

FAST FACTS AND CONCEPTS #315**OLANZAPINE FOR NAUSEA, DELIRIUM, ANXIETY, INSOMNIA, AND CACHEXIA****Maria Felton PharmD, Richard Weinberg MD, and Jennifer Pruskowski PharmD**

Background Olanzapine is a second-generation atypical antipsychotic that has shown off-label efficacy for the treatment of nausea, delirium, anxiety, insomnia, and cachexia in adults. Consequently, palliative care clinicians may utilize it to target multiple symptoms common among their patients. This *Fast Fact* will review its pharmacology and the available evidence for these off-label symptoms.

Pharmacology Olanzapine has a unique receptor profile amongst antipsychotics, which in part accounts for its various uses and side effects. In addition to antagonizing dopamine receptors in the CNS (nausea, delirium), it blocks serotonin (5HT₂) receptors (insomnia, anxiety, cachexia) and is anticholinergic (1-3). It reaches its peak concentration in ~6 hours but has a terminal half-life between 21 to 54 hours (4).

Adverse Reactions and Cautions When compared to other antipsychotics, olanzapine causes fewer extrapyramidal symptoms (5) and has lesser effect on the QTc interval compared to IV haloperidol (6), but it may have a higher prevalence of somnolence (7) and weight gain (8,9). Weight gain is even more apparent in children than adults (10). Additionally, olanzapine has been associated with dry mouth, hyperglycemia, edema, and an increased mortality in elderly patients with dementia-related psychosis, which complicates the availability of all neuroleptics in skilled nursing facilities. No dosage adjustments are required for patients with renal or hepatic impairment, although caution is recommended in end stage liver disease. Dosing and safety have not been well-studied in children less than 13 years old (11).

Research Data

- o **Nausea:** Two small case series and a retrospective study described the effective use of olanzapine (average dose of 5 mg per day) for chronic nausea and vomiting related to an incomplete bowel obstruction (12,13). In an open-label pilot study, advanced cancer patients receiving olanzapine at doses between 2.5 to 10 mg had a significant improvement in quality of life and a decrease in nausea compared to baseline (14). There is more robust evidence to support its efficacy in the treatment of chemotherapy-induced nausea and vomiting (CINV) (15). A double blinded randomized controlled trial of breakthrough CINV showed benefit of olanzapine compared to metoclopramide (no emesis, 70% vs 31%) with a number-needed-to-treat of 2.5 (16).
- o **Delirium:** Atypical antipsychotics, like olanzapine, have been shown to be equally safe and effective as haloperidol for delirium. Doses typically range from 2.5 to 10 mg daily but can reach a maximum of 20 mg daily (17). An open-label preliminary trial studied the tolerability of subcutaneous olanzapine for delirious patients with advanced cancer -- 37% of the patients responded to olanzapine at doses 5 mg or 10 mg (18). In another open-label prospective trial, 79 hospitalized cancer patients with delirium were treated with olanzapine and 76% had complete reversal of delirium (19).
- o **Anxiety:** Olanzapine has been studied for use in refractory generalized anxiety disorder (GAD). In a randomized, placebo-controlled trial, olanzapine (mean dose 8.7 mg/day) was better than placebo when added to GAD therapy in patients refractory to fluoxetine alone (20).
- o **Insomnia:** Olanzapine has been shown to improve sleep efficiency and sleep quality when combined with an SSRI in depressed patients starting with as little as 2.5 mg (21). In addition, an increase in both sleep time and slow wave sleep was shown via polysomnography and power spectral analysis after a single dose of 10 mg olanzapine was given in a separate study (3).
- o **Cachexia:** Olanzapine has been studied for use in cachexia related to chronic illnesses like cancer. Improvements have been seen in weight gain and appetite stimulation when olanzapine 5 mg/day was added to megestrol acetate therapy (22). In an open-label study, olanzapine at doses of 2.5 to 20 mg attenuated the weight loss of advanced cancer patients when used as monotherapy (23).

Cost: Generic olanzapine tablets are approximately ten times the cost of metoclopramide, fifteen times the cost of trazodone and 30 times the cost of haloperidol. Generic formulations of an oral disintegrating tablet (ODT) and an intramuscular injection are also available. The ODT tablet has been found to have similar efficacy and tolerability as the standard olanzapine tablet; many experts reserve its use for patients who have difficulty swallowing (24).

Summary: Olanzapine has modest evidence suggesting it has a role in treating CINV and other types of nausea. As such it is a worthwhile anti-emetic to consider especially if delirium, anxiety, insomnia, and cachexia are also present. However, due its cost and potential barriers with use in long term care facilities, palliative care clinicians should be cautious about its routine off-label use to address an array of symptoms common in serious illness.

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