Olanzapine: Palliative Medicine Update

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Abstract

Olanzapine is an atypical antipsychotic agent of the thienobenzodiazepine class. Olanzapine blocks multiple neurotransmitter receptors, including dopaminergic (D1, D2, D3, and D4), serotonergic (5-hydroxytryptamine 2A [5-HT2A], 5-HT2C, 5-HT3, and 5-HT4), adrenergic (α1), histaminic (H1), and muscarinic (M1, M2, M3, and M4) receptors. Olanzapine has a high affinity for the 5-HT2A receptor, which is up to 5 times greater than the dopamine receptor, resulting in less propensity to the development of extrapyramidal side effects. The affinity of olanzapine for multiple receptors has lead to the identification of olanzapine as an important agent in the treatment of delirium, nausea, and vomiting. Olanzapine has been demonstrated to have opioid-sparing properties. Olanzapine is principally metabolized by glucuronidation, with a smaller metabolic contribution from the cytochrome oxidase system. Adverse effects of olanzapine include somnolence, postural hypotension, constipation, dizziness, restlessness, and weight gain. The purpose of this article is to outline the pharmacodynamics, pharmacology, and evidence for the use of olanzapine in palliative care.

Keywords

olanzapine, pain, nausea, vomiting, delirium, pharmacology

Introduction

The World Health Organization describes palliative care as “care that focuses on the improvement of quality of life through the provision of symptom relief, as well as spiritual and psychological support for patients from the time they are diagnosed with a life limiting illness to the end of life.”

Neuroleptic agents such as haloperidol have played an important role in the management of symptoms in palliative care, despite the paucity of clinical trials supporting their use. Haloperidol and other dopamine antagonists are often used for the management of symptoms such as nausea, vomiting, and delirium at the end of life. Their use is associated with well-known adverse effects such as extrapyramidal effects, effects on cardiac conduction, and effects that cause clinicians to pause and look into the other options for symptom management.

The development of the atypical antipsychotics, with their improved adverse effect profile, has led to the evaluation of atypical antipsychotics for the management of these same symptoms. The atypical antipsychotics have a more favorable adverse effect profile due to their decreased affinity for the D2 dopamine receptor, which leads to less extrapyramidal effects. Olanzapine is one of the atypical antipsychotics to have been identified as being useful for the management of several symptoms commonly encountered in palliative care, such as delirium, nausea, vomiting, and pain. This article reviews the pharmacodynamics, the pharmacology, and the evidence for the use of olanzapine in palliative care.

Structure

Olanzapine (Figure 1), which has the chemical name 2-methyl-4-(4-methyl-1-piperazinyl)10H-thieno(2,3-b)[1,5]benzodiazepine, is a molecule that contains the thienobenzodiazepine structure. This class of drug was developed in an effort to create a benzodiazepine class of compounds with fewer muscle relaxant activities.

Pharmacodynamics

Atypical antipsychotics are characterized as having affinities for a variety of neurotransmitter receptor subtypes, including serotonergic (5-hydroxytryptamine 1A [5-HT1A], 5-HT2C, 5-HT6, and 5-HT7), dopaminergic (D1, D3, and D4), histaminic (H1), muscarinic receptors (M1, M2, M3, M4, and M5), and adrenergic (α1 and α2) receptors. Olanzapine binds with high affinity to D2 dopamine receptors with a Ki of 11 μmol/L. The affinity toward serotonin receptors differs by subtype. Olanzapine has weak affinity for 5HT1A, 5HT1B, and 5HT1D receptors with Ki values in the 800 to 1400 μmol/L range. On the other hand, olanzapine has high affinity for HT2A, 5HT2C, and 5-HT3.
receptors with Ki values of 4, 11, and 57, respectively, which are key receptors in nausea and vomiting. Olanzapine also has high affinity for M1,4 muscarinic receptors, with extremely high potency for the M1 with Ki values of 1.9 μmol/L. This affinity is much greater than the other atypical antipsychotics (eg, risperidone) and may contribute to adverse effects (see below). Olanzapine has a low affinity for gamma-aminobutyric acid (GABA) and benzodiazepine receptors. Olanzapine has minimal the N-methyl-D aspartate (NMDA) antagonist activities.

