Ondansetron use in psychiatry: a fact or fiction?

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In a recently published article by Grassi et al.,1 they characterized early-onset obsessive–compulsive disorder (OCD) biotype and phenotype. They highlighted the role of 5HT3 receptors in OCD and that blockade of these receptors boosts serotonergic tone by disinhibiting glutamergic terminals.2 This can be pharmacologically achieved by repurposing "setrons." A prototype of this group is ondansetron.

Ondansetron is a first-line antiemetic. It blocks 5HT3 receptors. Ondansetron exerts its effects in gastrointestinal tract (GIT) and chemoreceptor trigger zone (CTZ). It is generally very well tolerated barring occasional constipation. QTc prolongation has been reported with IV ondansetron and the maximum IV dose is now 16 mg (instead of 32 mg previously). An oral disintegrating tablets (ODT) formulation is available on the market and given sublingual (SL) for faster onset of action. It is a substrate for CYP 3A4.

Interestingly, ondansetron has been used off-label to address a multitude of psychiatric indications (Table 1). It should be borne in mind that the level of evidence supporting the use of ondansetron in these off-label indications is highly variable, and, hence, clinical acumen is necessary for its proper use and placement in real-life psychiatric practice. Here, we briefly touch on some of these indications while examining the extant evidence.

Selective serotonin reuptake inhibitors (SSRIs)-related nausea

Nausea associated with SSRIs and serotonin–norepinephrine reuptake inhibitors is believed to be due to excessive stimulation of 5-HT3 receptors. It emerges in about 25% of patients early on during treatment, and although it typically wanes after 2 weeks or so in most cases, it may persist in one-third of patients.3 "Setrons" help SSRIs nausea by blocking the postsynaptic 5-HT3 receptors.Clinicians should be vigilant when adding ondansetron to antidepressants that are potent inhibitors to CYP-450 (eg, paroxetine) which can risk QTc prolongation. Similarly, by virtue of 5-HT3 blockade, low dose of mirtazapine can help easing out antidepressant nausea. In the same vein, olanzapine, with 5-HT3 blockade, has been effective to address commonly encountered duloxetine-associated nausea.

Of related interest, ondansetron has been reported to help with venlafaxine discontinuation symptoms (nausea, GIT upset, headache, etc.).

Alcohol use disorder

Ethanol administration may facilitate the release of serotonin within the nucleus accumbens. This and other mechanisms may be involved in the enhancement of the function of 5-HT3A receptor produced by exposure to ethanol. Administration of 5-HT3A antagonists may inhibit ethanol-induced dopamine release in ventral tegmental area (VTA) and nor-adrenalin (NA). As such, ondansetron has been demonstrated to reduce drinking behavior among patients with early-onset alcoholism (prior to 25 years of age). Drinking was reduced in most of the individuals with the L/L genotype at 5-HTTLPR.4

Given that, 5-HT3A receptor may also be involved in the reinforcing effects of inhalants, it is plausible that ondansetron and other agents that antagonize this complex receptor may reduce or dampen the reward produced by inhalant use.

Obsessive–compulsive disorder

There have been at least six trials that have examined a short-term (8-12 weeks) role for ondansetron in patients with OCD. These include one placebo-controlled crossover trial (N = 11); one uncontrolled monotherapy trial (N = 8); two low-dose (0.5-1.0 mg/day), uncontrolled augmentation trials in patients who did not respond adequately to ongoing or earlier treatments (pooled N = 35); and two moderate- to high-dose (4-8 mg/day) randomized, placebo-controlled augmentation trials in patients with undocumented past treatment history (pooled N = 88). Ondansetron was modestly effective in the uncontrolled trials and strikingly
Ondansetron has shown efficacy for bulimia in three small trials.\(^5\)

Bulimia nervosa

Evidence is conflicting regarding the improvement of cognitive symptom domain, including EPS, and general psychopathology. Evidence is conflicting regarding the improvement of cognitive symptom domain and general psychopathology.

Schizophrenia

In a systematic review and meta-analysis, ondansetron adjuventia was demonstrated to be safe and efficacious in improving negative symptom domain, including EPS, and general psychopathology. Evidence is conflicting regarding the improvement of cognitive symptom domain.

Tardive dyskinesia

Twenty patients with schizophrenia who had neuroleptic-induced tardive dyskinesia were given 12 mg/day of ondansetron for 12 weeks in an open-label study. Administration of ondansetron resulted in a statistically significant improvement in tardive dyskinesia and psychotic symptoms. Likewise, co-administration of ondansetron with levodopa was effective in attenuating dyskinesia in the hemi-parkinsonian rat model attesting to the anti-dyskinetic efficacy of 5-HT\(_3\) antagonists. Ondansetron has been also shown to improve cerebellar tremors.

Panic disorder

Ondansetron also blocks the alpha-9 and alpha-10 receptors, and it has been hypothesized that this action increases cochlear sensitivity to external stimuli and may alleviate tinnitus as shown in one RCT.

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Discrimination

The authors do not have any competing interests or financial affiliations.

References


Table 1. Ondansetron’s Therapeutic Potential

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Abbreviations: OCD, obsessive-compulsive disorder; SRI, selective serotonin reuptake inhibitor.