Current Treatment Options in Oncology

# The Benefits of Olanzapine in Palliating Symptoms

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| **Corresponding Author:** | Mellar Davis<br><br>Danville, PA UNITED STATES |
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| **First Author:** | Mellar Davis |
| **First Author Secondary Information:** | |
| **Order of Authors:** | Mellar Davis |
| | Gareth J. Sanger |
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| **Abstract:** | Opinion statement<br><br>Olanzapine has become a major drug in the management of chemotherapy-induced nausea and vomiting as a prophylactic agent. In addition, a recent randomized trial has demonstrated its benefits in treating nausea and vomiting associated with advanced cancer. The added benefit to olanzapine is that it also stimulates appetite. As a result, since it treats multiple symptoms associated with advanced cancer, it is likely to become the antiemetic of choice in palliative care at least in the United States. The added benefit of treating insomnia and the avoidance of benzodiazepines should place olanzapine in at the top of the list of drugs to use for patients who do complain of insomnia. There is no good evidence that it potentiates the respiratory depression of opioids unlike benzodiazepines. The evidence is weak that olanzapine in as an adjuvant analgesic. Hopefully, future trials will explore this in greater depth. The benefits of adding olanzapine to potent opioids is that it may reduce craving, drug cues and opioid misuse. Other symptoms like anxiety and depression may be addressed by the addition of olanzapine to standard antidepressants. |

# The Benefits of Olanzapine in Palliating Symptoms

Mellor Davies MD FCCP FAAHPM[1], Gareth J. Sanger, DSc FBPhS FRSB[2]

[1]Geisinger Medical Center, Danville, PA, USA

[2]Blizard Institute and National Bowel Research Centre, Barts and The London School of Medicine and Dentistry, Queen Mary University of London.

Correspondence: Mellar P Davis

100 N Academy Ave

Danville, PA, 17822

e-mail: mdavis2@geisinger.edu

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## Opinion statement

Olanzapine has become a major drug in the management of chemotherapy-induced nausea and vomiting as a prophylactic agent. In addition, a recent randomized trial has demonstrated its benefits in treating nausea and vomiting associated with advanced cancer. The added benefit to olanzapine is that it also stimulates appetite. As a result, since it treats multiple symptoms associated with advanced cancer, it is likely to become the antiemetic of choice in palliative care at least in the United States. The added benefit of treating insomnia and the avoidance of benzodiazepines should place olanzapine in at the top of the list of drugs to use for patients who do complain of insomnia. There is no good evidence that it potentiates the respiratory depression of opioids unlike benzodiazepines. The evidence is weak that olanzapine in as an adjuvant analgesic. Hopefully, future trials will explore this in greater depth. The benefits of adding olanzapine to potent opioids is that it may reduce craving, drug cues and opioid misuse. Other symptoms like anxiety and depression may be addressed by the addition of olanzapine to standard antidepressants.

## Introduction

Patients with cancer, particularly with advanced cancer, have a multitude of symptoms which may not be volunteered without asking [1]. These include anorexia, insomnia, nausea, vomiting, pain, constipation, and other symptoms. The prevalence of nausea and vomiting in advanced cancer ranges from 20-30%; 42% of these patients have nausea and/ or vomiting without a known ethology [2, 4]. Patients tend to minimize nausea and vomiting, and physicians may underestimate its presence [4]. Further, these terms are sometimes combined in the literature and often in trials and in the minds of treating clinicians but should be assessed separately. Thus, although nausea and vomiting are strongly associated, they are recognised in different areas of the brain and have different sensitivities to different treatments [5]. In addition, anorexia and weight loss are two of the most common symptoms and signs of advanced cancer which have prognostic importance [6]. Pain is experienced in 50-60% of patients with advanced cancer. Approximately 15% of patients have problems sleeping or have clinical insomnia [7]. Finally, substance abuse in patients with cancer occurs in a higher prevalence than in the general population. Multiple cancers are related to tobacco abuse and alcohol misuse. Individuals may also be exposed to opioids or opioid-based medications in a higher frequency than the cancer-free population and may have a family risk or personal risk for substance abuse [8-10]. These patients require adjuvant medications to help reduce the risk and block the cravings that accompany drugs of addiction.

Because patients receiving palliative care have multiple symptoms, they are often exposed to polypharmacy and the risks of drug-drug interactions. Therefore, medications which target multiple symptoms will improve compliance and reduce the risk of drug reactions (side-effects) and interactions. Olanzapine, classified as an atypical antipsychotic, inhibits the functions of multiple G protein-coupled and other receptors, and is able to provide a range of benefits in palliating patients with advanced cancer.

## Pharmacology of olanzapine

Olanzapine is a well-established atypical antipsychotic and thienobenzodiazepine, first described in1980 [5]. Several studies used radioligand binding to examine the affinity (a measure of how strongly the compound binds to the site, expressed as a Ki value in nM) of olanzapine for a range of G protein-coupled and other receptors. Focussing on the human targets (usually recombinant), some variability exists in the data from different laboratories, but Table 1 provides a summary and an approximate rank order of affinity for the different targets. Following transfection of receptors into host cells, low concentrations of olanzapine antagonised at $H_1$, $D_2$, 5-$HT_{2A}$ and 5-$HT_{2B}$ receptors, with higher concentrations antagonising at 5-$HT_{2C}$, 5-$HT_6$, 5-$HT_7$, $D_3$, muscarinic $M_1$, $M_2$, $M_3$ and $M_4$ receptors [11-13]. Later studies indicated that olanzapine acted as an inverse agonist at the $H_1$, 5-$HT_{2A}$, 5-$HT_{2B}$ and 5-$HT_{2C}$ receptors, inhibiting function by internalising the receptor [14, 15]. The function of olanzapine at the human 5-$HT_3$ receptor has not been demonstrated but the drug antagonised responses to activation of this receptor in guinea-pig intestine [12]. However, species differences in 5-$HT_3$ receptor subunits (a ligand-gated ion channel composed of a pentameric ring of subunits) mean

that the effective concentrations of receptor antagonists in guinea-pig or rat functional studies do not necessarily translate to human receptor function [16].

## Olanzapine pharmacokinetics

Commercially, the preparations include tablets, dissolvable oral discs (zydis) and intramuscular preparations which can be given subcutaneous or by intravenous injection [17-21]. Olanzapine suppositories have been developed using bases consisting of different compositions of Witepsol H-15, Witepsol S-55 for delivery with demonstrated clinical effects but no pharmacokinetic data to demonstrate bioavailability [22].

There have been no studies on the pharmacokinetics of olanzapine when used as an anti-emetic drug (e.g., by intravenous or intramuscular routes during palliative care). Nevertheless, studies on oral doses of olanzapine to healthy individuals and psychiatric patients help to interpret mechanisms of action (see [23, 24] for detailed descriptions). In summary, olanzapine is well absorbed by mouth with bioavailability around 85%. The half-life of olanzapine is 30-60 hours with peak serum concentrations at 4-6 hours [25]. Olanzapine is highly metabolized by the liver, primarily through glucuronidation, but also by oxidative metabolism to 4'-N desmethyl-olanzapine (via the cytochrome P450 CYP1A2) and 2-hydroxymethyl-olanzapine (via CYP3A4 [26, 27]). Plasma concentrations can vary over a 4-fold range; men show greater clearance and smoking decreases olanzapine concentrations (tobacco smoke induces CYP1A2) [28, 29]. Single nucleotide polymorphisms of CYP2D6 can also influence olanzapine pharmacokinetics [30]. Notably, olanzapine has no ability to inhibit CYP3A, CYP2D6, CYP2C9, or CYP2C19, minimising drug-drug interactions [31].

