

**FAST FACTS AND CONCEPTS #314**  
**MIRTAZAPINE: A DRUG WITH MANY PALLIATIVE USES**  
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Patients referred to palliative care services often have between 3 and 7 distressing symptoms and may require multiple medications for effective symptom reduction (1). Due to its effects on multiple receptors, mirtazapine has the potential to target several common symptoms in serious illnesses with one medication. This *Fast Fact* provides an overview of the pharmacology and potential uses of mirtazapine in palliative care beyond its FDA indication as an antidepressant.

**Pharmacology** Mirtazapine is a tetracyclic antidepressant that antagonizes noradrenergic, histamine (H1), 5-HT2 and 5-HT3 receptors, thereby enhancing central norepinephrine and serotonergic transmission (2,3). It has a relatively high oral bioavailability (50%) for its medication class. It is absorbed relatively quickly reaching peak plasma concentrations within 2 hours and its absorption is not affected by food (3,4). The half-life is long and variable, between 20 to 40 hours, with the longest half-lives seen in elderly women. Consequently, steady state levels of the medication may not be achieved for a week (4). Dose reductions are necessary in liver and renal failure, as it is metabolized in the liver mainly by the cytochrome (CYP) P450 isoenzymes and >75% is excreted in the urine (2,3).

**Utility in Symptom Management:**

***Mood disorders:*** Mirtazapine has been shown to be effective in moderate-severe major depression in short-term and long-term (up to 72 weeks) studies of otherwise healthy adults (8). It is not considered to be any more or less effective than other modern antidepressants, though it may have a faster onset of antidepressant action with reductions in affective symptoms described in just 1-2 weeks (9). *Fast Fact* #309 for more information on pharmacotherapy for depression.

***Pruritus:*** In case reports, mirtazapine has been shown to be effective for chronic pruritus related to inflammatory skin disease, cancer, cholestasis and renal failure at doses of 15-30 mg/day (5,6).

***Anorexia:*** Mirtazapine is associated with short and long-term weight gain in otherwise healthy depressed children and adults likely due to appetite stimulation via effects on H1 and 5-HT2 receptors (7,8). This has led to an interest in using mirtazapine for anorexia related to cancer and other advanced illnesses. No well-designed studies have confirmed mirtazapine's effectiveness for this indication. A small open-label study demonstrated weight gain of >1 kg following 4 weeks of therapy in only 4 of 17 (24%) cancer patients. Secondary endpoints of improvements in appetite and health-related quality of life (QOL) were noted in only 24% and 6% of patients respectively (10).

***Insomnia:*** Cancer patients have reported improvements in early, middle and late insomnia scores over 6 weeks at doses of 7.5-15 mg/day (8). Its sedative effects are likely compromised at doses higher than 15 mg/day, as antihistamine activity may be offset by higher norepinephrine transmission (11,12).

***Nausea:*** Case reports of its antiemetic efficacy (assumed to be due to 5HT3 antagonism) in patients with hyperemesis gravidarum and postoperative nausea and vomiting suggest wider applicability. A small open-label study showed significant improvement in nausea in cancer patients but otherwise, evidence for a robust antiemetic effect in seriously ill populations is scant (13).

**Side effects** Dry mouth, day time sedation, and constipation are more commonly associated with mirtazapine compared with SSRIs (2,14). However, it may be less associated with sexual dysfunction (15). A QOL study in older cancer patients showed a relatively high drop-out rate (42%) after only 2 weeks due to somnolence, delirium, hallucinations, xerostomia, nausea, fatigue, or insomnia. Of note, less than 10% of the patients in this study reported a significant improvement in their QOL (16).

**Drug Interactions** Mirtazapine has little inhibitory effects on CYP isoenzymes, has few drug-drug interactions, and is postulated to hardly affect the pharmacokinetics of co-administered medications (4,14). Caution should still be exerted when used along with medications known to increase the risk of serotonin syndrome (17,18).

**Dosing** Mirtazapine is available in generic form in 7.5 mg, 15 mg, 30 mg and 45 mg oral tablets. It also comes as an orally disintegrating tablet for patients who cannot swallow or absorb enteric drugs. Starting

dose varies based on the indication of use, but is generally between 7.5 mg and 15 mg once daily or nightly. Dosing can be doubled every 1-2 weeks up to a maximum of 45 mg/day. Mirtazapine is commonly dosed at night due to its sedating properties.

**Pediatrics** Mirtazapine has been evaluated in children aged 7 to 17 with depression, but it was not found to have a significant effect when compared to placebo (18). It has not been well studied for off-label purposes in children.

**Cost** varies based on dose and tablet type. The monthly cost for a generic 15 mg oral disintegrating tab is about \$60 vs \$40 for the regular generic tablet. This makes mirtazapine slightly more expensive than citalopram, paroxetine, and sertraline but less expensive than escitalopram, or venlafaxine (20).

**Summary** Mirtazapine is an effective anti-depressant which targets multiple neurotransmitters and thereby may have potential in alleviating additional symptoms experienced by seriously ill patients. However, its known toxicity and lack of efficacy in improving quality of life measurements in non-depressed seriously ill patients should make clinicians refrain from using it routinely for off-label purposes.

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