PALLIATIVE CARE NETWORK OF WISCONSIN

FAST FACTS AND CONCEPTS #290
TRAMADOL IN PALLIATIVE CARE

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Background Tramadol is an important medication in palliative care. It is a Step II agent on the World Health Organization's (WHO) pain ladder (1) and has FDA approval for the treatment of moderate to severe pain in adults. This *Fast Fact* will review tramadol's pharmacology, its benefits, and limitations. Note that tramadol has similarities with tapentadol which is discussed in *Fast Fact* #228.

Pharmacology The analgesic effects of tramadol are likely due to mu-opioid agonist activity, and weak monoamine reuptake inhibition (specifically blocking norepinephrine and serotonin) in the CNS. Tramadol is a prodrug and must be metabolized via CYP2D6 to its pharmacologically active metabolite (O-desmethyl tramadol) (2). It is excreted 90% in the urine; therefore specific dosing adjustments are necessary in renal impairment (CrCl <30 mL/min). There are also dosing adjustments in the elderly and end-stage liver failure. Clinicians should be aware of tramadol's significant drug interactions with other CYP2D6 inhibitors (fluoxetine, paroxetine and amitriptyline) and CYP3A4 inhibitors (ketoconazole and erythromycin), which increase the risk of seizures and serotonin syndrome.

Dosing Tramadol is available as both generic and proprietary formulations: a 50 mg immediate-release (IR) tablet and 100 mg, 200 mg, and 300 mg extended-release (ER) tablet (Ultram ER®). Immediate-release tramadol also comes formulated with acetaminophen. Tramadol should be started at 25 mg/day in the morning and increased by 25-50 mg every 3 days. The maximum daily dose of tramadol is 400 mg/day (50-100mg every 4-6 hours). In patients with renal impairment (CrCl <30 mL/min), the dosing interval is 12 hours with a maximum daily dose of 200 mg/day. The maximal recommended dose for adult patients with cirrhosis is 50 mg every 12 hours. For elderly patients over 75 years old, the total daily should not exceed 300 mg/day. Approximately 120 mg of oral tramadol is equivalent to 30 mg of oral morphine (3). Oral morphine tablets are roughly half the cost of tramadol IR tablets, and one-sixth the price of tramadol ER tablets.

Adverse Drug Reactions Tramadol's adverse drug reaction profile is similar to other opioids, although it has a lower incidence of respiratory depression (4) and likely has a lower abuse potential. An early comparative study suggested that tramadol has less abuse potential than morphine (5) and more recent preclinical studies suggest that abuse-related behavioral effects of tramadol may be of lesser magnitude than other mu-opioid receptor agonists (6). However, there have been several reports of its abuse and misuse (7). Hence, in August of 2014 tramadol was made a Schedule IV controlled medication.

Cautions Tramadol carries four specific cautions:

1. Seizures have been reported with higher than recommended dosage and with concomitant use of SSRI/SNRIs, MAOIs, triptans, and other drugs that reduce the seizure threshold (8).
2. Serotonin-syndrome may occur only with the concomitant use of other serotonergic drugs and is characterized as a triad of clinical changes: cognitive (mental-status chances, agitation and hallucinations), neuromuscular (hyperreflexia, incoordination) and autonomic (tachycardia, labile blood pressure). Although the prevalence of serotonin-syndrome is unknown, the majority of cases present within 24 hours (and most within 6 hours), of a change in dose or initiation of a serotonergic medication (9).
3. A large population cohort study from the UK comparing tramadol with codeine found a significantly increased risk of hospitalization from hypoglycemia, especially in the first 30 days of initiation and non-diabetic patients (10).
4. Lastly in May of 2010, the FDA strengthened the warning for suicide risk for patients at high risk (defined as those who are addiction-prone, taking tranquilizers, or antidepressant drugs)(11).

Research Data Most of the literature examining tramadol's role in palliative care involves the management of cancer pain (12). In comparison studies, tramadol was favored over sublingual buprenorphine due to the lower prevalence of adverse drug reactions, but morphine was preferred in patients with more severe pain (13). It has been shown to be safe and effective following surgical

procedures, for neuropathic pain (14), as well as a variety of other pain conditions.

Summary Tramadol has an important position as a Step II agent on the WHO pain ladder, where it is effective for a variety of syndromes in patients with mild to moderate pain intensity. Its recommended dosing adjustments, potential ceiling effect, cost, pertinent drug-interactions, and risk for significant adverse drug reactions may limit its chronic use in patients with significant pain.

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