In one study, daily doses of olanzapine (5-30 mg/day) achieved mean plasma concentrations from 10 to 54 ng/ml [24]. This suggests good occupancy of $H_1$, 5-$HT_{2A}$, 5-$HT_{2C}$, 5-$HT_6$, 5-$HT_{2B}$, $D_2$, $D_4$, $\alpha_{2C}$-adrenoceptor, $M_4$, $D_1$, $D_3$, $M_5$, 5-$HT_3$ and perhaps other receptors expressed peripherally. However, a need to penetrate the blood-brain barrier (influenced by factors other than passive diffusion) means that higher concentrations are needed to affect the receptors expressed within the brain [32]. For example, higher doses of olanzapine are needed to access the $H_1$ receptors in the brain (and cause sedation) compared with those needed to access other receptors within the periphery (e.g., $D_2$, 5-$HT_3$) and exert anti-emetic activity.

## Summary of mechanisms of the clinical activity of olanzapine

The side-effects of olanzapine when used as an anti-psychotic medication are described by others [33], with the mechanisms summarised in Table 2.

Of the receptors antagonised by olanzapine, the $H_1$, $D_2$, $D_3$, $M_{4,5}$ and 5-$HT_3$ receptors have a known association with mechanisms of vomiting (Table 2). A similar involvement of 5-$HT_{2A}$ receptors remains equivocal [34]. Antagonism at the $H_1$ and $M_{4/5}$ receptors within the brain inhibits motion sickness and possibly other forms of emesis, although the evidence for the latter is not clear. Antagonism at the $D_2/D_3$ receptors within the area postrema (a region of brain outside the blood-brain barrier) confers a level of general anti-emetic activity, including reduction in emesis evoked by anti-cancer agents with low-to-moderate emetogenic potential. Antagonism at the 5-$HT_3$ receptor, mostly on abdominal vagal nerve terminals, inhibits

vomiting induced by anti-cancer agents with high emetogenic liability and can also reduce post-operative vomiting. Together, this profile endows a wide spectrum of use for olanzapine, which could be an advantage in patients with advanced cancer and potentially, multiple causes of nausea and vomiting. In patients with more well-defined causes of emesis, it is unclear if efficacy would be increased by these multiple actions. In patients receiving highly emetogenic chemotherapy co-prescription with dexamethasone and an $NK_1$ receptor antagonist would be required.

The ability of olanzapine to reduce nausea is unclear. Compared with vomiting, nausea remains poorly treated and is associated with activation of brain nuclei concerned with interoception (eg. amygdala, putamen, pons, locus coeruleus) and fear conditioning (eg. anterior insula and middle cingulate), whereas vomiting is initiated via the so-called vomiting centre, a collection of brainstem nuclei [5]. It might appear that a relationship between nausea and pathways of interoception is consistent with the hypothesis that the sensations of hunger, satiety and nausea and their control by gastrointestinal hormones are interrelated [35-37]. If so, then olanzapine could reduce nausea because antagonism at the $H_1$, 5-$HT_{2C}$ and 5-$HT_{2B}$ receptors are linked to increased appetite. Activity at the 5-$HT_{2C}$, 5-$HT_{2B}$ and the $D_2$ receptor may also modulate the activity of ghrelin (Table 2), with implications for appetite control [38, 39] but not necessarily nausea [40].

## Olanzapine in The Treatment of Nausea and Vomiting

Olanzapine has been used effectively as an antiemetic in a multitude of clinical circumstances. When reviewing the evidence, it is however, important to understand that nausea is not vomiting and can be more difficult to treat [5]. Clinical trial data which do not separate these terms (e.g. some describe all events as 'nausea') can give a misleading impression of the true efficacy of olanzapine and other drugs.

### Postoperative nausea and vomiting.

The use of chronic atypical antipsychotic therapy, including olanzapine, is associated with reduced need for postoperative antiemetic use [41]. In a randomized trial involving women undergoing gynaecologic surgery and plastic surgery, the addition of olanzapine 10 mg to dexamethasone and ondansetron reduced postoperative nausea and/ or vomiting by 60% (primary outcome achieved in 38% versus 14% placebo) with a relative risk for vomiting and/ or nausea of 0.37 (95% confidence interval 0.2-0.72, P=0.003) [42]

### Chemotherapy-induced nausea and vomiting

Olanzapine has been incorporated into guidelines for the treatment of nausea and vomiting induced by highly emetogenic chemotherapy (eg. cisplatin), as an effective prophylactic when combined with standard 'triple therapy' (5-$HT_3$ + $NK_1$ receptor antagonist + dexamethasone) and if not used prophylactically, as a rescue antiemetic. The addition of olanzapine is recommended because of its ability to further reduce the 'delayed' form of emesis in the days following the first 24h after treatment ('acute' emesis, normally well treated) [43-50]. In one of these studies the 5 mg dose of olanzapine appeared as effective as the 10 mg dose, as

measured primarily by the absence of vomiting or retching; nausea was reduced on some but not all days after treatment [44]. In a retrospective study, olanzapine alone increased the incidence of complete remission (no vomiting, nausea, or rescue antiemetics) in patients receiving chemotherapy for hematopoietic stem cell transplantation [51]. A systematic review of studies centered on stem cell transplantation for myeloma found that olanzapine added to standard anti emetics (5-$HT_3$ receptor antagonist with dexamethasone) was superior to the addition of an $NK_1$ receptor antagonist [52]. A Bayesian network meta-analysis of 9 randomized trials and 2959 patients found that in patients receiving highly-emetogenic chemotherapy, olanzapine together with dexamethasone and the 5-$HT_3$ receptor antagonist palonosetron, produced a greater complete remission rate for acute nausea (odds ratio 3.97), delayed nausea (odds ratio 5.62) and overall nausea control (odds ratio 4.79) than dexamethasone plus palonosetron alone [53]. In this study and in others [54, 55], the control of delayed nausea was equivalent to or superior to the use of an $NK_1$ receptor antagonist. Olanzapine has also been found to be superior to metoclopramide in providing rescue for breakthrough nausea and vomiting if not used prophylactically [56, 57]. In summary, the addition of olanzapine to the standard 3-drug regimen used to prevent chemotherapy-induced nausea and vomiting in patients receiving moderate to highly emetogenic chemotherapy, further reduces delayed nausea and possibly vomiting [58, 59]. Finally, concerns over the high level of sedation associated with the 10 mg dose of olanzapine have led to calls for use of a lower dose (5 mg), especially in older patients (over 75 years) and in those who are markedly affected by the sedation [60]. It remains to be determined however, if this lower dose retains the perceived superiority of olanzapine as a treatment of nausea when combined with standard medications.

**Nausea and vomiting with advanced cancer.**

Case reports, case series, prospective studies and a randomized trial have reported benefits [e.g., 43, 61-63]. In addition, there are 3 other antiemetics for which randomized trials have demonstrated benefit: haloperidol, metoclopramide and methotrimeprazine [64-66]. Methotrimeprazine is not available in the United States and produces significant sedation. Metoclopramide and haloperidol are associated with an increased risk of extrapyramidal side effects relative to olanzapine [67]. Haloperidol is also associated with dose dependent late increases in the QTC interval, leading to ventricular arrhythmias [68]. For olanzapine, a recent systematic review (13 studies ranging from case reports to retrospective and prospective studies) demonstrated significant reduction in vomiting and nausea in advanced cancer unrelated to radiation or chemotherapy. There were no serious adverse events recorded. Sedation was the major side effect [69].

In a pilot study of patients with advanced cancer and nausea or vomiting of at least 14 days duration unrelated to radiation in chemotherapy, patients were randomized between olanzapine 5 mg daily or placebo plus a rescue antiemetic; the study was over 7 days. Within 24 hours of initiating olanzapine, the nausea/ vomiting severity went from 9 (numerical rating scale 0-10 with 10 being severe) to 2. The benefits persisted for the 7 days of the study whereas nausea/ vomiting on the placebo arm persisted at 9/10 ($P<0.001$ between treatment arms). Olanzapine also improved appetite, fatigue and well-being [43].

