## Ondansetron-Induced Myoclonus With Escitalopram and Highly Active Antiretroviral Therapy: A Closer Look at 5-$HT_3$ Receptors

**To the Editor:** Kolli and Addula[1] reported an interesting case of possible serotonin syndrome as a pharmacokinetic interaction of ondansetron, escitalopram, and highly active antiretroviral therapy.

In September 2014, the US Food and Drug Administration changed the safety labeling for 5-$HT_3$ receptor antagonists—ondansetron, granisetron, palonosetron, and dolasetron. The new warning suggests advising patients of the possible development of serotonin syndrome with use of the 5-$HT_3$ receptor antagonists and agents used to treat depression and migraines.[2] It is known that 5-$HT_3$ stimulation (eg, by selective serotonin reuptake inhibitors [SSRIs] increasing the availability of serotonin in the synaptic cleft to stimulate these postsynaptic receptors) accounts for the side effects of headache, nausea, and vomiting.

The recent introduction of the multimodal agent vortioxetine has provided more insight into the functions of 5-$HT_3$ receptors. It has been demonstrated that when the 5-HT level increases after administration of an SSRI, activation of the ligand-gated ionic 5-$HT_3$ receptors by 5-HT leads to stimulation of γ-aminobutyric acid (GABA) release. This release then inhibits cortical pyramidal neurons, and, thus, there is no amplification of 5-HT release by downstream glutamate.[3] Hence, blockade of 5-$HT_3$ receptors removes GABA inhibition and disinhibits pyramidal neurons, enhancing downstream release of 5-HT due to glutamatergic stimulation of serotonergic neurons in the midbrain raphe.[3] This pharmacologic receptor portfolio implies that agents with 5-$HT_3$ antagonism (eg, ondansetron) can, in theory, contribute to the development of serotonin syndrome through pharmacodynamic mechanisms as well. Serotonin syndrome is more likely to develop if agents with 5-$HT_3$ antagonism are combined with other serotonergic agents or in the setting of overdose.[4] Such cases are documented in the literature.[5] On the other hand, these 5-$HT_3$–blocking agents have been used to boost 5-HT tone in conditions such as treatment-resistant obsessive-compulsive disorder.[6]

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