

Kim, Dominic, PGY2
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Reference: Navari RM et al. Olanzapine for the prevention of chemotherapy-induced nausea and vomiting. *N Engl J Med.* 375;2. 14 Jul 2016.

Question: How efficacious is olanzapine in the prevention of nausea and vomiting in patients receiving highly emetogenic chemotherapy?

Introduction: Chemotherapy-induced nausea and vomiting has the potential to cause great morbidity in addition to the already-morbid condition of a malignancy. Many cocktails have been created to combat these symptoms, to include a combination of 5-HT₃ receptor antagonists, dexamethasone, and neurokinin-1 (NK1) receptor antagonists. Despite clinicians' best efforts, nausea and vomiting remains a troublesome part of some chemotherapy agents. While traditionally thought of as an atypical antipsychotic agent, olanzapine acts upon many receptors, to include the D₂, 5-HT₂, and 5-HT₃ receptors, which have been known to moderate nausea and vomiting. Two single institution phase 3 trials have shown promise in utilizing olanzapine in alleviating nausea and vomiting in those undergoing emetogenic chemotherapy. This specific journal article wished to expand upon these single center trials in hopes of substantiating olanzapine as an additional option for poorly controlled nausea and vomiting.

Methods: This was a randomized, double-blind, phase 3 trial comparing olanzapine with placebo, in combination with dexamethasone, aprepitant or fosaprepitant, and a 5-HT₃ receptor antagonist, in patients who had not received previous chemotherapy, but were scheduled to receive cisplatin or cyclophosphamide-doxorubicin. The participants had to meet an exuberant amount of other criteria to be eligible for this trial (perhaps a weakness?). In terms of the specific arms of therapy, all participants received a 5-HT₃ receptor antagonist on day 1. All participants also received an NK1-receptor antagonist on day 1. All participants received dexamethasone days 1-4 as well. Finally, the treatment arm received the aforementioned pharmacopeia in addition to olanzapine from days 1-4, while the non-treatment arm received placebo from days 1-4 in lieu of olanzapine. Nausea prevention was the primary endpoint, assessed during 0-120hrs, 0-24hrs, as well as 25-120hrs. Complete response—no emetic episodes and no use of rescue medication—was the secondary end point.

Results: A total of 401 patients were enrolled from 46 academic or community practice facilities in the United States. 192 were assigned to the olanzapine group and 188 were assigned to placebo. The proportion of patients without chemotherapy-induced nausea was significantly greater in the treatment arm than the placebo arm, especially within the first 24hrs—74% versus 45%, $P=0.002$. Statistical significance was also seen from 25-120hrs (42% versus 25%, $P=0.002$) and the overall 120hr period (37% versus 22%, $P=0.002$). Likewise, success was also discovered in terms of the secondary end point—complete response—with P values of <0.001 , 0.007, and <0.001 in the early, later, and overall periods, respectively. One statistically significant adverse effect was seen in the olanzapine group, to include sedation on day 2 of therapy that resolved without issue on days 3, 4, and 5. While atypical antipsychotics are also known to have an undesired effect on appetite, this was not found to be statistically significant when compared to placebo.

Discussion: I think it is fairly clear from this study that adding olanzapine to the prophylactic anti-emetic armamentarium can lead to a profound decrease in undesirable chemotherapy-induced nausea and vomiting. This has great potential for the EM provider wishing to alleviate suffering in the nauseous chemotherapy patient. Patients who received this therapy were more likely to be free of nausea and emesis in all three stages of analysis—early, later, and overall. While increased sedation was seen on day 2 of olanzapine

therapy, no interventions were required to combat this side effect. Furthermore, in terms of safety measures, no patients had to cease olanzapine therapy for its potential toxic effects. Although the ER may not be a hot bed for individuals with malignancies undergoing their first round of chemotherapy—more specifically with cisplatin or cyclophosphamide-doxorubicin—in those with uncontrolled nausea and vomiting, olanzapine has the awesome potential to provide unbelievable relief to a select subset of the population.

Limitations: As mentioned briefly above, the exclusion criteria listed by the authors was extensive, possibly top 3 I have seen all-time amongst the literature. In addition to being older than 18 years old, one had to have a serum creatinine <2.0 , an AST or ALT that was no more than 3 times the upper limit of normal, an absolute neutrophil count of >1500 , no nausea or vomiting in the 24 hours preceding enrollment, no severe cognitive compromise, no known history of CNS dysfunction, no treatment with another antipsychotic agent within 30 days of enrollment, no long-term use of phenothiazine as an antipsychotic agent, no concurrent use of abdominal radiotherapy, no chronic alcoholism, etc. The applicability of this study to the general patient with a malignancy who is undergoing chemotherapy and presents with uncontrolled emesis is extremely low given these factors. Furthermore, the authors only used one dose of olanzapine (10mg). Perhaps decreasing or increasing the dose may have resulted in similar results while decreasing adverse side effects. Finally, the study failed to demonstrate efficacy in those who had been receiving chemotherapy for greater than five days. Although this particular article had great potential to effect change in the ER, I am not quite sure if any patient will fulfill both the inclusion and exclusion criteria mentioned in this paper.