Olanzapine has been helpful in clinical situations where nausea was difficult to control. In a prospective single arm trial, olanzapine 5 mg on average improved nausea and vomiting associated with partial bowel obstruction [70]. Patients with nausea and vomiting associated with cerebral metastases who have not responded to multiple anti-emetics have responded to olanzapine [71-73].

## Olanzapine and Appetite

A retrospective review of olanzapine in advanced cancer used pre and post olanzapine in food consumption as the main outcome. Eighty of 951 patients received an average dose of 2.28 mg per day. Food consumption increased to 149% ($P = 0.001$). In the subset with anorexia without nausea, food consumption increased to 143% ($P<0.001$). Doses as low as 1.5 mg a day increased food consumption 124% ($P < 0.01$) [74], an interesting finding given the likely need for brain penetration by olanzapine in order to affect the central mechanisms controlling appetite (Table 2). In an exploratory randomized trial of different doses of olanzapine (2.5 mg to 20 mg daily) in patients with advanced cancer and greater than 10% weight loss, olanzapine reduced the slope of weight loss over time; there were no changes in blood levels of leptin, total ghrelin or growth hormone although interleukin 6 blood levels increased, possibly because of tumor progression [75]. A second randomized trial involving patients with greater than 10% body weight loss in advanced cancer, compared thalidomide alone with thalidomide, olanzapine and megestrol acetate. The dose of olanzapine was 5 mg. Thalidomide was used because it may inhibit inflammatory cytokines released in association with anorexia, weight loss and sarcopenia. The combination attenuated weight loss and anorexia compared with thalidomide alone, and also reduced sarcopenia measured by mid arm muscle mass [76]. A third randomized trial of patients with advanced lung and gastrointestinal cancer compared megestrol acetate to olanzapine plus megestrol acetate. Patients had 5% or greater weight loss and anorexia. The combination improved weight gain (greater than 5%), appetite, nausea and quality of life relative to megestrol acetate alone [77]. Finally, a randomized trial of olanzapine versus placebo plus antiemetic rescue in patients with cancer and nausea unrelated to chemotherapy or radiation, found that olanzapine rapidly reduced nausea and/ or vomiting over 24 hours but also significantly improved appetite [63].

## Other actions of olanzapine

### Insomnia

Olanzapine (5 – 10 mg; average dose 6.67 mg) improved sleep architecture (sleep efficiency, total sleep time and sleep latency) in patients with major depression, independent of depression responses [78]. In patients with schizophrenia treated with olanzapine 5-25mg daily, the sleep architecture was found to be more physiologic than when treated with clozapine [79]. A systematic review of the use of antipsychotics, found that olanzapine 5-20 mg in randomized trials improved slow wave sleep, had variable effects on REM sleep and reduced sleep latency while improving total sleep time [80]. Further, olanzapine 10mg daily, improved recalcitrant paradoxical insomnia whereas risperidone had little effect [81]. Insomnia associated with

combat post-traumatic stress disorder (5 case reports) improved with olanzapine 10 or 20mg [82]. In a small double-blind study, olanzapine 15mg/day, unlike haloperidol 10mg/day, treated manic episodes in patients with bipolar disorders, improved sleep efficiency and reduced waking after sleep onset [83] Overall, olanzapine may improve sleep efficiency, total sleep time, reduce sleep latency and increase slow wave sleep, unlike other antipsychotics such as clozapine, quetiapine, risperidone or haloperidol. The mechanisms are unclear but may be related to the ability of olanzapine to cause sedation by antagonism at cortical $H_1$ receptors (Table 2).

**Analgesia**

In an animal study olanzapine reduced morphine-induced vomiting and retching as well as the thermal hyperalgesia, increased wakefulness and decrease in non-REM sleep associated with sciatic nerve lesion [84]. In a mouse tail-flick assay olanzapine had weak anti-nociceptive activity, prevented by alpha -2 adrenergic receptor antagonism [85].

In a case report, olanzapine 5mg daily improved glossodynia unresponsive to other non-opioid analgesics [86]. Some reports suggest that olanzapine was effective in reducing pain from disorders such as migraines and fibromyalgia [87]. In a retrospective study of 50 patients with refractory headaches unresponsive to at least 4 other therapies, olanzapine 5-35 mg per day (average 5-10 mg daily) reduced headache days and the severity of headaches [88]. In 3 case studies, olanzapine reduced cervical neck pain from rheumatoid arthritis at doses as low as 1.25-2.5 mg per day and appeared to be opioid sparing [89]. Olanzapine at doses of 2.5 mg has been combined with duloxetine 30 mg to treat chronic pelvic pain [90]. Cancer pain is reported to respond to olanzapine with the added benefit of reducing craving. A patient with colon cancer and substance abuse given olanzapine 10 mg at night had reduced craving and pain, allowing for reductions in fentanyl doses [91]. A series of 8 patients with severe cancer pain despite escalating doses of opioids, responded to olanzapine 2.5-7.5 mg daily, resulting in improved cognition, anxiety and stabilizing doses of opioids within 24h of initiating olanzapine [92]. In summary, these reports of olanzapine as an analgesic or adjuvant are case reports or case series. Randomized clinical trials are needed to confirm these findings and studies are needed to determine the mechanisms of action.

**Delirium**

There is little evidence that antipsychotics in general or olanzapine are helpful in managing delirium in advanced cancer. A comparison of olanzapine to haloperidol found that about half of patients responded but responses took longer when patients were treated with olanzapine (4.5 days versus 2.8 days) [93]. This study was stopped for futility. In a systematic review of antipsychotics in the management of delirium in terminally ill patients, no difference was found in responses between haloperidol and placebo or between olanzapine and haloperidol [94].

**Substance Abuse Disorders**

Substance abuse before and after a diagnosis of cancer is not unusual. Tobacco and alcohol abuse are responsible for several cancers. Individuals with cancer may use illicit substances to control symptoms and to cope chemically with their diagnosis. Opioids are the main analgesics used for moderate to severe cancer pain. Cannabis use during cancer therapy and as treatment for symptoms is a growing practice. It is estimated that 21% of patients with cancer are at high risk for substance use and that on average 34% chemically cope with their illness [95].

The influence of olanzapine on craving and substance abuse has been explored in patients with dual diagnoses (bipolar or schizophrenia plus substance abuse disorder) and in the addiction population. Case series have shown that olanzapine may reduce craving and substance abuse in patients with dual diagnoses [e.g., 96-105]. It is suggested that the ability of olanzapine to block craving may be related to rapid dissociation from the dopamine $D_2$ receptor, reducing the risk of dysphoria and super sensitivity to dopamine upon drug withdrawal [106, 107], reducing the risk for extrapyramidal symptoms (providing greater acceptance and better compliance [108]) and causing a positive mood and improving cognitive function, perhaps by antagonism at the different 5-HT receptors and adrenoceptors [106].

Even among second generation antipsychotics there are differences. Quetiapine is known on the street as "baby heroin" or "Susie Q" and is a drug of abuse whereas olanzapine is known as the "ideal trip terminator/modulator" after a psychedelics drug binge and is known to treat unwanted "come-down" symptoms related to drug abuse [109-112]. An open label comparison suggested that olanzapine may be as effective as clonidine, if not better in managing withdrawal symptoms from heroin [113].

*Cocaine and Amphetamine Abuse:* Several studies reported no benefits of olanzapine in the treatment of cocaine dependence [97, 114, 115] but although positive randomized studies exist [116] a systematic review concluded that at present, the evidence for beneficial activity was weak [117]. Olanzapine reduced the acute psychiatric reactions to amphetamine abuse quicker than haloperidol and in rats, pre-treatment with olanzapine prevented conditioned place preference related to amphetamines [116, 118].

*Cannabis Abuse:* Olanzapine reduced cannabis craving in patients with a dual diagnosis of schizophrenia and cannabis abuse [97]. In a 14-week trial, olanzapine reduced cannabis craving in cannabis-dependent individuals [105]. A randomized trial of olanzapine versus haloperidol for cannabis psychiatric reactions found both drugs were effective, but olanzapine had fewer extrapyramidal side effects [119]. In rats, olanzapine unlike haloperidol, reversed the memory deficits and decrease in extracellular ACh levels within the hippocampus caused by delta9-tetrahydrocannabinol; the mechanisms of action were unclear [120].