Formulations
Olanzapine is available as an oral tablet, an orally disintegrating formulation, and a powder to be made into solution for intramuscular administration. There is a depot formulation available, but this has not been evaluated for use in palliative care. Olanzapine has been given subcutaneously for the treatment of delirium with good results and no local skin irritation.

Pharmacokinetics

Oral Olanzapine
The oral bioavailability of olanzapine is 80%. Olanzapine reaches a peak concentration in approximately 6 hours. There are no differences in bioequivalency between the oral tablet and the orally disintegrating formulation, with both exhibiting linear kinetics over the usual dosage range. The mean half-life in healthy individuals is 33 hours. The mean plasma clearance is 26 L/h.

Intramuscular Administration
Intramuscular olanzapine is rapidly absorbed, with peak plasma concentrations occurring in less than 45 minutes.

Subcutaneous Administration
There are no pharmacokinetic data for subcutaneous administration.

Metabolism
Olanzapine experiences first-pass metabolism, with 40% of the original dose metabolized prior to entering the systemic circulation. Olanzapine is extensively glucuronidated to 10-N and 4-N glucuronides, both of which have no activity. The formation of the 10-N glucuronide is the predominant metabolic pathway, and the 10-N glucuronide is the most abundant metabolite. Radiolabeling studies show that olanzapine is excreted in both urine (60%) and feces (30%). Olanzapine binds to albumin (90%) and α-1-acid glycoprotein (77%). Studies suggest that CYP1A2 and 2D6 are involved in olanzapine oxidation, with CYP1A2 exerting the most influence, with little interaction with CYP3A4. The elderly individuals, children, and adolescents exhibit higher plasma levels of olanzapine for any given oral dose, but the clinical significance of this is not known.

Drug Interactions
Drugs that influence the metabolic pathways of olanzapine can interfere with the elimination of the drug. Despite the predominance of glucuronidation as a major pathway of olanzapine metabolism, there is evidence that drugs influencing the cytochrome oxidase system can affect serum concentration levels of olanzapine. No comparisons have been made to morphine. Olanzapine has interacted with antidepressants, such as fluvoxamine, which through the inhibition of cytochrome P450 1A2 (CYP1A2) has led to the elevations of serum concentration levels of olanzapine leading to possible adverse effects. In view of this interaction, patients should be monitored closely for adverse effects such as sedation, orthostatic hypotension, tachycardia, transaminase elevations, or seizures, when the 2 drugs are given together. Inducers of CYP3A4, such as carbamazepine, can lower serum concentration levels of olanzapine by 36% to 71%. Olanzapine does not inhibit CYP isozymes. Olanzapine neither affects nor is affected by the commonly used palliative care drugs such as mirtazapine or imipramine. When drugs that are metabolized by glucuronidation, such as valproic acid, are given with olanzapine, there is no effect on olanzapine levels. The disposition of olanzapine is not affected by other drugs such as methadone.

Adverse Effects
The adverse effects of olanzapine in the palliative care population have not been systematically studied. In the psychiatric population, short-term placebo-controlled studies (6 weeks duration) are associated with adverse effects, which include (incidence of >5%) postural hypotension (5%), constipation (9%-11%), dizziness (11%-18%), and dry mouth (22%). Olanzapine antagonizes muscarinic receptors and is a potent

Figure 1. Structure of Olanzapine
antimuscarinic agent, which predicts significant anticholinergic effects. It has been reported to cause delirium, based on this anticholinergic effect. Olanzapine is also associated with a low rate of extrapyramidal side effects (EPS). In schizophrenia studies, the incidence of EPS was dose dependent, with 25% to 32% of patients taking ≥7.5 mg/d of olanzapine in acute registration trials of schizophrenia and experiencing extrapyramidal events. In these studies, there was a statistical separation from placebo for adverse effects only for dosages of ≥12.5 mg/d. Akathisia can occur with olanzapine; and in the short-term psychiatric studies, it occurred with a frequency of 10% to 11%, which at a dosage of ≥7.5 mg was significantly greater than the reports with placebo. The incidence of tardive dyskinesia is lower in the atypical antipsychotics such as olanzapine. The incidence of tardive dyskinesia is lower in the atypical antipsychotics such as olanzapine.

