

# Use of Atypical Antipsychotic Agents for Symptom Control in Patients With Advanced Cancer

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To understand and appreciate the potential role of atypical antipsychotics in symptom management in patients with cancer, it is useful first to reflect on the role of conventional antipsychotics in this patient population. Conventional antipsychotic medications (also called neuroleptics or major tranquilizers) have been used for the management of difficult symptoms in patients with cancer for more than 30 years. These agents act by blocking dopamine 2 (D<sub>2</sub>) receptors throughout the brain, including the area postrema and the chemoreceptor trigger zone. These agents also have some anticholinergic effects that contribute to control of nausea. For example, prochlorperazine is a phenothiazine agent commonly used to treat nausea; chlorpromazine is an agent in the same category and is used to treat nausea and refractory hiccups.

Another conventional antipsychotic agent, haloperidol, blocks D<sub>2</sub> receptors but lacks potent anticholinergic effects. Although indicated for the treatment of psychotic disorders, the most common use of haloperidol at The University of Texas M. D. Anderson Cancer Center is for the treatment of nausea. Haloperidol is also used in inpatient and hospice settings, in which parenteral doses are administered to treat delirium-induced agitation. In such cases, the D<sub>2</sub> blockade of the mesolimbic dopamine pathway reduces the positive symptoms of psychosis, such as hallucinations and agitation [1]. Haloperidol doses are extemporaneously prepared by our pharmacy as capsules containing

1.5 mg of haloperidol, 0.34 mg of lorazepam, and 25 mg of diphenhydramine.

## Second-Generation Antipsychotics

In contrast to conventional antipsychotic agents, the atypical antipsychotics (also called second-generation antipsychotics) are agents that have been available only since the early 1990s. These drugs include risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), ziprasidone (Geodon), aripiprazole (Abilify), and clozapine. Clozapine was the first drug approved in this class (1990), and ziprasidone and aripiprazole are the most recently approved (2001 and 2002, respectively). Few non-psychiatrists have much experience with clozapine, ziprasidone, or aripiprazole for symptom management; thus, this discussion will concentrate on risperidone, olanzapine, and quetiapine.

Common features of all these agents include hepatic metabolism and extensive protein binding. Rare but important side effects include seizures; prolongation of the QT<sub>c</sub> interval, which may lead to serious arrhythmia (particularly in patients with heart disease); and increased risk of obesity, diabetes, and dyslipidemia (metabolic syndrome). QT<sub>c</sub> prolongation is most significant with ziprasidone, followed by quetiapine and risperidone [2]. Fortunately, QT<sub>c</sub> prolongation of more than 450 milliseconds occurs in less than 2% of patients treated with these three agents. Dyslipidemia is more strongly associated with olanzapine, followed by risperidone and quetiapine, and is not associated with ziprasidone [3]. The metabolic syndrome problem has received increased attention in the news media.

For patients undergoing prolonged treatment with these agents, monitoring of key metabolic parameters, such as weight and lipid and glucose levels, has been recommended [3]. Risperidone, olanzapine, and quetiapine may also cause extrapyramidal side effects, although they occur in less than 10% of patients, which is significantly less

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**Table 1****Characteristics of Three Atypical Antipsychotics Used to Treat Cancer Symptoms**

DRUG	STARTING DOSE (mg)	HALF-LIFE (h)	DOSAGE FORMS	DRUG CLASS	YEAR OF FDA APPROVAL	TYPICAL DAILY MAINTENANCE DOSE RANGE IN CANCER PATIENTS (mg/d)	TYPICAL DAILY DOSE RANGE IN PSYCHIATRIC PATIENTS (mg/d)
Olanzapine	2.5–5.0	30	Tablet Dissolving wafer Intramuscular	Thienobenzodiazepine	1996	2.5–5.0	5–20
Quetiapine	12.5–25.0	6	Tablet	Dibenzothiazepine	1997	25–100	50–800
Risperidone	0.5–1.0	20	Tablet Dissolving wafer Oral solution Intramuscular	Benzisoxazole	1993	0.5–1.0	1–8

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frequent than with conventional antipsychotics [4]. Some important properties of these agents are summarized in Table 1, and the frequencies of some of their important side effects are shown in Table 2 [5].