*Alcohol Abuse:* In a series of individuals who were heavy social drinkers, 5 mg of olanzapine reduced alcohol-related visual cues but not the rewarding effect of alcohol consumption [103]. A randomized trial demonstrated that 2.5-5 mg of olanzapine reduced alcohol craving and intake, yet a second trial found that olanzapine failed to reduce the relapse rate in individuals with an alcohol dependence disorder [121, 122]. The differences in trials may be related to genotype. In individuals with the L allele for the dopamine receptor $D_4$, olanzapine reduced

alcohol intake [122]. In a retrospective study olanzapine with superior to haloperidol in treating agitation caused by drugs of abuse including alcohol [123].

*Nicotine Addiction:* In one small study, patients with a dual diagnosis of schizophrenia and nicotine abuse were found to have an increase in nicotine use on haloperidol whereas olanzapine had no effects [124]. In other studies, olanzapine reduced tobacco or nicotine craving and nicotine withdrawal symptoms [101, 125-127].

*Opioid Abuse:* Olanzapine reduced condition place preference in mice exposed to morphine [128]. In a randomized trial, olanzapine 10 mg treated opioid withdrawal symptoms more effectively than clonidine and in a prospective observational trial, olanzapine reduced the dropout rate from opioid maintenance therapy which correlated with a reduction in craving [113, 129].

## Future Directions

Olanzapine has multiple benefits for patients with advanced cancer. Not only has it become part of the recommended guidelines as prophylaxis for chemotherapy-induced nausea and vomiting (reducing the occurrence of delayed nausea/ vomiting), but it can reduce nausea and vomiting unrelated to radiation or chemotherapy. The examples include post-operative nausea and vomiting and use in patients with advanced cancer. The main side-effect is sedation which can be minimised by reducing the recommended dose from 10 to 5 mg daily. Added benefits to the use of olanzapine include improved appetite and sleep. The mechanisms of improved appetite are argued to contribute to the mechanisms by which olanzapine may reduce nausea (as distinct from vomiting), but trials are needed to determine if this potential advantage is maintained at the lower dose of 5mg. Randomized trials regarding analgesic benefits are needed, although the case reports and case series are encouraging. There is evidence that olanzapine as an adjuvant may reduce craving and misuse of multiple drugs that have a risk for abuse and addiction but are needed to palliate symptoms of advanced cancer. Additional randomized studies are needed to confirm this.

## Summary

Olanzapine can antagonise at multiple receptors. Antagonism at $H_1$, $M_5$ prevents motion sickness and may have benefits in treatment of patients with advanced cancer. Antagonism at $D_2/_3$ prevent mild-to-moderate vomiting evoked by chemotherapy and vomiting evoked by a variety of other stimuli. Antagonism at 5-$HT_3$ prevents severe forms of acute emesis induced by chemotherapy (notably the first 24h after treatment) and post-operative nausea and vomiting. Together, these different actions improve the likelihood of managing vomiting during advanced cancer caused by multiple causes. Olanzapine also increases appetite, acting via the $H_1$, 5-$HT_{2B}$ and 5-$HT_{2C}$ receptors; certain of these and other receptors may dimerise with the ghrelin receptor and when antagonised, enhance ghrelin release and receptor activity, with further promotion of appetite. This type of activity may also inhibit nausea and some evidence suggests that olanzapine has superior ability to inhibit late-stage nausea during chemotherapy, compared with other anti-emetics including the $NK_1$ antagonists. Olanzapine

10mg may cause sedation (via $H_1$ antagonism), minimised by reducing the dose to 5mg, without loss of ability to inhibit chemotherapy-induced vomiting, although trials are needed to examine the effects on nausea. These and other actions of olanzapine may also reduce insomnia, facilitate analgesic drug activity and prevent different addictions often found among patients with advanced cancer and/ or alleviate symptoms of withdrawal.

## Compliance with Ethics Guidelines

### Conflict of Interest

Mellar Davis has no conflict of Interest

Gareth Sanger currently receives research funding from Takeda Pharmaceuticals

### Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by either of the authors.

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### *Of importance

### ** Of major importance


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# The Benefits of Olanzapine in Palliating Symptoms

Mellor Davies MD FCCP FAAHPM[1], Gareth J. Sanger, DSc FBPhS FRSB[2]

[1]Geisinger Medical Center, Danville, PA, USA

[2]Blizard Institute and National Bowel Research Centre, Barts and The London School of Medicine and Dentistry, Queen Mary University of London.

Correspondence: Mellar P Davis

100 N Academy Ave

Danville, PA, 17822

e-mail: mdavis2@geisinger.edu

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## Opinion statement

Olanzapine has become a major drug in the management of chemotherapy-induced nausea and vomiting as a prophylactic agent. In addition, a recent randomized trial has demonstrated its benefits in treating nausea and vomiting associated with advanced cancer. The added benefit to olanzapine is that it also stimulates appetite. As a result, since it treats multiple symptoms associated with advanced cancer, it is likely to become the antiemetic of choice in palliative care at least in the United States. The added benefit of treating insomnia and the avoidance of benzodiazepines should place olanzapine in at the top of the list of drugs to use for patients who do complain of insomnia. There is no good evidence that it potentiates the respiratory depression of opioids unlike benzodiazepines. The evidence is weak that olanzapine in as an adjuvant analgesic. Hopefully, future trials will explore this in greater depth. The benefits of adding olanzapine to potent opioids is that it may reduce craving, drug cues and opioid misuse. Other symptoms like anxiety and depression may be addressed by the addition of olanzapine to standard antidepressants.

## Introduction

Patients with cancer, particularly with advanced cancer, have a multitude of symptoms which may not be volunteered without asking [1]. These include anorexia, insomnia, nausea, vomiting, pain, constipation, and other symptoms. The prevalence of nausea and vomiting in advanced cancer ranges from 20-30%; 42% of these patients have nausea and/ or vomiting without a known ethology [2, 4]. Patients tend to minimize nausea and vomiting, and physicians may underestimate its presence [4]. Further, these terms are sometimes combined in the literature and often in trials and in the minds of treating clinicians but should be assessed separately. Thus, although nausea and vomiting are strongly associated, they are recognised in different areas of the brain and have different sensitivities to different treatments [5]. In addition, anorexia and weight loss are two of the most common symptoms and signs of advanced cancer which have prognostic importance [6]. Pain is experienced in 50-60% of patients with advanced cancer. Approximately 15% of patients have problems sleeping or have clinical insomnia [7]. Finally, substance abuse in patients with cancer occurs in a higher prevalence than in the general population. Multiple cancers are related to tobacco abuse and alcohol misuse. Individuals may also be exposed to opioids or opioid-based medications in a higher frequency than the cancer-free population and may have a family risk or personal risk for substance abuse [8-10]. These patients require adjuvant medications to help reduce the risk and block the cravings that accompany drugs of addiction.

Because patients receiving palliative care have multiple symptoms, they are often exposed to polypharmacy and the risks of drug-drug interactions. Therefore, medications which target multiple symptoms will improve compliance and reduce the risk of drug reactions (side-effects) and interactions. Olanzapine, classified as an atypical antipsychotic, inhibits the functions of multiple G protein-coupled and other receptors, and is able to provide a range of benefits in palliating patients with advanced cancer.

