Will DEA Scheduling of Tramadol be Enough to Stem The Tide of Addiction?  
By Joseph Salerno, Science Writer, USDTL

On August 18, 2014, the pain reliever tramadol (Ultram®) will become a Class IV controlled substance with the U.S. Drug Enforcement Administration (DEA).¹ Many research and healthcare professionals have argued that it should have been scheduled when first approved by the U.S. Food and Drug Administration (FDA) in 1995.² Now, 30 years later, data on tramadol addiction supports DEA scheduling. So, why wasn’t it scheduled in the first place? What finally convinced the DEA to schedule tramadol?

Tramadol is an opioid pain reliever similar in strength to codeine. It was first produced in 1977 by the West German company Grunenthal. It was not sold in the United States until 1994. In 2012, more than 40 million tramadol prescriptions were written in the United States. Only hydrocodone and oxycodone were prescribed more often.³

How Did Tramadol Dodge DEA Scheduling?

Early data from Europe suggested tramadol had a very low abuse potential. Based on this, the Drug Abuse Advisory Committee (DAAC) of the FDA recommended that tramadol did not need to be listed as a controlled substance.

Over the last 30 years, however, research into tramadol abuse seems to indicate the European data was incomplete. The early evidence used by the DAAC was based on injectable forms of tramadol, not oral forms such as pills and tablets. Research done prior to 1994 showed the euphoria associated with injectable tramadol was no more than one tenth that of morphine. Based on this, the abuse potential of tramadol seemed small.²

In its FDA approved form, tramadol is a tablet taken by mouth. Research has now shown that oral dosing of tramadol produces a different level of euphoria in patients than when it is injected. When taken by mouth, tramadol is converted by the liver to an active metabolite. The active metabolite binds to the same opioid receptor in the brain that is affected by morphine and oxycodone. As a result, tramadol produces a euphoric high similar to oxycodone, a Class II DEA controlled substance. When taken at very high doses, beyond prescription therapeutic levels, tramadol has an addiction reinforcing effect akin to morphine and oxycodone.

Mounting Evidence For DEA Scheduling

The DEA considers many factors when deciding to make a drug a controlled substance. First, does the drug represent a hazard to the public? From 2004 through 2012, emergency department visits that were the result of non-medical use of tramadol went from more than 4,800 incidents to more than 16,000.¹ Harmful side effects of tramadol use have emerged since its FDA approval. Many side effects are similar to those from other opioids such as sedation, dizziness, nausea, and respiratory depression.⁴ As well, tramadol use has been found to cause seizures and serotonin syndrome, effects not typically seen with opioid use. One study showed a strong link between tramadol abuse and both apnea and death, likely due to respiratory depression.⁵

Adverse side effects of tramadol use have been shown to increase with rising levels of use. This is typically an indication of drug dependence effects.⁴ Opioid-like and tramadol-specific

Continued on page 2, Tramadol.

Tramadol Quick Facts

- Tramadol is a Class IV DEA Controlled Substance as of August 18, 2014.
- More than 16,000 emergency room visits in 2012 resulted from non-medical use of tramadol.
- High-dose use of tramadol has addiction potential similar to Oxycontin.
- Over 40 million tramadol prescriptions were written in the United States in 2012, more than any other opioid pain reliever except hydrocodone and oxycodone.
- Injected versus oral dosing of tramadol produces different pharmacological effects.
- Tramadol use can be detected in fingernail and hair specimens.
Tramadol, continued from page 1.

withdrawal symptoms often occur after abrupt interruption of tramadol use. Patients using tramadol under prescription guidelines have also shown withdrawal effects even when they were slowly tapered off the drug. Adverse effects and withdrawal symptoms strongly suggest an issue of drug dependence for tramadol users even when used under prescription guidelines.

Another criterion for DEA scheduling is the potential for a drug to be diverted for non-medical abuse. In the year 2000, tramadol was present in only 82 law enforcement drug seizures. This number went up to 1806 by 2012.1 A 2002 study found that 87 out of 140 healthcare professionals who tested positive for tramadol took the drug with illegal prescriptions. Data from the National Survey on Drug Use and Health estimate the number of people who have abused tramadol at least once in their lifetime at nearly 2.0 million in 2008. By 2011 the number had risen to more than 2.6 million. Clearly non-medical use of tramadol has become an issue since its approval in 1995.