Other Adverse Effects

Hyperprolactinemia

Drugs that block the normal inhibitory mechanisms of dopamine production, such as olanzapine, can cause elevated prolactin levels and have potential consequences. In a study of nearly 600 psychiatric patients, the incidence of hyperprolactinemia was greater for those receiving olanzapine than for those receiving placebo. At 10 mg doses, the incidence of prolactin elevation was 30%. The incidence of clinical complications such as menstrual-related events and sexual function-related events was 2%.

Agranulocytosis

Case reports have implicated olanzapine in the development of leucopenia/neutropenia.

Cardiac Arrhythmias

Olanzapine appears to have no difference from placebo in the proportions of patients experiencing potentially important changes in electrocardiogram parameters, such as QT, QTc (corrected), and PR intervals.

Weight Gain

The use of olanzapine is associated with weight gain, with studies suggesting average weight gains of 4 kg over 10 weeks of use. This effect has not been studied in the palliative care patient, close monitoring of blood sugars may be necessary.

Glucose Intolerance

Hyperglycemia has been associated with olanzapine use, and if glycemic control is important to the palliative care patient, close monitoring of blood sugars may be necessary.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a neurologic emergency associated with neuroleptic use. The NMS is usually associated with “typical” antipsychotic agents, such as haloperidol, but has been observed with the “atypical” antipsychotics such as olanzapine. The literature reports 20 cases of NMS caused by olanzapine. Factors contributing to olanzapine-associated NMS include the presence of psychomotor agitation, dehydration, a history of previous episodes of NMS, rapidly increasing olanzapine doses, and the use of other dopamine antagonists given by parenteral routes. Unexplained anxiety may precede the cognitive changes associated with NMS.

Olanzapine Clinical Trials

Phase I Antiemetic Trials

A phase I study to establish a tolerable dose for olanzapine use in delayed chemotherapy-related nausea and vomiting was conducted in patients receiving emetogenic chemotherapy agents, such as cyclophosphamide, doxorubicin, cisplatin, ≥70 mg/m², and/or irinotecan. The maximum dose that was tolerated was 5 mg (2 days before chemotherapy) with 10 mg given for the rest of the 7 days. Of the 6 patients, 4 received cis-platinum-based therapy, and all 9 of the patients receiving moderately emetogenic chemotherapy had no episodes of delayed nausea and vomiting. No grade 4 toxicities were seen, and 3 patients experienced a dose-limiting toxicity (grade 3) of sedation.

Phase II Trials and Chemotherapy

In a subsequent phase II study, 30 patients receiving either highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC) were treated with an olanzapine dose of 5 mg daily for 2 days before chemotherapy, followed by 10 mg daily for 4 days in patients receiving a standard antiemetic regimen consisting of granisetron and dexamethasone. In the acute phase, all patients demonstrated a complete antiemetic response. In the delayed phase, 80% of patients receiving HEC and 85% of patients receiving MEC experienced a complete response. Olanzapine was well tolerated in these patients.