## Pharmacology of olanzapine

Olanzapine is a well-established atypical antipsychotic and thienobenzodiazepine, first described in1980 [5]. Several studies used radioligand binding to examine the affinity (a measure of how strongly the compound binds to the site, expressed as a Ki value in nM) of olanzapine for a range of G protein-coupled and other receptors. Focussing on the human targets (usually recombinant), some variability exists in the data from different laboratories, but Table 1 provides a summary and an approximate rank order of affinity for the different targets. Following transfection of receptors into host cells, low concentrations of olanzapine antagonised at $H_1$, $D_2$, 5-$HT_{2A}$ and 5-$HT_{2B}$ receptors, with higher concentrations antagonising at 5-$HT_{2C}$, 5-$HT_6$, 5-$HT_7$, $D_3$, muscarinic $M_1$, $M_2$, $M_3$ and $M_4$ receptors [11-13]. Later studies indicated that olanzapine acted as an inverse agonist at the $H_1$, 5-$HT_{2A}$, 5-$HT_{2B}$ and 5-$HT_{2C}$ receptors, inhibiting function by internalising the receptor [14, 15]. The function of olanzapine at the human 5-$HT_3$ receptor has not been demonstrated but the drug antagonised responses to activation of this receptor in guinea-pig intestine [12]. However, species differences in 5-$HT_3$ receptor subunits (a ligand-gated ion channel composed of a pentameric ring of subunits) mean

that the effective concentrations of receptor antagonists in guinea-pig or rat functional studies do not necessarily translate to human receptor function [16].

## Olanzapine pharmacokinetics

Commercially, the preparations include tablets, dissolvable oral discs (zydis) and intramuscular preparations which can be given subcutaneous or by intravenous injection [17-21]. Olanzapine suppositories have been developed using bases consisting of different compositions of Witepsol H-15, Witepsol S-55 for delivery with demonstrated clinical effects but no pharmacokinetic data to demonstrate bioavailability [22].

There have been no studies on the pharmacokinetics of olanzapine when used as an anti-emetic drug (e.g., by intravenous or intramuscular routes during palliative care). Nevertheless, studies on oral doses of olanzapine to healthy individuals and psychiatric patients help to interpret mechanisms of action (see [23, 24] for detailed descriptions). In summary, olanzapine is well absorbed by mouth with bioavailability around 85%. The half-life of olanzapine is 30-60 hours with peak serum concentrations at 4-6 hours [25]. Olanzapine is highly metabolized by the liver, primarily through glucuronidation, but also by oxidative metabolism to 4'-N desmethyl-olanzapine (via the cytochrome P450 CYP1A2) and 2-hydroxymethyl-olanzapine (via CYP3A4 [26, 27]). Plasma concentrations can vary over a 4-fold range; men show greater clearance and smoking decreases olanzapine concentrations (tobacco smoke induces CYP1A2) [28, 29]. Single nucleotide polymorphisms of CYP2D6 can also influence olanzapine pharmacokinetics [30]. Notably, olanzapine has no ability to inhibit CYP3A, CYP2D6, CYP2C9, or CYP2C19, minimising drug-drug interactions [31].

In one study, daily doses of olanzapine (5-30 mg/day) achieved mean plasma concentrations from 10 to 54 ng/ml [24]. This suggests good occupancy of $H_1$, 5-$HT_{2A}$, 5-$HT_{2C}$, 5-$HT_6$, 5-$HT_{2B}$, $D_2$, $D_4$, $\alpha_{2C}$-adrenoceptor, $M_4$, $D_1$, $D_3$, $M_5$, 5-$HT_3$ and perhaps other receptors expressed peripherally. However, a need to penetrate the blood-brain barrier (influenced by factors other than passive diffusion) means that higher concentrations are needed to affect the receptors expressed within the brain [32]. For example, higher doses of olanzapine are needed to access the $H_1$ receptors in the brain (and cause sedation) compared with those needed to access other receptors within the periphery (e.g., $D_2$, 5-$HT_3$) and exert anti-emetic activity.

## Summary of mechanisms of the clinical activity of olanzapine

The side-effects of olanzapine when used as an anti-psychotic medication are described by others [33], with the mechanisms summarised in Table 2.

Of the receptors antagonised by olanzapine, the $H_1$, $D_2$, $D_3$, $M_{4,5}$ and 5-$HT_3$ receptors have a known association with mechanisms of vomiting (Table 2). A similar involvement of 5-$HT_{2A}$ receptors remains equivocal [34]. Antagonism at the $H_1$ and $M_{4/5}$ receptors within the brain inhibits motion sickness and possibly other forms of emesis, although the evidence for the latter is not clear. Antagonism at the $D_2/D_3$ receptors within the area postrema (a region of brain outside the blood-brain barrier) confers a level of general anti-emetic activity, including reduction in emesis evoked by anti-cancer agents with low-to-moderate emetogenic potential. Antagonism at the 5-$HT_3$ receptor, mostly on abdominal vagal nerve terminals, inhibits

vomiting induced by anti-cancer agents with high emetogenic liability and can also reduce post-operative vomiting. Together, this profile endows a wide spectrum of use for olanzapine, which could be an advantage in patients with advanced cancer and potentially, multiple causes of nausea and vomiting. In patients with more well-defined causes of emesis, it is unclear if efficacy would be increased by these multiple actions. In patients receiving highly emetogenic chemotherapy co-prescription with dexamethasone and an $NK_1$ receptor antagonist would be required.

The ability of olanzapine to reduce nausea is unclear. Compared with vomiting, nausea remains poorly treated and is associated with activation of brain nuclei concerned with interoception (eg. amygdala, putamen, pons, locus coeruleus) and fear conditioning (eg. anterior insula and middle cingulate), whereas vomiting is initiated via the so-called vomiting centre, a collection of brainstem nuclei [5]. It might appear that a relationship between nausea and pathways of interoception is consistent with the hypothesis that the sensations of hunger, satiety and nausea and their control by gastrointestinal hormones are interrelated [35-37]. If so, then olanzapine could reduce nausea because antagonism at the $H_1$, 5-$HT_{2C}$ and 5-$HT_{2B}$ receptors are linked to increased appetite. Activity at the 5-$HT_{2C}$, 5-$HT_{2B}$ and the $D_2$ receptor may also modulate the activity of ghrelin (Table 2), with implications for appetite control [38, 39] but not necessarily nausea [40].

## Olanzapine in The Treatment of Nausea and Vomiting

Olanzapine has been used effectively as an antiemetic in a multitude of clinical circumstances. When reviewing the evidence, it is however, important to understand that nausea is not vomiting and can be more difficult to treat [5]. Clinical trial data which do not separate these terms (e.g. some describe all events as 'nausea') can give a misleading impression of the true efficacy of olanzapine and other drugs.

### Postoperative nausea and vomiting.

The use of chronic atypical antipsychotic therapy, including olanzapine, is associated with reduced need for postoperative antiemetic use [41]. In a randomized trial involving women undergoing gynaecologic surgery and plastic surgery, the addition of olanzapine 10 mg to dexamethasone and ondansetron reduced postoperative nausea and/ or vomiting by 60% (primary outcome achieved in 38% versus 14% placebo) with a relative risk for vomiting and/ or nausea of 0.37 (95% confidence interval 0.2-0.72, P=0.003) [42]

