since started on a regime of calcitonin for osteoporosis and acupuncture for her chronic pain condition.

CASE 2

An 88-year-old white female with a history of bipolar disorder had been treated with a stable regime of paroxetine 10 mg daily and valproate 250 mg twice daily for the previous 2 years. Other medications included quinapril 5 mg twice daily for hypertension, timolol ophthalmic solution 0.25% daily for glaucoma and aspirin 80 mg daily due to a history of a myocardial infarction 10 years earlier. After suffering a fall, she was evaluated in an emergency room and tramadol 50 mg four times per day was prescribed for pain. On the second day she developed nausea and reduced the tramadol to twice daily. On the third day she developed diaphoresis, vomiting, mild confusion, insomnia and dizziness. She adamantly refused to return to the emergency room or visit her internist. She was advised to stop the tramadol and paroxetine, and cyproheptadine 2 mg three times daily was prescribed. Her symptoms improved over a 4–5 day period, with the nausea and vomiting resolving after taking two doses of cyproheptadine. She subsequently used acetaminophen for pain relief and resumed paroxetine 10 mg daily with no recurrence of symptoms.

These cases appear to demonstrate the temporal association of a clinical serotonin syndrome with the concomitant administration of tramadol with a stable dose of paroxetine. In both cases, no other changes in medications occurred, and the syndrome resolved upon discontinuation of the agents. In addition, the paroxetine was later resumed and tolerated by both patients. In case 2, the patient received some benefit from cyproheptadine, which may alleviate some symptoms through its antagonistic affect on serotonin receptors (Lappin and Auchincloss, 1994).

While the development of symptoms in these cases strongly implicates the combination of tramadol with paroxetine in producing the syndrome, cases have been attributed to antidepressants alone in the elderly (Fischer, 1995; Kolecki, 1997).

There is increasing attention to the diagnosis and treatment of both depression and pain syndromes in the elderly. As it is expected that these conditions will require medication and other management, it is important to recognize and remain vigilant to the potential drug interactions, including the serotonin syndrome, which may result from the use of the multiple concurrent medications often prescribed for these conditions.

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