Olanzapine and Dexamethasone for the Chemotherapy-Induced Nausea and Vomiting

An additional phase II study was performed to determine the control of acute and delayed chemotherapy-induced nausea and vomiting (CINV) in patients receiving MEC or HEC, this time with the addition of dexamethasone to the olanzapine and serotonin receptor antagonist antiemetic regimen. Again in a population of 40 patients receiving either MEC or HEC regimens, patients received dexamethasone (8 mg orally or intravenously [IV] for MEC or 20 mg orally or IV for HEC) and palonosetron...
(0.25 mg IV) 30 to 60 minutes before chemotherapy administration. In addition, patients were also given olanzapine 10 mg orally on the day of chemotherapy (day 1) and continued on 10 mg orally daily for days 2 through 4 after chemotherapy. Complete elimination of nausea, an important end point, was 100% acutely, 50% in the delayed period, and 75% overall in the 8 patients receiving HEC. In those receiving MEC, complete absence of nausea was observed in the acute period for 100% of the patients, 78% in the delayed period, and 78% overall. Over half of the patients completed at least 4 cycles of chemotherapy. Responses did not change as additional chemotherapy was given. There were no grade 3 to 4 toxicities. Unfortunately, this study was not designed to investigate whether or not the addition of dexamethasone enhances the antiemetic effect of olanzapine.

**Comparison With Serotonin Antagonists for Chemotherapy**

Lijun and coworkers\(^3^2\) compared the activity and safety of olanzapine with 5-HT\(_3\) receptor antagonists for the prevention of CINV in patients receiving HEC or MEC. Two hundred and twenty-nine patients received either (1) olanzapine (10 mg orally), azasetron (10 mg IV), and dexamethasone (10 mg IV) on day 1 and then olanzapine (10 mg orally) once a day on days 2 to 5 of chemotherapy or (2) azasetron (10 mg IV) and dexamethasone (10 mg IV) on day 1 and then dexamethasone (10 mg IV) once daily on days 2 through 5. The primary end point was the complete response, which was defined as the percentage of patients with no nausea or vomiting, without rescue therapy need, for the acute period (24 hours post-chemotherapy), the delayed period (days 2-5), and the whole period (days 1-5). Secondary end point was the quality of life. Safety and toxicity were also recorded. Compared with the control group, there was no difference in complete response for acute nausea and vomiting \((P > .05)\). With respect to delayed nausea and vomiting, the treatment group was superior to the control group in both highly emetogenic and moderately emetogenic therapy. A statistically significant improvement \((P < .05)\) for nausea (39%) and vomiting (22%) was observed when given HEC. Nausea improved by 22% and vomiting improved by 13% in those receiving MEC. Quality of life was improved in the olanzapine arm with differences noted in the areas of global health status, social functioning, fatigue, insomnia, and appetite \((P < .01)\).

**Nausea and Vomiting in Palliative Care**

Jackson and Tavernier\(^3^3\) described 6 patients who suffered from nausea, which was resistant to initial treatment with traditional antiemetics such as prochlorperazine, promethazine, haloperidol, and lorazepam. Etiologies of the nausea included brain metastasis, opioid-related nausea, drug-related nausea (eg, digoxin and theophylline), and cerebrovascular accident. When prior antiemetics failed, each patient exhibited marked improvement, when treated with olanzapine at doses of 2.5 to 7.5 mg at bedtime. Although one of the commonly reported side effects of olanzapine is sedation, they reported that careful dose titration over a period of 7 to 10 days (in the range of 2.5-7.5 mg) prevented excessive sedation, even in patients that could not tolerate other antiemetics due to sedation. The experience represented in the series showed that olanzapine can be useful in nausea and vomiting of multiple etiologies based on the variety of neurotransmitters that olanzapine affects. Olanzapine could also be used along with other antiemetics without drug interaction. The series also demonstrated safe use in the elderly individuals, with gradual dose titration.

**Opioid-Induced Nausea**

In an open-label trial of olanzapine in 15 patients with opioid-induced nausea, Passik et al\(^3^4\) reported that olanzapine (at a dose levels of 2.5-10 mg) significantly reduced nausea (compared with baseline) at every dosage level. They also found that sedation was not dose limiting and that patients’ overall quality of life was improved, especially with the 5 mg dose, as measured by standardized scales.