### Actions Are Complex

These drugs have complex pharmacologic actions in multiple neurotransmitter systems. They block D<sub>2</sub> and serotonin (5-hydroxytryptamine, 5-HT) 2A receptors; blocking 5-HT<sub>2A</sub> receptors results in anxiolysis and sedation (with fewer sexual side effects than with conventional antipsychotics). Moreover, these drugs may have anticholinergic, anti-adrenergic, and antihistaminic actions and may block D<sub>1</sub>, D<sub>3</sub>, D<sub>4</sub>, and 5-HT<sub>1A</sub> receptors [1]. The benefits and possible side effects of some of these actions for risperidone, olanzapine, and quetiapine are summarized in Table 3. In psychiatry, these newer agents have become important options in the management of schizophrenia and bipolar disorder.

Because of the many different neurotransmitter systems these drugs affect, atypical antipsychotic agents may influence mood, appetite, cognition, and sleep patterns, in addition to improving psychotic symptoms and controlling emesis. These drugs are not first-line agents for the treatment of any specific symptom in patients with cancer, but case reports and small case series indicate that there is some interest in exploring the use of olanzapine for control of symptoms such as refractory nausea [6–9], delirium in inpatients [10, 11], pain [12], and vasomotor symptoms [13]. In palliative care, these drugs may be effective in the treatment of patients with multiple physical and psychological symptoms that are not responding to

conventional multi-agent regimens. Under these circumstances, an atypical antipsychotic agent is sometimes prescribed in doses lower than those generally used to treat primary psychiatric disorders as part of a time-limited therapeutic trial, an approach that is considered good practice in palliative care. Consider the following case vignette.

### Case Vignette

A 53-year-old man with metastatic gastric adenocarcinoma with peritoneal carcinomatosis was referred for symptom management and palliative care. The patient's medical history was notable only for hyperlipidemia, and he had no history of psychiatric illness. He had been diagnosed with a T3N1 distal gastric adenocarcinoma 7 months earlier and had undergone a staging laparotomy followed by concurrent chemotherapy and radiation therapy. His symptoms did not respond to treatment, and a salvage gastrectomy was performed. The patient was referred to us for palliative care 1 month later. Use of palliative systemic therapy was to be considered if some improvement in his symptom status could be achieved.

The patient reported poor appetite, early satiety, and chronic nausea. He rated his appetite disturbance a 7 on a symptom-rating scale of 0–10, where 10 represented the worst imaginable intensity of the symptom. He described his abdominal pain as “reflux” and rated it a 4, but it was clearly a bothersome problem on the basis of his description. Fatigue was rated a 3 and nausea a 5 with occasional emesis. He reported no depressed mood or anxiety. He experienced no drowsiness or shortness of breath. Sleep disturbance was rated a 5. He was receiving metoclopramide, rofecoxib (Vioxx), 60 mg/d of prednisone, and a proton-pump inhibitor.

Supportive-expressive counseling was initiated, and some changes in his symptom management regimen were recommended. He was given a strong opioid analgesic (2.5 mg of methadone twice daily), an atypical antipsychotic (2.5 mg of olanzapine at bedtime), a laxative, and a stool softener.

At follow-up 5 days later, the patient and his spouse agreed that he had experienced a substantial improvement in his symptoms. His nausea had resolved, and he reported both increased oral intake and improvement in his abdominal pain. He had been able to leave his house and do some chores outside. He expressed some desire to return to work part time if possible. The patient ultimately did not return to work, but he continued to improve and was followed closely on an outpatient basis. He progressed and developed further problems with nausea 2 months later and was admitted to the inpatient palliative care unit. During that admission, his olanzapine dose was escalated to 5 mg at bedtime. He continued on the 5-mg nightly dose of olanzapine for another 3 months, until he died at home under the care of hospice.

### Patterns of Symptom Expression

This case vignette is representative of many patients with advanced cancer with multiple difficult-to-treat symptoms and reduced functional status. Each patient has a unique pattern of symptom expression that may be difficult to understand at the time of an initial consultation, and the pattern of symptom expression is dynamic and can be influenced by the relationship created by the provider [14].

This patient was believed to have substantial and chronic cancer-related abdominal pain, but he tended to understate it. He also appeared to have more anxiety than he reported, and this was thought to be one of several factors that influenced his experience of nausea. In the context of nausea, sleep disturbance, and suspected anxiety and depression, the patient was started on low-dose olanzapine with the intent of achieving improved symptom control. The co-administration of other medications (methadone and a bowel regimen) and concomitant counseling made it difficult to ascertain the relative contribution of olanzapine to his short-term improvement. More effective pain-control medications, a bowel regimen, and effective counseling may have produced similar results.

