Serotonin syndrome after electroconvulsive therapy for refractory depression

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ABSTRACT
Serotonin syndrome is a toxicological entity with potential morbidity and mortality if unrecognized and untreated. Toxicity can occur after dose or increase or initiation of additional serotonergic medication, but can also be idiopathic. We report a case in which serotonin syndrome occurred after electroconvulsive therapy in the absence of escalation of medical therapy, and theorize a pathophysiologic mechanism based on basic science of blood–brain barrier integrity change after ECT.

KEYWORDS
Serotonin syndrome; electroconvulsive therapy; ECT; depression; toxicity

Introduction
An estimated 16.2 million adults in the United States experience major depression and about 50% receive medical therapy [1]. Most antidepressant medications act by increasing serotonin (5-HT) signaling, either via enhancing serotonin secretion, preventing re-uptake of synaptic serotonin, or hindering breakdown of the neurotransmitter. This hyperserotonergic state places patients at risk of developing serotonin syndrome, a condition comprised of altered mental status, tremor, clonus, hyperreflexia, seizures, and autonomic instability. A detailed discussion of its pathophysiology, diagnosis, and management exists elsewhere [2].

Patients with medication resistant major depressive disorder, often with debilitating psychotic features, may be candidates for ECT once they fail a reasonable trial of antidepressants, and combination therapies. Under general anesthesia, patients receive a cerebral electric stimulus above seizure threshold. Electroconvulsive therapy produces temporary retrograde and anterograde amnesia, but serotonin syndrome is not a known adverse event of ECT. The body of scientific literature describes three cases that feature strong temporal association between ECT and onset of serotonin syndrome [3–5].

Case
A 56-year-old woman with pertinent past medical history of depression, excessive fatigue, and hypothyroidism whose medication regimen included lamotrigine 400 mg daily, levothyroxine 125 mcg daily, mirtazapine 15 mg at bedtime, and venlafaxine 450 mg daily underwent ECT due to poorly controlled symptoms. She remained on these medications for the past 2 years with last dosage adjustment 4 months prior to her presentation. She had not previously experienced psychotic features with her depression.

On day 0, the patient received ECT under general anesthesia including labetalol 20 mg IV, glycopyrrolate 0.2 mg IV, rocuronium 2.5 mg IV, succinylcholine chloride 100 mg IV, and methohexital 100 mg IV. After awakening, the patient began feeling restless and had insomnia. Her symptoms worsened the on day 1 and she developed subjective akathisia, but did not seek care. She was again unable to sleep, and her son found her sitting on her couch with confusion and restlessness on day 2. He brought her to the ECT suite for her appointment, but the medical staff referred her to the emergency department (ED) for medical clearance to facilitate psychiatric evaluation.

Upon arrival in the ED, she was tachycardic (126 bpm, sinus), hypertensive (160/87 mmHg), mildly tachypneic (20 rpm), and euthermic (37.2 °C). The physical exam revealed mydriasis, psychomotor agitation with restlessness but no aggression, and verbal perseveration. She was oriented to person and place only, mildly diaphoretic, and able to follow basic commands. The initial medical provider did not document clonus, tremor, hyperreflexia, or nystagmus.
as present or absent. Cerebral computed tomography was grossly normal, and laboratory evaluation showed normal serum electrolyte concentrations with mildly depressed bicarbonate (22 mEq/L), normal complete blood count, normal thyroid stimulating hormone (2.90 mIU/L), normal lactate (1.0 mEq/L), and negative urine drug immunoassay. An electrocardiogram featured sinus tachycardia at 119 bpm with the following electrical intervals: PR 136 ms, QRS 105 ms, and QT/QTc 340 ms/478 ms.

The initial medical provider suspected worsening depression with psychotic features or delirium from sleep deprivation. A psychiatry consultant recommended trazodone 50 mg by mouth at bedtime in addition to her home dose of mirtazapine to help the patient re-establish a circadian rhythm. The patient remained in the ED overnight. The following day, the medical team noted the patient was diaphoretic with worsening confusion, and noted spontaneous rhythmic movements in her lower extremities. The treating physician consulted a medical toxicologist.

