

Serotonin Syndrome After Electroconvulsive Therapy in a Patient on Trazodone, Bupropion, and Quetiapine: A Case Report

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Background: Serotonin syndrome is a potentially fatal complication that usually occurs in the combination use of several serotonergic agents. We presented a patient with major depressive disorder under the treatment of bupropion, trazodone, and quetiapine. Serotonin syndrome developed soon after she received the first session of electroconvulsive therapy (ECT).

Method: This study is a case report.

Results: A 70-year-old female with major depressive disorder developed serotonin syndrome after the first session of ECT in combination with bupropion, trazodone, and quetiapine. Serotonin syndrome did not reappear in the subsequent ECT treatment while in the treatment with different therapeutic agents.

Conclusions: The superimposing effect of ECT in conjunction with serotonergic agents might contribute to the development of serotonin syndrome.

Key Words: serotonin syndrome, electroconvulsive therapy, antidepressant, drug interaction

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Serotonin syndrome is characterized by a triad of symptoms, namely, mental status change, neuromuscular hyperactivity, and autonomic instability. It is a potentially life-threatening condition that results from increased serotonin activity or concentration in the central nervous system. Serotonin syndrome can occur in high doses of serotonergic antidepressant monotherapy or the combination of multiple serotonergic agents. Concomitantly using drugs that directly or indirectly increase the central serotonin transmission may lead to serotonin syndrome.¹

Although the effect of electroconvulsive therapy (ECT) on depression is not clearly understood, some studies have indicated that ECT has serotonergic effects. A few case reports have indicated that serotonin syndrome occurred when ECT and selective serotonin reuptake inhibitors were combined.^{2,3} We present a case of transient serotonin syndrome that occurred after the first session of ECT combined with trazodone, bupropion, and quetiapine treatment.

CASE PRESENTATION

Mrs A, a 70-year-old woman, had major depressive disorder since the age of 67 years. She was first treated with escitalopram (10 mg daily) and sulpiride (200 mg daily) in our outpatient department. Her initial response to treatment was favorable. However, before admission, she had deteriorating depressive symptoms, including persistent poor intake, considerable weight loss, psychomotor retardation, reduced self-care, and recurrent suicidal

ideations, for 3 months. After admission, the medications were initially shifted to trazodone (50 mg daily), bupropion (150 mg daily), and quetiapine (200 mg daily). However, her clinical depression was deteriorated with mood-congruent psychosis involving auditory hallucination (voices commenting) and somatic delusion. The medication dosage was gradually adjusted to 100 mg of trazodone, 300 mg of bupropion, and 400 mg of quetiapine administered daily. However, there was no considerable improvement after 6 weeks of treatment. Electroconvulsive therapy was then suggested for her refractory symptoms.

Before ECT, the following workups were performed: brain computed tomography, electroencephalography, electrocardiography, blood tests, and physical and detailed neurological examination; there was no noteworthy finding. A bifrontal brief pulse ECT was administered using a Thymatron system after intravenous propofol anesthesia. However, after the first ECT session, the patient was noted to demonstrate prolonged confusion, agitation, disorientation, and disorganized speech. She was hypertensive (blood pressure, 178/99 mm Hg) and had tachycardia (90–110 beats per minute), an elevated temperature (37.8°C), and diaphoresis. Comprehensive blood tests, electroencephalography, and a physical examination were repeated for the delirious feature. There were no notable findings. The neurological examination revealed inducible myoclonus, hyperreflexia, bilateral hand tremors, and subtle limb rigidity. Her clinical condition was suspected to be serotonin syndrome. Trazodone and bupropion were discontinued because of concerns about the possible serotonergic effects. The symptoms of serotonin syndrome were completely resolved within the next 2 days, and her depressive symptoms persisted. We shifted the antidepressant to mirtazapine (30 mg daily), and the coadministered medications were trazodone (100 mg daily) and quetiapine (400 mg daily). Electroconvulsive therapy was reinitiated 1 week later. Both the depressive symptoms and psychotic symptoms resolved after the patient completed 6 sessions of ECT, and no further serotonin syndrome was noted in the subsequent ECT treatment. She was subsequently discharged and received regular follow-up at our outpatient department.

DISCUSSION

Serotonin syndrome presents as a triad of neuroexcitatory symptoms, namely, mental status change, autonomic hyperactivity, and neuromuscular abnormality. The onset of serotonin syndrome is rapid in that it usually develops within 24 hours after a change of medication or self-poisoning,⁴ and it usually resolves within a few days after the causal agents are withdrawn. The traditional diagnostic tool for this syndrome is the Sternbach criteria.⁵ Dunkley et al⁶ established the Hunter Serotonin Toxicity Criteria, and they reported that these criteria are highly sensitive and specific.

