

FAST FACTS AND CONCEPTS #228 TAPENTADOL

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Background Tapentadol is a newly available oral analgesic, approved by the FDA in 2009 for the management of moderate to severe acute pain in adults. This *Fast Fact* reviews its pharmacology and use.

Pharmacology

- Tapentadol is a centrally-acting, synthetic, oral mu-opioid receptor agonist which also inhibits norepinephrine and serotonin reuptake within the CNS. It is structurally and pharmacologically similar to tramadol (see *Fast Fact* #290 for more information on tramadol).
- Oral bioavailability ranges from 32% to 42%, with a half-life of 4 ½ hours.
- The drug is metabolized in the liver (97% by Phase-2 conjugation) and excreted in the urine.
- Tapentadol has no known pharmacologically active metabolites, no relevant CYP interactions, and no drug-drug interactions through cytochrome induction or inhibition (1).
- There are no dosing adjustments required in mild-to-moderate renal or hepatic impairment (Child class A or B); it has not been studied in patients with severe hepatic impairment (Child class C).

Research Data The FDA approval was based on industry-coordinated, randomized controlled studies conducted in patients with osteoarthritis and after bunionectomy. In these studies 50 mg doses of tapentadol was shown to be non-inferior to 10 mg of oxycodone immediate-release in the treatment of pain, but the incidence of nausea, vomiting, dizziness, and constipation was significantly lower (2,3). In another single-dose study involving patients undergoing molar extraction, tapentadol 200 mg demonstrated improved analgesia but higher sedation than 60 mg of oral morphine (4). Total daily doses greater than 700 mg on the first day of therapy and 600 mg on subsequent days have not been tested, nor has tapentadol been studied in children. Tapentadol has not been tested in a randomized, controlled fashion for cancer pain nor in palliative care settings; however, prospective observational studies showed it to be well tolerated and effective for opioid naïve (doses 100 mg per day) and opioid tolerant patients (doses 350 to 450 mg per day) with moderate to severe cancer pain (5,6). There are not enough data to comment on whether the drug has a ceiling effect, nor its long-term safety and efficacy (the longest study is a 1 year safety study). It has not been comparatively studied against tramadol.

Side Effects and Cautions Tapentadol's side effect profile is generally similar to opioids: nausea, vomiting, constipation, addiction, respiratory depression, pruritus, dizziness and drowsiness. A pooled analysis of randomized controlled trials suggest that gastro-intestinal side effects are likely milder than other opioids (7). As with tramadol, there is a theoretical increased risk of seizures, as well as serotonin syndrome if given with other serotonergic agents (e.g. antidepressants, drugs with monoamine oxidase inhibitory effects). Abuse and addiction are possible as with any opioid agonist. An abstinence syndrome has not yet been described; in one study drug tapering was not required after 90 days of treatment (2).

Dosing and Cost Tapentadol is available as 50, 75 and 100 mg immediate-release tablets and 50, 100, 150, 200, and 250 mg extended release tablets. The initial dose is 50-100 mg every 4 hours (although a second dose can be given one hour after the initial dose). The average wholesale pricing for tapentadol is approximately \$5 to \$7 per immediate release tab and \$5 to \$15 per extended release tablet. For comparison, tramadol costs \$0.07/tab (50 mg), oxycodone costs \$0.70 (15 mg tab), and morphine costs \$0.18 (15 mg tab).

Summary Tapentadol is a novel analgesic, with a 50 mg dose similar in efficacy to 10 mg of oxycodone. Currently its only clearly defined benefit over established opioids is its gentler GI side effect profile. Its cost, potential ceiling effect, safety concerns with drug interactions, and uncertainty about long-term efficacy and safety limit its current application.

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