**Table 2**

**Relative Frequency of Key Side Effects of Olanzapine, Quetiapine, and Risperidone**

SIDE EFFECT	WORST OFFENDERS	LESSER OFFENDERS
Drowsiness	Olanzapine and quetiapine (> 30%)	Risperidone (> 10%)
Agitation		All > 10%
Akathisia		All > 10%
Anticholinergic effects	Olanzapine (> 10%)	Others > 2%
Orthostatic hypotension	Risperidone (> 30%) Quetiapine (> 10%)	Olanzapine (> 2%)
Weight gain	Olanzapine (> 30%)	Others > 10%
Sexual dysfunction	Risperidone (> 10%)	Olanzapine (> 2%) Quetiapine (< 2%)
Galactorrhea	Risperidone (> 2%)	Olanzapine (< 2%) Quetiapine (0%)

Adapted from Bezchlibnyk-Butler et al<sup>5</sup>

In this case, an atypical antipsychotic was prescribed for symptoms outside its labeled indications to improve an array of bothersome physical and psychological symptoms. Specifically, low-dose olanzapine was given with the intent of relieving nausea and improving appetite, as well as for sedative and anxiolytic effects. In this case, along with olanzapine, multiple other medications were administered over the final 5 months of the patient's life, including methadone, a serotonin-reuptake inhibitor, a therapeutic trial of corticosteroids, a sedative-hypnotic to use as needed for sleep, and other medications. Olanzapine, like risperidone and quetiapine, are well tolerated in combination with a robust set of medications commonly used in palliative care.

A representative patient who might benefit from treatment with low-dose atypical antipsychotics might have any of the following symptoms: sub-syndromal or low-level depression or anxiety; no subjective psychological symptoms but significant neurovegetative symptoms (eg, disturbance in appetite, weight, sleep, energy, or interests); symptoms that are treatment refractory or only partially responsive to treatment with standard selective serotonin-reuptake inhibitors; or complex physical symptoms (eg, chronic pain, weight loss, or fatigue) that are unresponsive to multiple first-line treatments.

### Dosage and Length of Treatment

Starting doses of atypical antipsychotics for such patients are well below those for typical psychiatric use, with maintenance doses often not

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**Table 3**

### Relative Effects of Atypical Antipsychotics on Important Central Nervous System Receptors

BLOCKED RECEPTOR	RELATIVE BLOCKADE	POSSIBLE BENEFITS	POSSIBLE SIDE EFFECTS <sup>a</sup>
D <sub>2</sub>	Risperidone > olanzapine > quetiapine	Reduced delusional or disorganized thinking Reduced hallucinations Reduced nausea and vomiting	Extrapyramidal symptoms <sup>b</sup> Gynecomastia Prolactin elevation Sexual dysfunction
H <sub>1</sub>	Olanzapine = quetiapine > risperidone	Improved sleep Weight gain Increased appetite	Hypotension Dry mouth
5-HT <sub>2</sub>	Risperidone > olanzapine > quetiapine	Reduced extrapyramidal symptoms Less anxiety and depression Improved sleep Weight gain	Sexual dysfunction Hypotension
Acetylcholine	Olanzapine > risperidone	Reduced nausea Reduced extrapyramidal symptoms Improved sleep	Blurred vision Dry mouth Constipation Urinary retention Memory dysfunction Sinus tachycardia
α <sub>1</sub> Adrenergic	Risperidone > quetiapine > olanzapine	Improved urine flow Improved salivation	Postural hypotension Reflex tachycardia
α <sub>2</sub> Adrenergic	Risperidone > quetiapine > olanzapine	Improved salivation	Sexual dysfunction

<sup>a</sup> Possible side effects derived from studies of patients treated with therapeutic doses for indicated mental illnesses (rather than for symptom management in cancer)

<sup>b</sup> Bradykinesia, stiffness, akathisia, and tardive dyskinesia

From Bezchlibnyk-Butler et al<sup>8</sup> and Jibson and Tandon<sup>15</sup>

much higher than the starting dose. For example, a typical starting dose for quetiapine in a patient with schizophrenia is 25 mg twice daily, with rapid dose titration upward to doses of 800 mg/d and sometimes higher. In comparison, a cancer patient with complex symptomatology would be given a starting dose of quetiapine of 25 mg/d or less, and the dose would likely be titrated upward to no higher than 75–100 mg/d for maintenance treatment. Often, cancer patients can benefit from a starting dose without further need for dosage increase. Table 1 provides dosing guidelines for olanzapine, risperidone, and quetiapine.