Tramadol is available in both single dose forms (25-100 mg) and as time release tablets containing 100-300 mg of the drug. Abusers of tramadol have begun crushing time release tablets and ingesting them for an instant, high-dose euphoria.2 The effect is described by abusers as similar to the euphoria of OxyContin (time release oxycodone) but without the cognitive impairment. Unfortunately, it’s at these high doses of tramadol that effects such as respiratory depression, apnea, and death are most likely to occur.

Schedule IV

The FDA’s findings indicate tramadol has an abuse potential that is about equal to other Schedule IV drugs such as propoxyphene and pentazocine.1 Bringing tramadol under DEA control should limit its non-medical availability greatly. Restricted access would hopefully curb high-dose abuse of the drug and reduce addiction. Restricting use to therapeutic levels lessens much of the potential danger of tramadol use. At therapeutic levels, Schedule IV would be the logical placement for tramadol.

Now That Tramadol is a Controlled Substance, Can You Test For it?

The answer is “yes.” Tramadol has been detectable in human samples at least since 1985. Today, tramadol can be detected in several different samples with both long- and short-term windows of detection. Urine and oral-fluid samples will detect tramadol use for up to 1-3 days of use. Hair testing will detect tramadol use for up to three months. Fingernails provide up to a six month history of use.

References

The Shifting Landscape of Opiate and Opioid Abuse
By Joseph Salerno, Science Writer, USDTL

The need for opiate and opioid drug testing has grown in the last three decades. 2.4 million people in the United States abused opioid pain relievers in 1985, the year before President Ronald Reagan announced his Federal Drug-Free Workplace Program.\(^1\) That number swelled to 4.9 million - a 104% increase - by 2012.\(^2\) During that same time, the population of the United States grew only 32%.

The original opiate testing panel created in 1986 is an incomplete tool for today’s drug testing needs. No other category of drugs has evolved as much as opiates and opioids. Addiction to high strength pain relievers and newer opioid compounds has eclipsed codeine, morphine, and heroin addiction addressed by the original 1986 five-panel drug test.

Based on the most recent data on emergency department visits related to illicit substance abuse, it is clear that opiate and opioid abuse has shifted dramatically. Screening for opiate abuse using only 1986 drug testing guidelines for the opiate drug class misses the past 30 years of pharmaceutical and drug testing advancements.\(^3\)

### Increase in Emergency Department (ED) Visits 2004-2011

<table>
<thead>
<tr>
<th>Drug</th>
<th># of ED Visits in 2011</th>
<th>Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>18,224</td>
<td>438%</td>
</tr>
<tr>
<td>Morphine</td>
<td>21,483</td>
<td>384%</td>
</tr>
<tr>
<td>Codeine</td>
<td>20,000</td>
<td>312%</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>151,218</td>
<td>263%</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>82,480</td>
<td>107%</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>66,870</td>
<td>104%</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>34,593</td>
<td>82%</td>
</tr>
<tr>
<td>Tramadol</td>
<td>9,927</td>
<td>38%</td>
</tr>
</tbody>
</table>

The only two drugs included in the 5-panel drug test.

---

References


© 2014 United States Drug Testing Laboratories, Inc.
United States Drug Testing Laboratories, Inc.

Quarterly Forensic Newsletter

Upcoming Events:

• October 7-9 – 2014 National Alliance for Drug Endangered Children Conference – Lake Buena Vista, FL
• October 15-18 – American Bar Association Fall 2014 CLE Conference – Stowe, VT
• October 21 – Fall 2014 Clinical Laboratory Management Association Meeting – Naperville, IL
• November 6-8 – Association of Family and Conciliation Courts 11th Symposium on Child Custody Evaluations – San Antonio, TX
• November 6-8 – American Academy of Matrimonial Lawyers – Chicago, IL