### Chemotherapy-induced nausea and vomiting

Olanzapine has been incorporated into guidelines for the treatment of nausea and vomiting induced by highly emetogenic chemotherapy (eg. cisplatin), as an effective prophylactic when combined with standard 'triple therapy' (5-$HT_3$ + $NK_1$ receptor antagonist + dexamethasone) and if not used prophylactically, as a rescue antiemetic. The addition of olanzapine is recommended because of its ability to further reduce the 'delayed' form of emesis in the days following the first 24h after treatment ('acute' emesis, normally well treated) [43-50]. In one of these studies the 5 mg dose of olanzapine appeared as effective as the 10 mg dose, as

measured primarily by the absence of vomiting or retching; nausea was reduced on some but not all days after treatment [44]. In a retrospective study, olanzapine alone increased the incidence of complete remission (no vomiting, nausea, or rescue antiemetics) in patients receiving chemotherapy for hematopoietic stem cell transplantation [51]. A systematic review of studies centered on stem cell transplantation for myeloma found that olanzapine added to standard anti emetics (5-$HT_3$ receptor antagonist with dexamethasone) was superior to the addition of an $NK_1$ receptor antagonist [52]. A Bayesian network meta-analysis of 9 randomized trials and 2959 patients found that in patients receiving highly-emetogenic chemotherapy, olanzapine together with dexamethasone and the 5-$HT_3$ receptor antagonist palonosetron, produced a greater complete remission rate for acute nausea (odds ratio 3.97), delayed nausea (odds ratio 5.62) and overall nausea control (odds ratio 4.79) than dexamethasone plus palonosetron alone [53]. In this study and in others [54, 55], the control of delayed nausea was equivalent to or superior to the use of an $NK_1$ receptor antagonist. Olanzapine has also been found to be superior to metoclopramide in providing rescue for breakthrough nausea and vomiting if not used prophylactically [56, 57]. In summary, the addition of olanzapine to the standard 3-drug regimen used to prevent chemotherapy-induced nausea and vomiting in patients receiving moderate to highly emetogenic chemotherapy, further reduces delayed nausea and possibly vomiting [58, 59]. Finally, concerns over the high level of sedation associated with the 10 mg dose of olanzapine have led to calls for use of a lower dose (5 mg), especially in older patients (over 75 years) and in those who are markedly affected by the sedation [60]. It remains to be determined however, if this lower dose retains the perceived superiority of olanzapine as a treatment of nausea when combined with standard medications.

**Nausea and vomiting with advanced cancer.**

Case reports, case series, prospective studies and a randomized trial have reported benefits [e.g., 43, 61-63]. In addition, there are 3 other antiemetics for which randomized trials have demonstrated benefit: haloperidol, metoclopramide and methotrimeprazine [64-66]. Methotrimeprazine is not available in the United States and produces significant sedation. Metoclopramide and haloperidol are associated with an increased risk of extrapyramidal side effects relative to olanzapine [67]. Haloperidol is also associated with dose dependent late increases in the QTC interval, leading to ventricular arrhythmias [68]. Olanzapine as assessed in five meta-analyses and twenty RCTs does not increase the QT interval[1] For olanzapine, a recent systematic review (13 studies ranging from case reports to retrospective and prospective studies) demonstrated significant reduction in vomiting and nausea in advanced cancer unrelated to radiation or chemotherapy. There were no serious adverse events recorded. Sedation was the major side effect [69].

In a pilot study of patients with advanced cancer and nausea or vomiting of at least 14 days duration unrelated to radiation in chemotherapy, patients were randomized between olanzapine 5 mg daily or placebo plus a rescue antiemetic; the study was over 7 days. Within 24 hours of initiating olanzapine, the nausea/ vomiting severity went from 9 (numerical rating scale 0-10 with 10 being severe) to 2. The benefits persisted for the 7 days of the study whereas

nausea/ vomiting on the placebo arm persisted at 9/10 (P<0.001 between treatment arms). Olanzapine also improved appetite, fatigue and well-being [43].

Olanzapine has been helpful in clinical situations where nausea was difficult to control. In a prospective single arm trial, olanzapine 5 mg on average improved nausea and vomiting associated with partial bowel obstruction [70]. Patients with nausea and vomiting associated with cerebral metastases who have not responded to multiple anti-emetics have responded to olanzapine [71-73].

## Olanzapine and Appetite

A retrospective review of olanzapine in advanced cancer used pre and post olanzapine in food consumption as the main outcome. Eighty of 951 patients received an average dose of 2.28 mg per day. Food consumption increased to 149% (P = 0.001). In the subset with anorexia without nausea, food consumption increased to 143% (P<0.001). Doses as low as 1.5 mg a day increased food consumption 124% (P < 0.01) [74], an interesting finding given the likely need for brain penetration by olanzapine in order to affect the central mechanisms controlling appetite (Table 2). In an exploratory randomized trial of different doses of olanzapine (2.5 mg to 20 mg daily) in patients with advanced cancer and greater than 10% weight loss, olanzapine reduced the slope of weight loss over time; there were no changes in blood levels of leptin, total ghrelin or growth hormone although interleukin 6 blood levels increased, possibly because of tumor progression [75]. A second randomized trial involving patients with greater than 10% body weight loss in advanced cancer, compared thalidomide alone with thalidomide, olanzapine and megestrol acetate. The dose of olanzapine was 5 mg. Thalidomide was used because it may inhibit inflammatory cytokines released in association with anorexia, weight loss and sarcopenia. The combination attenuated weight loss and anorexia compared with thalidomide alone, and also reduced sarcopenia measured by mid arm muscle mass [76]. A third randomized trial of patients with advanced lung and gastrointestinal cancer compared megestrol acetate to olanzapine plus megestrol acetate. Patients had 5% or greater weight loss and anorexia. The combination improved weight gain (greater than 5%), appetite, nausea and quality of life relative to megestrol acetate alone [77]. Finally, a randomized trial of olanzapine versus placebo plus antiemetic rescue in patients with cancer and nausea unrelated to chemotherapy or radiation, found that olanzapine rapidly reduced nausea and/ or vomiting over 24 hours but also significantly improved appetite [63].

## Other actions of olanzapine

### Insomnia

Olanzapine (5 – 10 mg; average dose 6.67 mg) improved sleep architecture (sleep efficiency, total sleep time and sleep latency) in patients with major depression, independent of depression responses [78]. In patients with schizophrenia treated with olanzapine 5-25mg daily, the sleep architecture was found to be more physiologic than when treated with clozapine [79]. A systematic review of the use of antipsychotics, found that olanzapine 5-20 mg in randomized trials improved slow wave sleep, had variable effects on REM sleep and reduced sleep latency

while improving total sleep time [80]. Further, olanzapine 10mg daily, improved recalcitrant paradoxical insomnia whereas risperidone had little effect [81]. Insomnia associated with combat post-traumatic stress disorder (5 case reports) improved with olanzapine 10 or 20mg [82]. In a small double-blind study, olanzapine 15mg/day, unlike haloperidol 10mg/day, treated manic episodes in patients with bipolar disorders, improved sleep efficiency and reduced waking after sleep onset [83] Overall, olanzapine may improve sleep efficiency, total sleep time, reduce sleep latency and increase slow wave sleep, unlike other antipsychotics such as clozapine, quetiapine, risperidone or haloperidol. The mechanisms are unclear but may be related to the ability of olanzapine to cause sedation by antagonism at cortical $H_1$ receptors (Table 2).

**Analgesia**

In an animal study olanzapine reduced morphine-induced vomiting and retching as well as the thermal hyperalgesia, increased wakefulness and decrease in non-REM sleep associated with sciatic nerve lesion [84]. In a mouse tail-flick assay olanzapine had weak anti-nociceptive activity, prevented by alpha -2 adrenergic receptor antagonism [85].

In a case report, olanzapine 5mg daily improved glossodynia unresponsive to other non-opioid analgesics [86]. Some reports suggest that olanzapine was effective in reducing pain from disorders such as migraines and fibromyalgia [87]. In a retrospective study of 50 patients with refractory headaches unresponsive to at least 4 other therapies, olanzapine 5-35 mg per day (average 5-10 mg daily) reduced headache days and the severity of headaches [88]. In 3 case studies, olanzapine reduced cervical neck pain from rheumatoid arthritis at doses as low as 1.25-2.5 mg per day and appeared to be opioid sparing [89]. Olanzapine at doses of 2.5 mg has been combined with duloxetine 30 mg to treat chronic pelvic pain [90]. Cancer pain is reported to respond to olanzapine with the added benefit of reducing craving. A patient with colon cancer and substance abuse given olanzapine 10 mg at night had reduced craving and pain, allowing for reductions in fentanyl doses [91]. A series of 8 patients with severe cancer pain despite escalating doses of opioids, responded to olanzapine 2.5-7.5 mg daily, resulting in improved cognition, anxiety and stabilizing doses of opioids within 24h of initiating olanzapine [92]. In summary, these reports of olanzapine as an analgesic or adjuvant are case reports or case series. Randomized clinical trials are needed to confirm these findings and studies are needed to determine the mechanisms of action.

