

## Tramadol's Potential as a Gateway to Opioid Use Disorder

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### INTRODUCTION

Tramadol was introduced into the U.S. market in 1995 as a non-scheduled drug.<sup>1</sup> It was made a schedule IV drug in 2014.<sup>2</sup> According to the Drug Enforcement Agency (DEA), schedule IV drugs have “low potential for abuse and low risk of dependence”.<sup>2</sup> There are very few studies from the U.S. about tramadol abuse with literature from Egypt and its abuse potential being recognized more in the Middle East. This case report highlighted the potential of tramadol abuse and its significance as a gateway drug to developing opioid use disorder.<sup>3-5</sup>

We report a patient who was exposed to long-term use of tramadol for cervical disc protrusion and later developed opioid use disorder (OUD). We suspect exposure to tramadol set the patient on a course to seek other opiates, perpetuating opioid abuse. While tramadol (Schedule IV) is believed to have a lower abuse potential compared to other opiates (Schedule II), providers should be aware of the abuse potential that this drug holds.

### CASE REPORT

A 30-year-old female presented with an 8-year history of OUD and a history of degenerative disc disease. At 16 years old, the opioid naïve patient had a bulging disc of the cervical spine for which she was prescribed 50 mg tramadol four times a day. After completion of treatment with tramadol for a year, the patient did not experience cravings or withdrawal symptoms. She subsequently used ibuprofen for mild cervical and thoracic back pain.

At 22 years of age, the patient developed worsening cervical pain and was prescribed 50 mg of tramadol, four times a day. After about four and half months of this regimen, she reported tolerance and increased cravings requiring medication more frequently than prescribed. While she remained on this prescribed regimen for two years, she also began buying tramadol from the streets. After several months, the patient's increased tolerance to tramadol caused her to seek out oxycodone from the streets with variable doses. She was able to stop the use of opiates but was unable to quit tramadol abuse.

While struggling to find sellers, the patient attempted to quit tramadol and had unsuccessful efforts in cutting down. While trying to taper, she developed withdrawal symptoms including opioid hyperalgesia causing full-body pain with worsening of her cervical spine pain, nausea, vomiting, diarrhea, restlessness, insomnia, and anxiety. The patient attempted to quit without assisted withdrawal five to six times and developed unrelenting withdrawal symptoms. She also reported significant mood changes and thoughts of suicide, with no plan, during

these periods of withdrawal. She later started methadone through an opioid treatment program for unrelenting withdrawal symptoms and relapses on tramadol. She developed excessive sedation, nausea, and vomiting due to methadone. As she developed intolerability to medication, she quit to follow-up with a relapse on tramadol.

The patient was seen later in an addiction clinic, initiated on buprenorphine-naloxone therapy and maintained at eight 2 mg doses twice a day with no relapses. At that time, the patient reported no cravings, no withdrawal symptoms, no extraneous opiate use, and appeared to be tolerating the treatment well.

### DISCUSSION

Tramadol is a centrally acting analgesic that works on mu opioid and monoamine receptors.<sup>6</sup> The drug is both a weak opioid agonist and a weak inhibitor of the reuptake of norepinephrine and serotonin. Tramadol is administered as a racemic mixture, where each enantiomer has its own active metabolite, (+)-O-desmethyltramadol or (-)-O-desmethyltramadol thought to be responsible for mu-agonist properties.<sup>1</sup> Tramadol's antagonistic properties on the 5-HT<sub>2C</sub> receptor could contribute to the drug's effects on depressive and obsessive-compulsive symptoms in patients with pain.<sup>6</sup> The half-life for tramadol is about 5.5 hours with extensive first-pass metabolism in the liver and primary excretion (90%) through the kidneys. The drug can be administered intravenously, intramuscularly, or orally.

The recommended dose for tramadol ranges from 50-100 mg every six hours, orally or parenterally, for mild to moderate pain.<sup>1</sup> Guidelines for tramadol use in pediatric populations vary between countries. In the U.S., tramadol is not recommended for those less than 16 years old.<sup>6</sup> Our case report showed a 16-year-old who was first introduced to tramadol without any complication. However, no conclusions could be made on whether her exposure to tramadol at a young age may have predisposed her to tramadol abuse later. In some populations, it also has been used to relieve distress related to depression and anxiety.<sup>7</sup> Tramadol generally is well tolerated with common adverse effects of nausea, vomiting, dizziness, drowsiness, sweating, and dry mouth. Unlike other opioids, tramadol reports lower adverse effects on respiratory or cardiovascular parameters at clinical doses in adults or children.<sup>6</sup> With these findings, tramadol (schedule IV) has been thought to be a safer alternative, regarding abuse and adverse effects, compared to other opiates (schedule II).

Tramadol was introduced in the U.S. market in 1995 as a non-scheduled drug for treatment of moderate to moderately severe pain.<sup>1</sup> The MedWatch program of the Food and Drug Administration (FDA) received 766 case reports of tramadol abuse and 482 cases of withdrawal associated with tramadol since the drug entered the market in 1995 through 2004.<sup>8</sup> However, the FDA had no recommendations to change the scheduling of tramadol at this point. Tramadol eventually was classified as a schedule IV controlled substance in 2014. Schedule IV drugs, according to the DEA, are drugs with a low potential for abuse and low risk of dependence. Tramadol also has been reported to have a low potential for abuse or dependence with reports of 0.7 to 1.5 cases of abuse per 100,000 individuals.<sup>6</sup> Anecdotally in clinical practice, many physicians believe tramadol to be safer. However, tramadol's low potential for abuse or dependence may be overestimated. Furthermore,

tramadol exposure in opioid-addicted communities likely is concealed by access to more potent opioids.<sup>8</sup>

This case revealed an opioid naïve individual who became dependent on tramadol after being prescribed for a medical condition. Her long-term exposure to this schedule IV opiate, without careful monitoring, eventually brought her to find other opiates with more abuse potential. More research should be performed to determine the risks of opiate addiction due to tramadol in naïve individuals and whether more careful monitoring and control of this substance should be undertaken.

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