Duration of treatment with atypical antipsychotics is inexact, as no data exist as to how long these select patients should remain on antipsychotic medication. Treatment duration should be decided on a case-by-case basis. For example, in the palliative care setting, these medications are often initiated and never discontinued prior to the death of the patient (as demonstrated in the previous case vignette). However, there are patients with prolonged cancer remission who may no longer benefit from these medications. In gen-

eral, discontinuation of an atypical antipsychotic medication may be considered 2–6 months after symptom improvement.

Rather than abrupt discontinuation of the medication, which can lead to uncomfortable side effects, tapering over 1–2 weeks with careful monitoring is generally the most successful way to stop treatment. The reappearance or exacerbation of treated symptoms is an important signal for the clinician perhaps to reinstate the atypical antipsychotic medication, as the patient may have benefited from continued symptom control even after a stressful life event had passed. This situation may be realized only when the medication is withdrawn.

### Caveats

Side effects may occur with these medications, even at the very low doses used in cancer patients. Frequent side effects that may occur with the use of these atypical antipsychotics are detailed in Tables 2 and 3 [5, 15]. If a patient experiences unmanageable side effects to one atypical antipsychotic agent, switching to another may be

a useful strategy, as patients respond differently to these medications. Because such low doses are used, often a direct switch to another agent can be completed without tapering the dosage of the offending medication. For example, a patient who develops daytime somnolence with risperidone (0.5 mg orally before bedtime) could be switched directly to quetiapine (25 mg twice daily) or olanzapine (2.5 mg orally before bedtime).

Antipsychotic drugs are metabolized through the cytochrome P450 system, particularly as substrates for CYP2D6. Olanzapine is also metabolized through the CYP1A2 enzyme system, and this metabolism can be induced in smokers, reducing the net clinical effect of a given olanzapine dose. Some agents commonly prescribed for patients with cancer and also metabolized via the CYP2D6 and CYP3A4 enzyme pathways are summarized in Table 4 [15, 16]. The clinical significance of these potential drug interactions is poorly understood in patients with cancer, particularly for atypical antipsychotics used at low doses. The frequency and severity of the adverse effects of these agents when used in this vulnerable and heterogeneous population of symptomatic patients with cancer are also unknown.

Although the case vignette is an example of the effective use of an atypical antipsychotic agent for cancer symptom control, the frequency of this favorable effect and the durability of its benefits are unknown. Moreover, this approach can be expensive because of the high cost of these newer agents, even at the low doses used. At the M. D. Anderson pharmacy, the average wholesale price of a 30-day supply of olanzapine (2.5 mg/d) is \$128, whereas the price of a 30-day supply of risperidone (0.5 mg/d) is \$65 and that of quetiapine (25 mg/d) is \$36.

The biology of symptoms in patients with cancer is an area that is undergoing intense research. The results of clinical and preclinical studies suggest that neurodegeneration is a feature of men-

**Table 4**

**Selected Cytochrome P450 Interactions**

	2D6	3A4
<b>Substrates</b>	<b>Quetiapine</b> <b>Risperidone</b> <b>Olanzapine</b> <b>Haloperidol</b> <b>Phenothiazines</b> Amitriptyline Nortriptyline Venlafaxine Fluoxetine Oxycodone Hydrocodone Beta-adrenergic blockers Ondansetron	<b>Quetiapine</b> Alprazolam Midazolam Methadone Cyclosporine Tacrolimus Tamoxifen Etoposide Vinca alkaloids Paclitaxel Calcium-channel blockers Imatinib
<b>Inhibitors</b>	Fluoxetine Paroxetine Methadone Doxorubicin Vinblastine	Nefazodone Fluoxetine Ciprofloxacin Erythromycin Ketoconazole Grapefruit juice HIV protease inhibitors
<b>Inducers</b>		St. John's wort Phenytoin Corticosteroids

Drugs shown in boldface type are conventional and atypical antipsychotic medications. From Jibson and Tandon<sup>15</sup> and Fisch<sup>16</sup>

tal disorders such as depression, bipolar disorder, and schizophrenia. Moreover, brain-derived neurotrophic factor (BDNF) may play a role in the maintenance and function of several neuronal systems; psychotropic medications that affect dopamine or serotonin systems alter BDNF levels in several brain regions. In academic internal medicine and other disciplines, symptoms are increasingly conceptualized as functional disturbances of the central nervous system [17]. It is important that symptom researchers from a variety of disciplines work together and strive to elucidate these issues. Meanwhile, there will be some patients with cancer for whom a time-limited therapeutic trial of an atypical antipsychotic agent is reasonable and appropriate.

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