**Delirium**

There is little evidence that antipsychotics in general or olanzapine are helpful in managing delirium in advanced cancer. A comparison of olanzapine to haloperidol found that about half of patients responded but responses took longer when patients were treated with olanzapine (4.5 days versus 2.8 days) [93]. This study was stopped for futility. In a systematic review of antipsychotics in the management of delirium in terminally ill patients, no difference was found in responses between haloperidol and placebo or between olanzapine and haloperidol [94].

**Substance Abuse Disorders**

Substance abuse before and after a diagnosis of cancer is not unusual. Tobacco and alcohol abuse are responsible for several cancers. Individuals with cancer may use illicit substances to control symptoms and to cope chemically with their diagnosis. Opioids are the main analgesics used for moderate to severe cancer pain. Cannabis use during cancer therapy and as treatment for symptoms is a growing practice. It is estimated that 21% of patients with cancer are at high risk for substance use and that on average 34% chemically cope with their illness [95].

The influence of olanzapine on craving and substance abuse has been explored in patients with dual diagnoses (bipolar or schizophrenia plus substance abuse disorder) and in the addiction population. Case series have shown that olanzapine may reduce craving and substance abuse in patients with dual diagnoses [e.g., 96-105]. It is suggested that the ability of olanzapine to block craving may be related to rapid dissociation from the dopamine $D_2$ receptor, reducing the risk of dysphoria and super sensitivity to dopamine upon drug withdrawal [106, 107], reducing the risk for extrapyramidal symptoms (providing greater acceptance and better compliance [108]) and causing a positive mood and improving cognitive function, perhaps by antagonism at the different 5-HT receptors and adrenoceptors [106].

Even among second generation antipsychotics there are differences. Quetiapine is known on the street as "baby heroin" or "Susie Q" and is a drug of abuse whereas olanzapine is known as the "ideal trip terminator/modulator" after a psychedelics drug binge and is known to treat unwanted "come-down" symptoms related to drug abuse [109-112]. An open label comparison suggested that olanzapine may be as effective as clonidine, if not better in managing withdrawal symptoms from heroin [113].

*Cocaine and Amphetamine Abuse:* Several studies reported no benefits of olanzapine in the treatment of cocaine dependence [97, 114, 115] but although positive randomized studies exist [116] a systematic review concluded that at present, the evidence for beneficial activity was weak [117]. Olanzapine reduced the acute psychiatric reactions to amphetamine abuse quicker than haloperidol and in rats, pre-treatment with olanzapine prevented conditioned place preference related to amphetamines [116, 118].

*Cannabis Abuse:* Olanzapine reduced cannabis craving in patients with a dual diagnosis of schizophrenia and cannabis abuse [97]. In a 14-week trial, olanzapine reduced cannabis craving in cannabis-dependent individuals [105]. A randomized trial of olanzapine versus haloperidol for cannabis psychiatric reactions found both drugs were effective, but olanzapine had fewer extrapyramidal side effects [119]. In rats, olanzapine unlike haloperidol, reversed the memory deficits and decrease in extracellular ACh levels within the hippocampus caused by delta9-tetrahydrocannabinol; the mechanisms of action were unclear [120].

*Alcohol Abuse:* In a series of individuals who were heavy social drinkers, 5 mg of olanzapine reduced alcohol-related visual cues but not the rewarding effect of alcohol consumption [103]. A randomized trial demonstrated that 2.5-5 mg of olanzapine reduced alcohol craving and intake, yet a second trial found that olanzapine failed to reduce the relapse rate in individuals with an alcohol dependence disorder [121, 122]. The differences in trials may be related to genotype. In individuals with the L allele for the dopamine receptor $D_4$, olanzapine reduced

alcohol intake [122]. In a retrospective study olanzapine with superior to haloperidol in treating agitation caused by drugs of abuse including alcohol [123].

*Nicotine Addiction:* In one small study, patients with a dual diagnosis of schizophrenia and nicotine abuse were found to have an increase in nicotine use on haloperidol whereas olanzapine had no effects [124]. In other studies, olanzapine reduced tobacco or nicotine craving and nicotine withdrawal symptoms [101, 125-127].

*Opioid Abuse:* Olanzapine reduced condition place preference in mice exposed to morphine [128]. In a randomized trial, olanzapine 10 mg treated opioid withdrawal symptoms more effectively than clonidine and in a prospective observational trial, olanzapine reduced the dropout rate from opioid maintenance therapy which correlated with a reduction in craving [113, 129].

## Future Directions

Olanzapine has multiple benefits for patients with advanced cancer. Not only has it become part of the recommended guidelines as prophylaxis for chemotherapy-induced nausea and vomiting (reducing the occurrence of delayed nausea/ vomiting), but it can reduce nausea and vomiting unrelated to radiation or chemotherapy. The examples include post-operative nausea and vomiting and use in patients with advanced cancer. The main side-effect is sedation which can be minimised by reducing the recommended dose from 10 to 5 mg daily. Added benefits to the use of olanzapine include improved appetite and sleep. The mechanisms of improved appetite are argued to contribute to the mechanisms by which olanzapine may reduce nausea (as distinct from vomiting), but trials are needed to determine if this potential advantage is maintained at the lower dose of 5mg. Randomized trials regarding analgesic benefits are needed, although the case reports and case series are encouraging. There is evidence that olanzapine as an adjuvant may reduce craving and misuse of multiple drugs that have a risk for abuse and addiction but are needed to palliate symptoms of advanced cancer. Additional randomized studies are needed to confirm this.

## Summary

Olanzapine can antagonise at multiple receptors. Antagonism at $H_1$, $M_5$ prevents motion sickness and may have benefits in treatment of patients with advanced cancer. Antagonism at $D_2/_3$ prevent mild-to-moderate vomiting evoked by chemotherapy and vomiting evoked by a variety of other stimuli. Antagonism at 5-$HT_3$ prevents severe forms of acute emesis induced by chemotherapy (notably the first 24h after treatment) and post-operative nausea and vomiting. Together, these different actions improve the likelihood of managing vomiting during advanced cancer caused by multiple causes. Olanzapine also increases appetite, acting via the $H_1$, 5-$HT_{2B}$ and 5-$HT_{2C}$ receptors; certain of these and other receptors may dimerise with the ghrelin receptor and when antagonised, enhance ghrelin release and receptor activity, with further promotion of appetite. This type of activity may also inhibit nausea and some evidence suggests that olanzapine has superior ability to inhibit late-stage nausea during chemotherapy, compared with other anti-emetics including the $NK_1$ antagonists. Olanzapine

10mg may cause sedation (via $H_1$ antagonism), minimised by reducing the dose to 5mg, without loss of ability to inhibit chemotherapy-induced vomiting, although trials are needed to examine the effects on nausea. These and other actions of olanzapine may also reduce insomnia, facilitate analgesic drug activity and prevent different addictions often found among patients with advanced cancer and/ or alleviate symptoms of withdrawal.

## Compliance with Ethics Guidelines

### Conflict of Interest

Mellar Davis has no conflict of Interest

Gareth Sanger currently receives research funding from Takeda Pharmaceuticals

### Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by either of the authors.

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### *Of importance

### ** Of major importance


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***Table 1: Summary and rank order of affinity of olanzapine for human receptor targets.***

**$H_1$** (0.7-2.8 nM) > **5-$HT_{2A}$** (2-24), **5-$HT_{2C}$** (6-14), **5-$HT_6$** (6.3-10) > **5-$HT_{2B}$** (12) > **$D_2$** (20-78), **$D_4$** (28-60), **$\alpha_{2C}$-adrenoceptor** (29-210), **$M_4$** (32), **$D_1$** (35-118) > **$D_3$** (43-49), **$M_5$** (48), ***5-$HT_3$*** *(57)* > **$M_1$** (73), **$D_5$** (74), **$\alpha_{2B}$-adrenoceptor** (82-180), **$M_2$** (96) > **$M_3$** (105-132), **5-$HT_7$** (105-365), **$\alpha_{1A}$-adrenoceptor** (115) > **$\alpha_{2A}$-adrenoceptor** (192-470), **5-$HT_{1F}$** (310).