In the current case, the patient's neuromuscular and autonomic symptoms as well as the change in her mental status were pathognomonic signs of serotonin syndrome. Her condition was consistent with both the Hunter Serotonin Toxicity Criteria and Sternbach criteria for serotonin syndrome.^{5,6} The rapid onset of the symptoms

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and rapid resolution after the cessation of possible serotonergic agents also support the diagnosis.

Serotonin syndrome is considered to be caused by the hyperstimulation of the 5-HT_{1A} and 5-HT_{2A} receptors in the gray matter and spinal cord of the central nervous system⁷; furthermore, drugs that directly or indirectly increase central serotonin neurotransmission at the postsynaptic 5-HT_{1A} and 5-HT_{2A} can induce serotonin syndrome.⁷ A single therapeutic agent may induce serotonin syndrome; however, a combination of therapeutic agents is usually required to produce this syndrome. Moreover, the process of adding drugs that inhibit cytochrome isoforms CYP2D6 and CYP3A4 to therapeutic selective serotonin reuptake inhibitors has been associated with the risk of developing the condition.^{1,8}

Our patient was treated with trazodone (100 mg daily), bupropion (150 mg daily), and quetiapine (400 mg daily). Trazodone acts as a dual serotonin agonist and serotonin reuptake inhibitor; although its exact mechanism of action is not clearly understood, trazodone seems to increase serotonin activity,⁹ and it was reported to be associated with serotonin syndrome.¹⁰ In contrast to trazodone, debates are ongoing regarding whether bupropion is serotonergic. A previous study reported that bupropion overdose may induce serotonin syndrome¹¹; however, there is insufficient evidence that bupropion has remarkable serotonin activity in the central nervous system.¹² The role of bupropion in inducing serotonin syndrome may be attributed to its specific inhibition of the cytochrome P450 2D6 pathway, and bupropion could increase serotonin levels indirectly when combined with other serotonergic agents.⁸ Previous studies have reported the occurrence of serotonin syndrome in association with atypical antipsychotics such as quetiapine.^{7,13} Conversely, atypical antipsychotics were used in treating serotonin syndrome.¹ Although the role of atypical antipsychotics in serotonin syndrome is still not understood, atypical antipsychotic agents are suggested to induce serotonin syndrome by antagonizing 5-HT_{2A} and 5-HT_{3A} receptors, thereby leading to the selective activation of 5-HT_{1A}.⁷

Trazodone is extensively metabolized by cytochrome p450 isoform 3A4 (primary) and cytochrome p450 2D6,⁹ whereas bupropion is a strong inhibitor of CYP2D6. The interaction between trazodone and bupropion may increase the level of trazodone in the blood, consequently predisposing the body to serotonin toxicity. Moreover, our patient rapidly developed serotonin syndrome after the first ECT session, and we concluded on the basis of the temporal association that ECT may have induced serotonin syndrome in the patient.

Few studies have examined ECT-induced serotonin syndrome; a previous study reported that serotonin syndrome was induced by ECT in combination with lithium and mirtazapine.¹⁴ Another report showed that concurrently using ECT and the serotonin reuptake inhibitors paroxetine and fluoxetine may evoke transient serotonin syndrome.^{3,15} Similar to our patient, transient serotonin syndrome induced by ECT occurred in a few hours, improved within 24 hours, and completely disappeared in 2 to 4 days. Common features of these 3 cases are an elderly age, the female sex, and a diagnosis of major depressive disorder, which may be predictors of vulnerability to ECT-associated serotonin syndrome.

The mechanism of ECT in triggering serotonin syndrome must be investigated further. A previous study reported that ECT enhanced serotonergic neurotransmission and activities.¹⁶ Furthermore, another study suggested that ECT may alter several 5-HT receptor subtypes in the central nervous system and that repeated ECT may sensitize 5-HT_{1A} receptors in postsynaptic neurons.¹⁷ These studies have indicated that ECT may affect the serotonin activity in the central nervous system. In addition, another study suggested that ECT may cause transiently increased blood-brain barrier (BBB) permeability in humans and enhance the transmissibility

of antidepressants to the brain.² In line with our case, 1 study reported that age and ECT are both risk factors for a change in the BBB permeability to certain drugs.¹⁴ Therefore, we propose that ECT may have an add-on effect in triggering serotonin toxicity by enhancing the effect of serotonin and increasing the permeability of antidepressants, particularly in elderly patients. Notably, concomitant use of ECT and serotonergic drugs is not uncommon; however, the incidence of ECT-induced serotonin syndrome is relatively low. Moreover, ECT has been suggested to be a treatment option for serotonin syndrome. Age and unknown genetic variations^{1,7} may play a critical role in individual vulnerability.

CONCLUSIONS

Electroconvulsive therapy may induce serotonin syndrome by enhancing the serotonergic effect or increasing the BBB permeability. Clinicians should be aware of this rare but lethal adverse effect of serotonin syndrome possibly induced by combining ECT and antidepressants. Further research must be conducted to clarify the role of ECT in serotonin syndrome.

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