On evaluation by the medical toxicologist, the physical exam revealed diaphoresis and mydriasis (6 mm) without nystagmus or ocular clonus. She was hyperreflexic in all extremities, had non-extinguishable ankle clonus and patellar clonus, as well as positive Hoffman’s reflex. The patient satisfied Hunter Serotonin Toxicity Criteria [6]. She received lorazepam 2 mg IV and the medical provider discontinued all serotonergic drugs. The patient required two additional lorazepam 1 mg IV doses over the subsequent 5 h. The patient’s symptoms resolved over the subsequent day, and she transitioned from the intensive care unit to the medical floor where she awaited placement to an inpatient psychiatric unit for further treatment of her depression. Her psychiatric provider discontinued lamotrigine and venlafaxine, but continued mirtazapine. The patient underwent repeat ECT 1 week after initial presentation without further complications.

### Discussion

Serotonin syndrome is a toxicological emergency with the potential for serious morbidity and mortality. Most cases arise from either therapeutic or intentional supratherapeutic ingestion of serotonergic medication, or their inadvertent interaction. Regardless of the type of medication, the pathophysiologic pathways converge to create an excess of serotonin in the synapses of both central and peripheral nervous system. The resulting supraphysiologic serotonergic tone results in a spectrum of symptoms ranging from mild akathisia to life-threatening hyperthermia, seizure, and death.

Several case reports detail a temporal association between electroconvulsive therapy and the development of serotonin syndrome [3–5]. Two case reports detail immediate onset of symptoms after the first procedure [3,4]. Another case [5] describes the onset of serotonin syndrome 2 d after the 5th session of ECT, which may have been confounded by induction of lithium therapy [7]. The serotonin syndrome resolved over 24–48 h in all cases, and patients underwent subsequent ECT sessions without complications with reduced or discontinued serotonergic medications [3,4]. Table 1 summarizes the medications and clinical courses.

Patients undergoing ECT often have used or are using serotonergic medications. It is unclear whether ECT can cause serotonin syndrome in the absence of any serotonergic medication.

| Author/reference | Age/sex | Medication prior to ECT | Anesthesia | Onset of symptoms | Symptoms | Treatment |
|------------------|---------|-------------------------|------------|-------------------|---------|-----------|
| This case        | 56 F    | Lamotrigine, mirtazapine, venlafaxine, levothyroxine | Methohexital | 1st ECT session, immediate | Confusion, tachycardia, hypertension, agitation, diaphoresis, mydriasis, clonus, Hoffman’s sign | Lorazepam |
| Okamoto [3]      | 67 F    | Paroxetine, zolpidem, bromazepam | Propofol | 1st ECT session, immediate | Tachycardia, Hypertension, Hyperthermia, diaphoresis, myoclonus, tremors, hyperreflexia confusion, agitation, disorganized speech, tachycardia, diaphoresis, myoclonus, hyperreflexia, tremors, mild rigidity | Flunitrazepam |
| Chen [4]         | 70 F    | Trazodone, bupropion, quetiapine | Propofol | 1st ECT session, immediate | Confusion, agitation, disorganized speech, tachycardia, diaphoresis, myoclonus, hyperreflexia, tremors, mild rigidity | Not specified |
| Deuschle [5]     | 45 F    | Mirtazapine, quetiapine | Not specified | 5th ECT session, 2 day delay | Agitation, auditory/visual hallucinations, tachycardia, hypertension, hyperreflexia | Diazepam, haloperidol |

The mechanism of action of ECT is understood poorly [9]. The procedure may enhance 5-HT1A receptor responsivity [10], but the data are
controversial [11]. If ECT enhances serotonergic signaling cascades, it is plausible that patients on serotonergic medication experience sufficient serotonergism to become symptomatic.

A proposed mechanism with some basic science support is that ECT enhances the permeability of the blood brain barrier. Plasma amyloid β peptides increase after electroconvulsive therapy [12]. Murine studies show increased cerebral drug uptake after ECT [13]. Magnetic resonance imaging in humans undergoing ECT shows higher brain water content, supporting the notion of capillary leak [14]. With compromised integrity of the blood brain barrier, it is, therefore, plausible that central compartment drug concentrations could increase drastically after ECT. Thus, ECT may facilitate the development of serotonin syndrome rather than directly cause it.

It remains intrinsically challenging to assess the contribution of ECT to the development of serotonin syndrome. Virtually all patients undergoing ECT receive serotonergic medications.

Conclusion
Serotonin syndrome may follow as a consequence of electro-convulsive therapy and may go unrecognized.

Disclosure statement
The authors report no conflict of interest.

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