*Beginning with the receptor with highest affinity for olanzapine, the range of values in parenthesis are the Ki's in nM [1-7]. The values for the muscarinic receptors were obtained using intact cell preparations [8]. The value for 5-$HT_3$ is for the rat receptor [9].*


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**Table 2. Mechanisms of action of olanzapine**

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|---|---|
| **SIDE EFFECTS** | |
| Extrapyramidal activity (akathisia, pseudo-Parkinsonism, tardive dyskinesia) | Caused by antagonism at $D_2$ receptors within the nigrostriatal dopamine system of the brain. Although olanzapine is a brain penetrant $D_2$ receptor antagonist, when compared with 'early' anti-psychotic drugs (e.g. chlorpromazine, haloperidol), the drug has a low propensity to cause extrapyramidal effects or sustained increases in prolactin levels. This may be explained by differences in the rates of drug-receptor association and dissociation during competition with endogenous dopamine [1], although it has been argued that the higher affinity of olanzapine for 5-$HT_{2A}$ and 5-$HT_{2C}$ receptors may also confer opposing effects [2, 3]. |
| Sedation | Caused by antagonism at $H_1$ receptors within the cerebral cortex [4]. |
| Weight gain and metabolic syndrome | Associated with hyperphagia and antagonism at the $H_1$ and 5-$HT_{2C}$ receptors [5-7]; in rat brain, continuous use of olanzapine may change $H_1$ receptor and histidine decarboxylase expression in a manner positively correlated with increased food intake [8]. |
| Dry mouth and constipation | Associated with antagonism at $M_3$ and in addition, $M_1$ and $M_2$ receptors which in the bowel, slows intestinal movements [9]. |
| **VOMITING** | |
| $H_1$, $M_5$ | $H_1$ receptors are involved in mechanisms of vomiting induced by abnormal motion. In this activity the receptors are located in the vestibular system and in the brainstem integrative circuitry which coordinates the different pathways needed to initiate vomiting (often referred to as the 'vomiting centre') [10-12]. Motion sickness can also be controlled by muscarinic receptor antagonists acting primarily at $M_5$ receptors in the vestibular nucleus. It is possible that simultaneous antagonism of $H_1$ and the muscarinic receptors provides greater protection against motion sickness than $H_1$ receptor antagonism alone [12]. |

| | |
|---|---|
| | Interestingly, the well-established anti-emetic drug cyclizine, is an antagonist at $H_1$ and muscarinic receptors [13] and is used to manage nausea and vomiting in other conditions (e.g. in cancer patients during palliative care), indicating a need to further explore the spectrum of anti-emetic activity created by a combination of antagonism at these receptors. |
| $D_2/_3$ | Dopamine $D_2$ receptor antagonists are anti-emetic because they block $D_2$ receptors within the area postrema (often called the 'chemosensitive trigger zone'), a densely vascularized circumventricular organ at the caudal extremity of the fourth ventricle, where the blood-brain and cerebrospinal fluid-brain barriers are relatively permeable. This exposes neurons in the perivascular sheaths of the capillaries to small and large molecules in the blood and cerebrospinal fluid [14]. Although dopamine and $D_2$-like receptor binding sites have been detected within the human area postrema [15] little is known about the mechanism by which dopamine is released or what represents the circulating emetic stimulus; adrenaline, glucagon-like peptide-1 and cholecystokinin are examples of possibilities [13]. The $D_3$ receptor may also be involved in the mechanisms of vomiting. Compared with the $D_2$ receptor, this receptor appears to be more homogenously expressed across the brainstem areas which constitute the 'vomiting centre' (*nucleus tractus solitarius*, area postrema, dorsal motor nucleus [16]. Selective $D_3$ receptor agonists cause vomiting in dogs and ferrets by acting at least in part within the area postrema [17, 18]. Experiments in shrews suggests a functional interaction between $D_2$ and $D_3$ receptors such that an antagonist at both receptors might be superior to an antagonist at $D_2$ alone [19]. $D_1$ and $D_4$ receptor agonists do not cause vomiting [17, 20]. |
| 5-$HT_3$ | 5-$HT_3$ receptors are synthesized within the cell bodies of vagal nerves and are transported to the central and peripheral terminals. The vagus (the Xth cranial nerve) projects over the pelvic, visceral and thoracic structures (the name is derived from the Latin for 'wanderer' with the majority of axons innervating the abdomen consisting of unmyelinated afferent C-fibres [21]. In terms of the vomiting caused by anti-cancer chemotherapy, 5-HT is released from the large store contained within enterochromaffin cells of the duodenum to activate adjacent vagal nerve terminals and sensitise the terminals to excitation by other excitatory substances, resulting in sustained activation [22]. The abdominal vagal terminals project mostly to the *nucleus tractus solitarius* (NTS) of the brainstem which in turn projects to the different brainstem nuclei which initiate the different motor components of vomiting [23]. Activation of 5-$HT_3$ receptors on the central terminals of the vagus nerve (by circulating 5-HT for example) remains a possibility but their pathophysiological significance remains unclear [22, 24]. |
| **NAUSEA** | |

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| Inhibition of $H_1$, 5-$HT_{2C}$ and 5-$HT_{2B}$ receptor functions and modulation of the functions of ghrelin | Antagonism of the functions of each of these receptors are linked to increased appetite and if appetite and nausea are interrelated, then it might be anticipated that olanzapine could reduce nausea. In support of this argument, nausea was a common side-effect of the 5-$HT_{2C}$ receptor agonist lorcaserin, used to reduce food consumption and treat obesity [25, 26]. In addition, some studies have linked the actions of $H_1$, 5-$HT_{2B}$, 5-$HT_{2C}$ and $D_2$ receptors with the release and actions of acylated ghrelin (the form of ghrelin which unlike the des-acylated form, activates the ghrelin receptor). Decreased plasma concentrations of total ghrelin are associated with nausea and vomiting [27] and ghrelin or ghrelin receptor agonists reduce cachexia in cancer patients [28], severity of vomiting and other symptoms in patients with gastroparesis [29] and alleviate anorexia and vomiting in animal models of dyspepsia and vomiting [30-32]. In the rat, a non-vomiting species without proven ability to experience nausea [13], chemotherapy (treatment with cisplatin) reduced secretion of acylated ghrelin by a mechanism mimicked by 5-$HT_{2B}$ or 5-$HT_{2C}$ receptor agonists and reversed by antagonism at these receptors (suggesting that cisplatin-induced release of 5-HT from GI enterochromaffin cells could directly inhibit ghrelin release from the stomach) and ghrelin secretion increased when a 5-$HT_{2C}$ receptor antagonist was given alone [33, 34]. In HEK293 cells, 5-$HT_{2C}$ receptor antagonism may reverse attenuation of ghrelin receptor function caused by 5-$HT_{2C}$ receptor-mediated heterodimerization of transfected ghrelin and 5-$HT_{2C}$ receptors and their subsequent internalization [35]. In the mouse hypothalamus, the $H_1$ and ghrelin receptor may also dimerize, a process disrupted by olanzapine, leading to increased ghrelin signalling and neuropeptide-Y release to increase appetite [36]. The $D_2$ and ghrelin receptors can dimerize in the mouse hypothalamus [37], potentially relevant to mechanisms of vomiting. Interestingly, in patients with cancer and lack of appetite the ratio of acylated to desacylated ghrelin was low [38] and in patients with schizophrenia treated with olanzapine, those with the better metabolic syndrome profiles had lower acylated/ des-acylated ratios [39]. Finally, relatively high concentrations of olanzapine (but not haloperidol) increased the ability of ghrelin to activate its receptor when transfected into a host cell [40]; the pathophysiological relevance of this observation is unknown. |


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