

CASE REPORT

Serotonin Syndrome in a Patient Using Paroxetine and Bupropion

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Abstract

Serotonin syndrome is an important clinical condition that can occur after excessive central serotonergic activity, generally secondary to the use of combinations of antidepressants. Selective serotonin reuptake inhibitors and bupropion are frequently used in the treatment of major depression in clinical practice. Few cases of serotonin syndrome due to the use of serotonergic antidepressants and bupropion have been reported in the literature. The current case report presents a patient who underwent the serotonin syndrome after the administration of paroxetine and bupropion.

Keywords: Serotonin Syndrome, Paroxetine, Bupropion

INTRODUCTION

Serotonin syndrome is a medical condition with symptoms that can vary from mild to life-threatening, secondary to excessive serotonergic activity in the central nervous system.^{1,2} Altered mental status (e.g. agitation, restlessness, anxiety and disorientation), neuromuscular abnormalities (e.g. rigidity, tremors, clonus and hyperreflexia) and autonomic hyperactivity (e.g. hypertension, hyperthermia, tachycardia and diarrhea) are its principal symptom clusters (1). This syndrome most frequently follows central serotonergic hyperactivity that may occur when combinations of psychotropic medications are taken, high doses of serotonergic antidepressants are used or, metabolism of serotonergic antidepressants is inhibited by medical drugs (2,3). The medications that are most commonly associated with the development of serotonin syndrome are monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants and venlafaxine (1,3,4).

Bupropion is a second generation antidepressant that is effective and generally well tolerated in the treatment of major depression. The most common reported adverse events related to bupropion are nausea, headache, dry mouth and anxiety (5). It is frequently used in combination with SSRIs in the clinical practice. There are few reports suggesting the occurrence of serotonin syndrome associated with the use of bupropion in the literature. The current report presents a patient diagnosed with serotonin syndrome due to use of a combination of paroxetine and bupropion.

CASE

A 35 year-old woman was admitted to the psychiatry outpatient clinic of an university hospital. The patient reported depressed mood, psychomotor retardation, thoughts of guilt, hopelessness, unwillingness, anhedonia, decreased attention, reduced sleep and appetite for 4 weeks at the admission. Three years ago, the patient was treated with sertraline at 100 mg/day and aripiprazole at 5 mg/day, following the diagnosis of a major depressive episode. The patient reported that although the symptoms were completely resolved after this treatment, reiteration of the symptoms occurred despite continued use of sertraline and aripiprazole at the same daily dosage.

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Psychiatric interview conducted by means of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (SCID-I) (6) indicated that the patient had major depressive disorder, recurrent episode. The score of 17-item Hamilton Rating Scale for Depression (HAM-D) (7) was 26. Aripiprazole was stopped and bupropion at 150 mg/day was added to the treatment regime. Three weeks later, the patient had similar symptom severity (HAM-D score=25); therefore, sertraline was changed with paroxetine at 30 mg/day. One day later, the patient reported fever, agitation, severe anxiety, diarrhea, and myoclonus in all extremities. Additionally, hyperprexia (38.2 °C, axillary temperature), tachycardia, hypertension (150/95 mm/Hg), tremor in bilateral hands and hyperreflexia were observed in the physical examination. Complete blood count, transaminases, creatine phosphokinase, electroencephalography, renal and thyroid function tests and electrolytes were normal. Based on the clinical picture, the patient was diagnosed with serotonin syndrome. The antidepressant medications were stopped and lorazepam at 1 mg/day was started. The symptoms were markedly decreased during the following day and were completely resolved within 36 hours. After that, the treatment included paroxetine at 30 mg/day and lamotrigine at 200 mg/day. No symptoms of serotonin syndrome were observed in the following weeks.

DISCUSSION

The current case appears to be the first report suggesting the development of serotonin syndrome associated with the concurrent use of paroxetine and bupropion. Previously, Dvir and Smallwood (4) reported serotonin syndrome in a patient who was administered fluoxetine (40 mg/day), olanzapine (5 mg/day), methadone (50 mg/day) and bupropion (150 mg/day). Munhoz (8) reported the case of female patient who developed serotonin syndrome after using a combination of sertraline (50 mg/day), bupropion (300 mg/day) and venlafaxine (75 mg/day). Thorpe et al. (9) diagnosed this syndrome due to bupropion toxicity in an adolescent patient. One other case report by Falls and Gurrera (10) included the combined use of bupropion, trazodone, tramadol and oxycodone leading to serotonin syndrome. Clinical symptoms including delirium, confusion, hemodynamic disturbances and hallucinations noted in these reports were more severe compared to the present case. Thus, the patient in the current case was not hospitalized and

improved within 36 hours following the discontinuation of bupropion. On the other hand, the prevalence rate of serotonin toxicity in single bupropion overdoses including ≥ 900 mg was reported to be 5.9-33% (11, 12). In addition, an international toxicology database study suggested that bupropion was antidepressant that the most frequently associated with serotonin toxicity (13).

Paroxetine is an SSRI that has the highest affinity for the serotonin transporter that is responsible for serotonin reuptake (14). The main pharmacodynamic effect of bupropion is inhibition of dopamine and norepinephrine reuptake. Its influence on serotonin neurotransmission is negligible, although it promptly increases 5-HT neuronal activity, due to early desensitization of the 5-HT_{1A} autoreceptor (15,16,17). Therefore, explaining the occurrence of serotonin syndrome in the current case with pharmacodynamic interactions between bupropion and paroxetine appears to be difficult. Bupropion and its main metabolite hydroxybupropion inhibit cytochrome P 450 (CYP) isoenzyme 2D6. Therefore, concomitant administration of this antidepressant with other medications that are metabolized by CYP2D6 should be carried out with caution (5). While paroxetine is primarily metabolized by CYP2D6 (18), sertraline is not a major substrate for this isoenzyme (19,20). It may be surmised that due to the specific pharmacokinetic properties of these drugs, serotonin syndrome in the current patient emerged from a combination of paroxetine with bupropion but not a combination of bupropion and sertraline, even though the latter has an affinity for the serotonin transporter almost as high as paroxetine (14).

In conclusion, the present case report suggests that concurrent use of bupropion and paroxetine may lead to serotonin syndrome. Clinicians should be careful about this syndrome and enlighten patients on its symptoms. Further studies are needed to determine the prevalence of serotonin syndrome in patients using bupropion and SSRIs, especially paroxetine.

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