



Olanzapine is an effective antiemetic agent

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Tienchaiananda *et al.* (1) reported that adding olanzapine to ondansetron and dexamethasone, in patients receiving doxorubicin/cyclophosphamide, significantly improved “no nausea” and “complete response” in the periods of 0–24 hours and 0–120 hours post chemotherapy (1). This study involved 39 patients who were double-blindly randomized to receive olanzapine versus placebo in addition to ondansetron and dexamethasone. They noted that side effects from treatment were similar in the two study groups, with the one exception being that somnolence was significantly more common in the olanzapine group.

Olanzapine is an atypical antipsychotic agent of the thienobenzodiazepine class. This agent, in 1996, was approved by the FDA for treating psychotic disorders (2,3). This drug inhibits multiple neurotransmitter receptors including dopaminergic (D1, D2, D3, D4 brain receptors), serotonergic (5-HT_{2a}, 5-HT_{2c}, 5-HT₃, 5-HT₆ receptors), catecholaminergic (alpha₁ adrenergic receptors), acetylcholinergic (muscarinic receptors), and histaminergic (H₁ receptors) (4). A generic formulation was approved in 2012. Olanzapine has a large affinity for 5-HT₂ receptors, more than for D₂ receptors (2-7). The pathophysiological mechanism for the efficacy of olanzapine in the control of nausea and vomiting is not well established, but most likely is due to its effect on serotonin-mediated 5-HT_{2c} receptors as well as other dopamine and serotonin receptors including 5-HT₃ (8,9).

Olanzapine has fewer drug interactions than many other

drugs (4,5). A common short term side effect is transient sedation, when the drug is initiated (5). Weight gain can occur, which may lead to diabetes mellitus when given for a long time (6).

Multiple phase III clinical trials, over the past five years, have demonstrated that olanzapine can effectively prevent chemotherapy-induced nausea and vomiting (CINV) (7-11). One such trial demonstrated that olanzapine, when added to a 5HT₃ receptor antagonist, an NK-1 receptor antagonist (NK1RA), and a corticosteroid, decreased nausea and improved complete response rates (7,12). An additional recent randomized controlled (but not patient blinded) trial, involving 100 patients receiving a variety of platinum-based treatments, reported that olanzapine, when added to palonosetron and dexamethasone (without an NK-1 receptor antagonist), led to a complete response rate of 96%, compared to 42% in a control group (P<0.0001), with a corresponding improvement in nausea control (P<0.0001) (8).

Olanzapine, when combined with dexamethasone and palonosetron, effectively controlled acute and delayed CINV for patients receiving highly emetogenic chemotherapy (HEC) in another single institution phase III clinical trial (9). Compared to an aprepitant, palonosetron, and dexamethasone regimen, the olanzapine, palonosetron, and dexamethasone regimen resulted in equivalent complete responses (no vomiting and no rescue medications) as was seen in the aprepitant regimen, but was significantly better in controlling nausea. This excellent control of nausea

occurred without the use of multiple days of dexamethasone. These results were confirmed in a randomized, double-blind, phase III, single-institution study (10) comparing olanzapine to fosaprepitant in patients with head and neck or esophageal cancer who were receiving concurrent chemotherapy and radiation therapy. Tan *et al.* (11) demonstrated that adding olanzapine, to azasetron, a 5HT₃ receptor antagonist, and dexamethasone improved delayed CINV in patients receiving high or moderate emetogenic chemotherapy.

These clinical data have led to olanzapine plus a 5-HT₃ receptor antagonist plus dexamethasone with or without a NK1RA being recommended for the prevention of CINV by the multiple antiemetic guidelines (NCCN, ASCO, MASCC/ESMO) for patients receiving highly emetic chemotherapy (13-15) and moderately emetic chemotherapy (13).

Adding to the effective prevention of CINV, olanzapine appears to effectively treat breakthrough chemotherapy-induced nausea/vomiting, that occurs despite the use of prophylactic antiemetic treatment. This contention is illustrated in a study that compared olanzapine to metoclopramide for treating breakthrough nausea/emesis in patients receiving guideline-directed antiemetic prophylaxis for HEC (16). This, interestingly, appears to be the first and, to date, the only published phase III study regarding the treatment of breakthrough emesis/nausea.

A recent study (17) also demonstrated that olanzapine effectively treated nausea and emesis and improved appetite, pain, and quality of life parameters in patients with advanced cancer. This double-blind, placebo-controlled trial was developed to study olanzapine for chronic nausea in patients with advanced cancer with persistent nausea/vomiting without having received chemotherapy and/or radiation therapy for the previous 14 days. The chronic nausea for each involve patient had to have been apparent for at least one week (with a worst daily score >3, as measured on a 0–10 numerical rating score; NRS) and/or they had to have vomited at least 5 times over the prior week. Patients were randomized, in a double-blind manner, to receive olanzapine (5 mg) or a placebo, orally, daily for 7 days. The primary study endpoint was the change in NRS nausea scores from baseline to the last treatment day. Thirty patients (15 per arm) were enrolled on this trial. Median nausea scores were 9 out of 10 on the baseline day, with a range of 8–10 in all patients. The median nausea scores in the placebo arm were 9/10 (range, 8–10) after 1 day and 1 week; in comparison the olanzapine arm scores were 2/10 (range, 2–3) after day 1 and 1/10 (range, 0–3) after one week

($P < 0.0001$). Correspondingly, the olanzapine arm patients reported less emesis, less use of other anti-emetic drugs, better appetite, less sedation, less fatigue and better well-being. The patients receiving olanzapine did not report any excess sedation or any other adverse event.

The results of the publication of Tienchaiananda *et al.* (1) further substantiate that olanzapine is a very effective antiemetic agent.

An unanswered question regards whether the adding an NK-1 receptor antagonist, to a relatively standard olanzapine, 5 HT₃ receptor antagonist, and dexamethasone cocktail, further improves the prevention of nausea and emesis. Navari *et al.* (7) demonstrated that olanzapine when added to a 5 HT₃ receptor antagonist, an NK-1 receptor antagonist, and a corticosteroid, decreases nausea and improves complete response rates (7). What is the contribution of the NK-1 receptor antagonist in this regimen? In order to answer this question, an Alliance for Clinical Trials in Oncology clinical trial (A221602) is currently accruing patients: Olanzapine with or without fosaprepitant for the prevention of CINV in patient receiving HEC. A phase III randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov Identifier: NCT03578081). In this trial, olanzapine + fosaprepitant + a 5 HT₃ receptor antagonist + dexamethasone is compared to olanzapine + placebo + a 5 HT₃ receptor antagonist + dexamethasone for the prevention of nausea and emesis. If the two regimens are equivalent, demonstrating that the NK-1 receptor antagonist is not essential, this would have major economic implications, especially in 3rd world countries where NK-1 receptor antagonists are not readily available.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/apm.2020.04.32>). CLL reports personal fees from PledPharma, personal fees from Disarm Therapeutics, personal fees from Asahi Kasei, personal fees from Metys Pharmaceuticals, personal fees from OnQuality, personal fees from Mitsubishi Tanabe, personal fees from NKMax, outside the submitted work, RMN has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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