(Ultram, Zydol, Tramake)

Tramadol is a centrally-acting analgesic agent which has a weak opiate agonist action but also inhibits norepinephrine reuptake and stimulates the release of serotonin([i]).

Tramadol has an affinity for m opiate receptors of 10 times less than that of codeine and 6000 times less than morphine([ii]).

It is therefore considered to carry less risk of physical dependence. Tramadol tolerance is mild and withdrawal symptoms are much less troublesome than those from other opioid drugs.

Although it has been found in trials to be no more effective than acetaminophen and codeine combinations ([iii]), it is ranked by WHO in the second step of pain management strategy.([iv])

Radbruch et al ([v]) assessed the risk: benefit ratio of tramadol and concluded that it is a safe and efficient drug but they noted that for patients with severe pain, change to a more potent opioid drug is frequently necessary.

Gibson ([vi]) concurred with the opinion that tramadol is effective as an analgesic and also that it has a low risk for addiction.

Various studies have been done looking at the use of tramadol in cancer pain and have found it to be effective.

For instance, Bono and Cuffari ([vii]) found that tramadol compared well with the opioid drug buprenorphine (Temgesic).

Recommended dose is between 50 and 100mg every 4-6 hours, with a maximum dose of 400mg daily.

Hummel et al ([viii]) have suggested that tramadol (like dihydrocodeine which they also studied) may exert a stronger analgesic effect when administered in the evening, and they recommend taking this into account if the usual routine of prescription leads to either an increase of pain in the morning (due to insufficient analgesia) or unnecessary excessive dose in the evening.

A slow-release preparation is available and can be given twice a day. (every 12 hours) and this may circumvent these problems.

Indeed, as neuropathic pain is often worse at night, if there is a greater analgesic effect in the evening, this may be beneficial when used for this purpose.

Adverse effects are dose-dependent so that a high loading dose is more likely to cause effects such as nausea.

Generally the adverse effects are similar to those of opioid drugs, but less marked; they include constipation, which may be a persistent problem (nausea and sedation usually reduce after a couple of weeks).

A post marketing surveillance program in the United States ([ix]), published last year, has found that levels of abuse of tramadol run at less than 1 case per 100,000 patients and the overwhelming majority (97%) of abuse cases had a previous history of substance abuse.

Interactions: tramadol should not be given concurrently with MAOI drugs. It is important to note that it also interacts with dietary supplements, which contain 5-HTP and L-tryptophan.

WARNING: there have been reports of seizures in patients taking tramadol. It should be used with caution in patients taking drugs which can lower the seizure threshold: especially SSRIs and tricyclic antidepressants (note these are often used as adjuvant analgesics to combat neuropathic pain.)

Note that in a tramadol overdose, use of naloxone as an antidote, may increase the risk of seizures.

Other problems that have been noted: hallucinations and confusion: especially in the elderly.

Allergic reactions are well recognised and include wheezing/bronchospasm or worsening of existing asthma.

Tramadol should not be discontinued abruptly, as there may be withdrawal symptoms, although they are unlikely to be severe.

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[iv] Aronson MD, *Clinical Therapeutics* 1997;19:420-432 Nonsteroidal anti-inflammatory drugs, traditional opioids and tramadol: Contrasting therapies for the treatment of chronic pain.

[v] Radbruch L, Grond S, Lehmann KA *Drug Saf* 1996 Jul;15(1):8-29 A risk-benefit assessment of tramadol in the management of pain.

[vi] Gibson TP Am J Med 1996 Jul 31;101(1A):47S-53S Pharmacokinetics, efficacy, and safety of analgesia with a focus on tramadol HCl.

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[viii] Hummel T, Kraetsch HG, Lotsch J, Hepper M, Liefhold J, Kobal G Chronobiol Int 1995 Feb;12(1):62-72 Analgesic effects of dihydrocodeine and tramadol when administered either in the morning or evening.

[ix] Cicero TJ, Adams EH, Geller A, Inciardi JA, Munoz A, Schnoll SH, Asenay EC, Woody GE Drug Alcohol Depend 1999 Nov 1;57(1):7-22 A postmarketing surveillance program to monitor Ultram (tramadol hydrochloride) abuse in the United States.

[vi] Gibson TP Am J Med 1996 Jul 31;101(1A):47S-53S Pharmacokinetics, efficacy, and safety of analgesia with a focus on tramadol HCl.

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