**Analgesic Trials**

**Cancer Pain**

Olanzapine has been shown to have antinociceptive activity in animal models.\(^3^5\) Clinical evaluation of its analgesic effects has been limited. Khojainova and coworkers\(^3^6\) prospectively collected the data on 8 patients with cancer having severe pain, which was uncontrolled in spite of aggressive opioid titration, who also received olanzapine to treat severe anxiety and mild cognitive impairment. Patients did not meet the criteria for delirium, and their cognitive impairment was defined as cognitive disorder not otherwise specified according to *Diagnostic and Statistical Manual of Mental Disorder* (Fourth Edition; *DSM-IV*). Patients received 2.5 to 7.5 mg of olanzapine daily. In all the patients, opioid requirements had escalated rapidly prior to starting olanzapine. Levels of pain, sedation, and opioid use were measured 2 days before and 2 days after olanzapine was started. Cognitive state was assessed daily. All 8 patients had marked reduction in the daily pain scores. The average daily opioid use decreased significantly in all patients. Cognitive impairment and anxiety resolved within 24 hours of initiating olanzapine. The author of this article suggested that olanzapine may have an intrinsic analgesic action, but also suggested that pain scores and opioid requirements may have resulted from improvement in cognitive function and the known anxiolytic effect of olanzapine.

**Delirium**

**Critical Care Setting**

Skrobik and coworkers compared the safety and response profile of olanzapine to haloperidol in the treatment of delirium in the critical care setting.\(^3^7\) The prospective trial evaluated all admissions to medical and surgical intensive care units (ICUs)
with a diagnosis of delirium. The study population consisted of surgical patients. The study was not blinded. Those excluded from the study were patients with gastrointestinal dysfunction. Patients were randomized to receive either enteral olanzapine or haloperidol. The study drugs could be given orally or via nasogastric tube. Haloperidol was initiated at 2.5 to 5 mg every 8 hours and olanzapine at 5 mg daily. Patients older than 60 years of age received haloperidol 0.5 to 1.0 mg every 8 hours or olanzapine 2.5 mg daily. Titration of study drug doses was based on clinical judgment. Need for supplemental benzodiazepines for additional sedation was recorded and compared between study arms. A total of 103 patients were considered eligible for the study. Patients’ delirium severity and benzodiazepine use were monitored over 5 days after diagnosis of delirium. The level of delirium, as measured by the Delirium Index, decreased over time in both the groups, as did the administered dose of benzodiazepines for rescue. Clinical improvement was similar in both the treatment arms. No side effects were noted in the olanzapine group, whereas the use of haloperidol was associated with extrapyramidal side effects. The study showed that olanzapine could potentially be a safe alternative to haloperidol for ICU delirium.

**Delirium and Cancer**

Breitbart and colleagues\(^\text{38}\) evaluated olanzapine for the treatment of delirium in 79 hospitalized cancer patients. This was an open-label prospective trial. Investigators used *DSM-IV* criteria for the diagnosis of delirium, and delirium severity was measured by the Memorial Delirium Assessment Scale (MDAS) over the course of the study (7 days). Seventy-six percent of patients receiving olanzapine experienced reversal of delirium. Sedation was the main adverse effect (30%). The severity of sedation was not severe enough to warrant discontinuation of the therapy. Response to olanzapine was decreased in association with several patient characteristics, such as age older than 70 years, delirium associated with brain metastasis or hypoxia, severe delirium MDAS scores of >23, and hypoactive delirium, with age being the most powerful predictor of poor response.

**Subcutaneous Olanzapine**

Elsayem and coworkers evaluated subcutaneously administered olanzapine due to the concerns about the use of intramuscular olanzapine for terminally ill patients.\(^\text{8}\) Twenty-four patients with hyperactive or mixed delirium, who did not respond to haloperidol (doses of 10 mg or higher), received olanzapine 5 mg subcutaneously every 8 hours for 3 days and continued haloperidol for breakthrough agitation. If patients required more than 8 mg of rescue haloperidol, the olanzapine dose was increased to 10 mg subcutaneously every 8 hours. End points were achievement of sedation as measured by the Richmond Agitation–Sedation Scale (scores ≤1 [sedated]), local and systemic toxicity, and ability to keep breakthrough doses of haloperidol of less than 8 mg/d. Fifteen patients completed the study, and achievement of sedation (Richmond Agitation–Sedation Scale scores ≤1 [sedated]) was reached in 9 of the original 24 patients. The average patient age was 58 years (range 49-79).

