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Letter to the Editor

From catatonic stupor to serotonergic overdrive: A case-series illustration

1. Introduction

Serotonin syndrome (SS) is a rare and potentially fatal side effect triggered by a drug overdose or interactions between drug classes which increase serotonergic neurotransmission (Boyer and Shannon, 2005). The symptoms manifest as altered mental status, neuromuscular abnormalities, and autonomic hyperactivity (Dunkley et al., 2003) and mortality rates vary between 2–12% (Frank, 2008). While drug combinations typically induce SS, co-prescription of medications with electroconvulsive therapy (ECT) can also precipitate a hyper-serotonergic state (Klysner et al., 2014; Okamoto et al., 2012). ECT is usually the treatment of choice in severe depression with catatonic features where anti-depressants are often initiated simultaneously. Here, we describe two patients who developed serotonin syndrome after a full course of ECT and highlight how catatonic depression might be a unique risk factor for this emergent adverse event.

1.1. Case 1

Mr. N, a 24-year-old male, presented with two-years of academic decline and social withdrawal; six-months of low mood, anhedonia, helplessness, hopelessness, death wishes and one-month of mutism, staring, posturing, reduced sleep and appetite. His Bush Francis Catatonia Rating Scale (BFCRS) score was 6 – immobility(1), mutism (1), staring(1), posturing(1), rigidity(1) and withdrawn behaviour(1). His hematological and biochemical invetsigations were unremarkable. He had failed a trial of escitalopram in the past and was started on Venlafaxine 37.5 mg, gradually increased to 300 mg and Tab. Lorazepam 2 mg TID, with no sustained improvement in catatonia over the next four-days. He received six bifrontal ECTs over two-weeks. There was complete remission of catatonic and depressive symptoms after six-ECTs. On the day of the sixth-ECT, Tab.Venlafaxine was increased to 300 mg and on the following day he was noted to have confusion, disorientation, overfamiliarity, disinhibition and agitation. His pulse was 116bpm, blood pressure was 120/80 mmHg, and pupils were mydriatic. There were bilateral postural fine tremors, with generalized hyperreflexia in all deep tendon reflexes, along with an ill-sustained ankle clonus. He had developed SS on a combination of ECT and Venlafaxine. His cognitive functions were monitored daily with Hindi Mental Status Examination (HMSE) (Ganguli et al., 1995); which was 24/31 on the first day of SS. All medications were stopped and he was started on Tab. Cyproheptadine 12 mg in divided doses. For agitation, Tab Quetiapine 200 mg was also initiated. The confusion and disorientation resolved on day five (HMSE score 31). Subsequently, there was a resurgence of catatonic and depressive symptoms and Tab. Lorazepam 2 mg TID was reinitiated, with which the catatonic symptoms resolved. He was serially monitored for signs of SS, all of which gradually improved over a period of three-weeks except hyperreflexia and tremors which persisted. Later, sertraline 25 mg was initiated for the treatment of depression. Quetiapine and cyproheptadine were tapered and stopped, and Lorazepam 2 mg TID was continued to prevent relapse of catatonia. After discharge, he did not follow-up and further clinical details were unavailable.

1.2. Case 2

Mrs. X, a 28-year-old lady, presented to the emergency with seven-months illness of low mood, anhedonia, fatiguability, insomnia and decreased appetite. In the past month, she developed psychomotor retardation which progressed to immobility, near mutism, and poor oral intake. Her BFCRS (Bush et al., 1996) score was 12 – mutism(3), immobility(2), posturing(3) and rigidity(2). Cap. Fluoxetine 20 mg and Tab Lorazepam 2 mg TID, were initiated, but there was no improvement in catatonia over the next two days. We initiated bifrontal ECTs, three per-week, administered over two-weeks. Catatonic symptoms resolved completely after the third-ECT; depression remitted after the sixth ECT. Two days after the sixth-ECT, she developed loose stools and examination revealed a pulse of 86bpm, blood pressure of 120/90 mmHg, mydriasis, hyperreflexia, clonus in ankle and knee, and hypertonia in all limbs. Mrs. X satisfied Hunter's criteria for serotonin toxicity (Dunkley et al., 2003); the number and nature of symptoms fell short of a syndrome. Fluoxetine was continued with close monitoring. Over a period of eight-days all neurological signs subsided. One-month post-discharge, she was asymptomatic, on fluoxetine and with no signs of serotonin toxicity.

2. Discussion

There are several mechanisms by which ECT can lead to serotonin syndrome when combined with serotonergic drugs. ECT is known to enhance serotonergic transmission as evidenced at various levels - neurotransmitter release, receptor binding and overall neurotransmission (Baldinger et al., 2014). ECT is also shown to cause transient blood-brain barrier breach (Andrade and Bolwig, 2014; Bolwig et al., 1977) that can lead to increased drug delivery to the brain resulting in serotonin toxicity. ECT can also alter the cortical excitation-inhibition balance by acting on γ-amino-butyric acid (GABA) and glutamate neurotransmitter systems. Serotonin is an important modulator of this GABA-glutamate homeostasis (Ciranna, 2006), and this dynamic interplay of neurotransmitter alterations caused by ECT and anti-depressants like fluoxetine and venlafaxine can potentially lead to SS. Interestingly, catatonia is also conceptualized based on the 'universal field hypothesis' that implicates an imbalance across several neurotransmitter systems including the serotonin-GABA interplay (Carroll, 2000). These speculations point towards catatonic depression and SS being diametrical disorders of this dysregulated serotonin-GABA interplay. There are two important clinical messages through these reports. First, from a clinical perspective, it is vital to have a high index of

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suspicion and hence be vigilant while starting concomitant ECTs and serotonergic drugs, especially in individuals with catatonic depression. Initiating antidepressant medications following ECT may serve as a preventive measure. Second, there needs to be more systematic research on the safety, tolerability and efficacy of prescribing concomitant antidepressant medications with ECT in individuals with severe depression (Haskett and Loo, 2010).

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Declaration of Competing Interest

None of the authors have any conflict of interest to report

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NV Vyjayanthi, Rakshathi Basavaraju, Urvakhsh Meherwan Mehta*
Department of Psychiatry, National Institute of Mental Health & Neurosciences (NIMHANS), Bangalore, India
E-mail address: urvakhsh@nimhans.ac.in (U.M. Mehta).

* Corresponding author at: National Institute of Mental Health & Neurosciences (NIMHANS), Bangalore 560029, India.