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Tramadol

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Tramadol was patented in 1963 and launched under the name "Tramal" in 1977 by the West German pharmaceutical company Grünenthal GmbH. In the mid-1990s, it was approved in the United Kingdom and the United States. Initially Tramadol was available over the counter (OTC) as a generic medication and marketed under many brand names worldwide, such as Ultram, Conzip, Rybix ODT, and Ultram ER. In 2018, the US Drug enforcement agency (DEA) placed Tramadol on a schedule IV of the Controlled Substance Act. In the United States, currently, the wholesale cost is less than US $0.05 per dose making the drug a relatively cheap way to treat pain. In 2016 Tramadol was the 39th most prescribed medication in the United States, with more than 19 million prescriptions. For comparative purposes Tramadol has about one tenth the potency of morphine and more closely resembles the strength of codeine. For moderate pain in severity, its effectiveness is equivalent to that of morphine; however, for severe pain it is less effective than morphine. The painkilling effects last about 6 h.

Tramadol is an opioid drug that, unlike classic opioids, suppresses the monoaminergic system, which results in the longer acting availability of serotonin. For this reason, Tramadol is considered an atypical opioid. These special pharmacological characteristics have made Tramadol one of the most commonly prescribed analgesic drugs to treat moderate to severe pain. The opioid system controls pain, reward, and addictive behaviors. Opioids exert their pharmacological actions through three opioid receptors, mu, delta and kappa whose genes have been cloned. Opiate addicts, who mainly abuse the opioids present a high incidence of depressive disorders that seem to contribute to the maintenance of the addictive state. Also, the treatment of chronic pain frequently includes antidepressant therapy. Therefore, in addition to Tramadol's potential analgesic activity, it may be useful in improving emotional states and thereby improve quality of life and attenuate drug seeking behavior.

Where cases of physical dependency have been reported, there is a companion history of substance abuse. Emergency room admissions and recreational accidents with elevated Tramadol concentrations would suggest that Tramadol is an addicting medication. The World Health Organization (WHO) studied the use, abuse and addiction of Tramadol in 2014 and concluded, along with a previous study, that there is a low abuse and low dependence potential of Tramadol. This re-confirmed the safety of the drug. This study was just prior to the DEA rescheduling the drug from OTC to Schedule IV. Recreational use and use as a companion drug (along with benzodiazepines and opioids) presents probably the biggest problem with Tramadol.

All drugs have adsorption, distribution, metabolism, and elimination that are controlled by the genetic makeup of the individual consuming the drug. Additionally, drugs act in concert with other drugs that either induce or inhibit their activity at the target cell receptor. In the case of Tramadol, it is metabolized to O-desmethyltramadol by the cytochrome p450 (CYP450) enzyme CYP2D6 and the metabolism of these two active drugs in the liver by the additional enzymes CYP2B6 and CYP3A2 prior to elimination. The two active drugs, Tramadol and O-desmethyltramadol, have asymmetric centers that give different conformations which results in four different molecules having varying elimination rates. Individual genetic makeup puts all people into individual categories with respect to the activity, or even the presence, of the CYP450 enzymes listed above. Enzyme activity in metabolism of Tramadol will clear the drug from the body at variable rates or, in the absence of enzyme activity, through slow secondary elimination pathways. As an example, a person with a slow rate of metabolism of these enzymes will have an exaggerated response to the drug Tramadol and will appear in the emergency room as an opioid overdose. This puts the recreational or the addicted user at extreme risk in self-medicating to achieve the opiate response or the serotonin response with unknown quantities of drug (or mixture). However, the proper use of Tramadol under the care of a knowledgeable clinician is considered, and proven to be, a valuable and safe medication with a long-term history.

In summary Tramadol is a controlled substance used to treat moderate pain, with minimum medication side effects. The additional feature of mimicking serotonin with an antidepressant activity adds to the patient comfort. It is widely used for this purpose and it has been determined to be safe and non-addictive when correctly prescribed and administered. It is the clandestine and recreational use that typically results in the loss of life.

References:

Expert Opin Drug Discov. 2017 Dec;12(12):1281-1291. doi: 10.1080/17460441.2017.1377697. Epub 2017 Sep 17.

The U.S. Drug Enforcement Administration (**DEA**) announced that **Tramadol** was placed into **schedule** IV of the Controlled Substances Act (CSA) effective August 18, 2014

Traynor JR, Elliott J. delta-Opioid receptor subtypes and cross-talk with mu-receptors. Trends Pharmacol Sci 1993;14(3):84-6

Matthes HW, Maldonado R, Simonin F, Valverde O, Slowe S, Kitchen I, Befort K, Dierich A, Le Meur M, Dolle P, Tzavara E, Hanoune J, Roques BP, Kiefer BL. Loss of morphine-induced analgesia, reward effect and withdrawal symptoms in mice lacking the mu-opioid-receptor gene. Nature 1996;383(6603):819-23

Tramadol - Update Review Report. WHO (16-20 June 2014).
J Pain. 2019 Apr 18. pii: S1526-5900(18)30815-0. doi: 10.1016/j.jpain.2019.04.005. [Epub ahead of print]