**Dementia and Behavior**

**Agitation/Psychosis Symptoms**

One trial evaluating the effectiveness of the atypical antipsychotics on the symptoms of agitation and psychosis was the Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer Disease. Patients experiencing psychosis and agitated behavior were randomly assigned to receive olanzapine, quetiapine, risperidone, or placebo.\(^\text{39}\) Average doses of the study drugs were olanzapine (5.5 mg/d), quetiapine (56.5 mg/d), and risperidone (1.0 mg/d). Doses were adjusted as clinically indicated. Neurocognitive function was measured by the Neuropsychiatric Inventory Total Score, Clinical Global Impression of Changes, and the Brief Psychiatric Rating Scale (BPRS), all of which measure symptoms of neuropsychiatric disturbance common in dementia. Other measures included were level of functioning, cognition, care needs, and quality of life. When compared with placebo, there were improved scores with olanzapine and risperidone on the Neuropsychiatric Inventory Total Score, risperidone on the Clinical Global Impression of Changes, with olanzapine and risperidone on the BPRS, hostile suspiciousness factor, and risperidone on the BPRS psychosis factor. There was worsening with olanzapine on the BPRS withdrawn depression factor. At 12 weeks, there were no significant differences between antipsychotics and placebo on cognition, functioning, care needs, or quality of life, except for worsened functioning with olanzapine compared with placebo.

**Vascular Dementia**

Meehan and coworkers conducted a randomized double-blind study investigating the efficacy and safety of intramuscular olanzapine on the treatment of agitation associated with Alzheimer’s disease and/or vascular dementia.\(^\text{40}\) A single dose of intramuscular olanzapine, lorazepam, and placebo were compared. There was an option for more doses if clinically indicated.

Both olanzapine (5.0 and 2.5 mg doses daily) and lorazepam (1.0 mg daily) were superior to placebo on agitation measurement scales such as the Positive and Negative Syndrome Scale Excited Component (PANSS-EC), Agitation-Calmness Evaluation Scale (ACES), and Cohen-Mansfield Agitation Inventory. After 1 day, both the olanzapine groups, but not the lorazepam group, were superior to the placebo group when agitation was measured by the PANSS-EC. There were no cognitive changes as measured by the Simpson-Angus and Mini-Mental State Examinations from baseline. There was no difference in terms of level of sedation as measured by the ACES compared with placebo for either treatment. At both 2 and 24 hours, there were no adverse effects due to
extrapyramidal symptoms or QTc prolongation. Orthostatic hypotension was not an adverse effect.

**Cancer Anorexia–Cachexia**

Clinical trials of olanzapine in the psychiatric population were associated with weight gain as an adverse effect. The weight gain associated with olanzapine was evaluated in diseases where this adverse effect may be “beneficial,” such as anorexia nervosa, and preliminary studies in cancer-related anorexia–cachexia. Two studies have evaluated olanzapine for anorexia–cachexia due to cancer. A phase I study evaluated olanzapine at the doses of 2.5, 5, and 7.5 mg/m². In addition, patients were analyzed for the impact of olanzapine on weight, nutrition, and performance status (eg, the 6-minute walk). Patients had blood samples analyzed for inflammatory cytokines and the effect of olanzapine on leptin, ghrelin, and adiponectin. Fourteen patients were enrolled at 3 dose levels (2.5, 5, and 7.5 mg/m², respectively). Weight gain was either stabilized or improved at 2 weeks in 6 of the 14 patients. Other symptoms on the Edmonton Symptom Assessment Scale that showed improvement were sleep, appetite, fatigue, and well-being. In a second study, olanzapine 5 mg/d and megestrol acetate were compared with megestrol acetate alone (800 mg/d) and demonstrated that the addition of olanzapine enhanced weight, appetite, nausea, and quality of life compared with megestrol acetate alone.

