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Think Tramadol Is a Safer Option? Think Again!

Prescribing Considerations for the Clinical Nurse Specialist

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First introduced in Germany during the 1970s, tramadol is available worldwide for moderate to severe pain.[1] First approved by Food and Drug Administration in 1995 as a noncontrolled analgesic under the trade name Ultram, tramadol was moved to Schedule IV of the Controlled Substance Act by the US Drug Enforcement Administration in 2014 to respond to increasing numbers of deaths associated with use.[1–3] Tramadol is also known as ConZip, GenRx Tramadol, Larapam SR, Rybix ODT, Ryzolt, Tramadol Hydrochloride ER, Tramahexal, Tramahexal SR, Tramal, Tramal SR, Tramedo, Ultram, Ultram ER, Ultram ODT, Zamadol, Zydol, and Zydol XL.[4]

TRAMADOL ACTIONS

Tramadol is a weak opioid analgesic with effects similar to codeine with dual activity: first, a weak agonist at the μ-opioid receptors in the brain and, second, inhibition of reuptake of noradrenaline and serotonin. Metabolized via the cytochrome P450 pathway (so watch out for drugs that engage cytochrome P450 that may interfere with tramadol metabolism!), peak effects occur in about 2 hours with a half-life of 6 hours. Analgesia is a function of the active metabolite O-desmethyltramadol with 30% of the drug excreted via the kidney, so use caution in prescribing in kidney disease.[1]

Inhibition of norepinephrine and serotonin uptake by tramadol may add to the pain relief; however, the exact mechanism remains unknown.[2] Because tramadol is structurally like codeine and morphine, use can lead to psychological and physical dependence, addiction, and withdrawal.[2] Available as immediate and extended release, tramadol tablets must be taken whole—never split, chewed, or crushed.[2]

Common adverse effects include headache, itching, nausea, vomiting, constipation, diarrhea, heartburn, dizziness, fatigue, anxiety, and stomach pain. Serious adverse effects include addiction, abuse, respiratory depression, neonatal abstinence syndrome, serotonin syndrome, adrenal insufficiency, hypotension, arrhythmia, allergic reaction, and withdrawal.[2]

PRESCRIBING CONSIDERATIONS

Persons with severe asthma, lung disease, or bowel obstruction or who have received monoamine oxidase inhibitor drug therapy in the last 14 days should not be prescribed tramadol. While respiratory depression is rare, the greatest risk is usually during the first 24 to 72 hours of therapy, after a dose change or if using with alcohol.[1] To avoid withdrawal symptoms and serotonin-norepinephrine reuptake inhibitor withdrawal syndrome, do not abruptly discontinue tramadol.[5] Exercise caution when prescribing to persons with obstructive sleep apnea, obesity, neuromuscular disease, and liver and kidney disease. Persons older than 75 years are at greater risk of adverse effects.[1,2] Exercise caution when prescribing to persons with depression, seizure disorders, active or previous addiction, or risk of suicide or if receiving selective serotonin reuptake inhibitors or central nervous system depressants. Serotonin syndrome is more likely to be fatal when tramadol is prescribed in persons receiving medications that increase serotonin activity.[1]

Tramadol should not be used to treat pain in children younger than 12 years and should not be prescribed for children younger than 18 years to treat pain after tonsil or adenoid removal.[2] Breastfeeding is not recommended because tramadol is excreted into human milk.[2,4] Exposed

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infants should be monitored for increased sleepiness, difficulty breastfeeding, breathing difficulties, or limpness and other breathing problems that could result in death.[4,6] Tramadol is not recommended for use during pregnancy, and chronic use may reduce fertility, which may not be reversible.[4]

RISKS IN PREGNANCY

Safe use in pregnancy has not been established by adequate clinical studies.[7] Tramadol was classified as Pregnancy Category C (before removal of pregnancy categories in 2015) directing to use tramadol hydrochloride extended-release capsules during pregnancy *only* if the potential benefit justifies the potential risk to the fetus.[8] Neonatal seizures, neonatal abstinence syndrome, fetal death, and stillbirth have been reported in postmarketing reports with tramadol HCl immediate-release products. Chronic use during pregnancy may lead to physical dependence.[7]

Only few studies report the teratogenic effects of tramadol when used in early pregnancy. In an examination of the *Swedish Medical Birth Register*, women who delivered from 1997 to 2013 and reported use of tramadol during early pregnancy were identified. Maternal characteristics as well as concomitant drug use were analyzed and for 1 682 846 women (1 797 678 infants). One thousand seven hundred fifty-one women (1776 infants) reported using tramadol, with 96 of the infants born with a congenital malformation, of which 70 were relatively severe. The adjusted odds ratio (OR) for a relatively severe malformation was calculated as 1.33 (95% confidence interval [CI], 1.05–1.70). The ORs for cardiovascular defects (1.56; 95% CI, 1.04–2.29) and pes equinovarus (3.63; 95% CI, 1.61–6.89) were also significantly increased. Study results for this sample suggest a moderate risk of teratogenic effect with tramadol use.[9]

A SAFER OPIOID?