**Schedule of Administration**

Olanzapine can be administered once daily but has been administered up to 3 times daily in 1 pilot study for delirium.

**Olanzapine Dosing**

**Delirium**

Studies of olanzapine indicated that the drug was approximately 70% to 76% effective in treating delirium at doses of 2.5 to 11 mg daily.

**Nausea and Vomiting: Chemotherapy**

Olanzapine doses ranging from 5 to 10 mg daily appeared to be effective for the management of acute and delayed nausea and vomiting.

**Nausea and Vomiting Palliative Care (Opioid Related)**

Dosing of 2.5 to 7.5 mg of olanzapine daily appeared to be effective in 1 case series. Five milligrams was beneficial from a quality-of-life perspective.

**Analgesic Effect**

Dosing of 2.5 to 7.5 mg of olanzapine daily appeared to have an opioid-sparing effect in 1 study.

**Pharmacoeconomics**

Our base cost for Zyprexa 5 mg tablets is $12.29 each (30 day supply $368.70) and generic $10.09 each (30 day supply $302.70).

**Conclusion**

Olanzapine is a thienobenzodiazepine atypical antipsychotic with lower affinity for the dopamine receptor than the traditional neuroleptics (eg, haloperidol). Olanzapine has a high affinity for several important serotonin receptors, including the HT₂A, 5HT₂C, and 5-HT₃ receptors, making it an appealing agent for symptom management in palliative medicine for the treatment of nausea, vomiting, and delirium. Flexibility in dosing has been a problem with atypical antipsychotics; but in the case of olanzapine, the development of an orally disintegrating tablet and the demonstration that the drug can be effectively given subcutaneously has improved drug delivery. The adverse effect profile of olanzapine has not been systematically studied in the palliative care population. Olanzapine antagonizes muscarinic receptors and is a potent antimuscarinic agent, predicting significant anticholinergic effects. Indeed, common adverse effects observed in the clinical trials of psychiatric patients include postural hypotension (5%), constipation (9%-11%), dizziness (11%-18%), and dry mouth (22%). Like other atypical antipsychotics, olanzapine has lower propensity for causing extrapyramidal side effects than traditional antipsychotics. Olanzapine has also been evaluated in chemotherapy-related nausea and vomiting. The addition of olanzapine to standard antiemetic prophylaxis (serotonin antagonist and steroids) leads to a high degree of antiemetic control in the acute phase of nausea and vomiting, and improvement in delayed nausea and vomiting control when compared with serotonin/steroid combinations alone. The addition of olanzapine to the serotonin/steroid combination has not been directly compared with the most commonly used combinations for acute and delayed nausea and vomiting such as neurokinin antagonists/serotonin/steroid combinations. The addition of olanzapine to steroids and serotonin antagonists improves quality of life global health status, emotional functioning, social functioning, fatigue, insomnia, and appetite loss in patients who are experiencing chemotherapy-related nausea and vomiting. For the treatment of delirium, olanzapine has been compared with haloperidol in the critical care setting and was found to be equivalent, although more rigorous testing is needed. Uncontrolled studies carried out in cancer-related delirium, agitation in dementia, and subtypes of dementia such as vascular dementia suggest potential usefulness in these disease subsets. The analgesic effect of olanzapine has not been studied in a controlled manner, but uncontrolled studies suggest opioid-sparing properties. Olanzapine appears to be a useful agent for the palliative medicine patient. If the analgesic effects can be explored further and clarified, olanzapine has the potential to be a drug with a true portmanteau effect. Olanzapine appears to be a promising agent in cancer-related...
anorexia–cachexia but as yet to be studied in anorexia–cachexia associated with other chronic illnesses. The cost of olanzapine may be prohibitive in the hospice setting.

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References
45. Mayo Clinic Hospital Pharmacy Cost. 2012.