The effectiveness and adverse effects of tramadol are mediated by cytochrome P450 metabolism.[10] Many believe tramadol has fewer risks compared with other opioids with less potential for misuse, dependence, and respiratory depression. However, tramadol is not the "safer opioid" and has significant euphoric effects like morphine, heroin, and oxycodone (OxyContin). Furthermore, tramadol has additional risks compared with standard opioids related to the reuptake of monoamines, which is associated with adverse effects such as tachycardia, high blood pressure, seizures, and serotonin syndrome. Although effective for pain, adverse effects are associated with increased emergency room visits particularly with high doses and adverse effects related to drug interactions.[2] Small studies with high risk of bias may have overemphasized the benefits of tramadol over a significant risk profile.[11]

Soon after tramadol was approved, reports of diversion and abuse emerged, which led to revisions in product labeling and addition of warnings related to abuse.[3] However, tramadol is becoming a popular drug of abuse.[1] Tramadol is the most common drug abused by narcotic addicts, persons with chronic pain, and health professionals. In 2016, nearly 1.6 million persons 12 years or older in the United States misused tramadol. Tramadol is accessible; 43.6 million prescriptions were written for tramadol in the United States alone.[3] Persons addicted to tramadol have a higher risk of seizures and serotonin syndrome.[10] Abrupt cessation is associated with 2 types of withdrawal; 90% experience flulike symptoms, restlessness, and craving, and 10% of cases experience an atypical withdrawal with hallucinations, paranoia, extreme anxiety, panic, confusion with numbness, and tingling in the extremities. Withdrawal symptoms may be relieved by beginning opioid therapy again followed by gradual dose reduction.[2]

In a recent study examining the association of tramadol with all-cause mortality in persons at least 50 years old with osteoarthritis, 88 902 patients, of which 61.2% were women, received pain medication during January 2000 to December 2016 as documented in a Health Improvement Database. All-cause mortality within 1 year was compared for tramadol (n = 44 451), naproxen (n = 12 397), diclofenac (n = 6512), celecoxib (n = 5674), etoricoxib (n = 2946), or codeine (n = 16 922). While there was no statistical difference in all-cause mortality between tramadol and codeine (32.2/1000 vs 34.6/1000 person-years), tramadol was associated with a higher all-cause mortality rate compared with celecoxib (31.2/1000 vs 18.4/1000), etoricoxib (not approved in the United States) (25.7/1000 vs 12.8/1000), and diclofenac (36.2/1000 vs 19.2/1000). Further research is needed to determine if this association is causal.[12]

Evidence supporting a lower dependence risk and greater safety for tramadol is in fact lacking. A recent study examined the risks in prolonged tramadol use in opioid-naive postoperative patients (n = 444 764).[13] Subjects had 1 of 20 possible elective surgery procedures from January 2009 to June 2018, and 357 884 had discharge prescriptions for either hydrocodone (53%), oxycodone (37.5%), or tramadol (4%). Study findings revealed that tramadol (Schedule IV), which is scheduled at a lower risk than hydrocodone and oxycodone (Schedule II), had a similar and somewhat greater risk of prolonged use after surgery. Unadjusted risk of prolonged opioid use after surgery was 7.1% (n = 31 431). Tramadol alone was associated with 47% increase in the adjusted risk of persistent opioid use (1.25–1.69; 0.5 percentage points; $P < .001$) and 41% increase in the adjusted risk of chronic opioid use (1.08–1.75; 0.2 percentage points; $P = .013$). Findings suggest that tramadol perhaps should be rescheduled to accurately reflect the risks associated with

use. Because tramadol alone after surgery had similar to somewhat higher risks of prolonged opioid use compared with other short-acting opioids, providers should use caution when prescribing tramadol.[13]

Tramadol is the first medication in its class with dual-analgesic effects. These pain-relieving effects also drive the higher risks of abuse related to tramadol's euphoric, relaxing, and stimulant effects. Patient education, monitoring, and careful prescribing are required to reduce risks with use. In areas of the world where tramadol is readily available without a prescription such as the Middle East, risks of addiction are particularly great for patients and their providers.[1,5]

And what about the reported risks of seizures? Evidence continues to suggest there is a link. In a recent retrospective nested case-control study of a cohort of patients residing in the same state in the United States for 3 years or more using a MarketScan database from 2009 to 2012, 96 753 persons were identified as having a seizure with 888 540 matched controls. Primary analysis revealed no association between risk of seizure and exposure to tramadol compared with codeine (OR, 1.03; 95% CI, 0.93–1.15). However, in a secondary analysis using a more explicit seizure definition, the association between risk of seizure and tramadol exposure was statistically significant (OR, 1.41; 95% CI, 1.11–1.79).[14] Again, further monitoring and research are needed.

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