American College of Physicians
Leading Internal Medicine, Improving Lives

November 21, 2019

The Honorable William P. Barr
Attorney General of the United States
United States Department of Justice
950 Pennsylvania Avenue, NW
Washington, DC 20530-0001

RE: Tramadol Scheduling

Dear Attorney General Barr:

On behalf of the American College of Physicians (ACP), I am writing to express our support for a review of the scheduling of prescription pain medication tramadol. We appreciate the actions taken to restrain misuse and abuse of this synthetic opioid medication. In light of trends from recent years and the experiences of our physicians in the capacity of treating substance use disorders, chronic pain illnesses, as well as our capacity in serving the primary care needs of patients, we would like to propose consideration for re-scheduling of tramadol.

ACP is the largest medical specialty organization and the second-largest physician group in the United States. ACP members include 159,000 internal medicine physicians (internists), related subspecialists, and medical students. Internal medicine physicians are specialists who apply scientific knowledge and clinical expertise to the diagnosis, treatment, and compassionate care of adults across the spectrum from health to complex illness.

Tramadol Overview

Tramadol is a medication that is Food and Drug Administration (FDA)-approved for treatment of moderate to severe pain as well as used off-label for treatment of premature ejaculation and restless leg syndrome[1,2,3]. It is a synthetic opioid that was released in 1995 under the brand name Ultram as a non-controlled analgesic. Tramadol is a "pro-drug", meaning that the active form has to be metabolized by additional reactions after ingestion. Commonly noted side

[1] Kirby EW, Carson CC, Coward RM. Tramadol for the management of premature ejaculation: a timely systematic review. Int J Impot Res. 2015 Jul;27(4):121-7.
[2]Martyn-St James M, Cooper K, Kaltenthaler E, Dickinson K, Cantrell A, Wylie K, Frodsham L, Hood C. Tramadol for premature ejaculation: a systematic review and meta-analysis. BMC Urol. 2015 Jan 30;15:6.
[3] Lauerma H, Markkula J. Treatment of restless legs syndrome with tramadol: an open study. J Clin Psychiatry. 1999 Apr;60(4):241-4.

effects of tramadol include nausea, dizziness, constipation, vomiting, somnolence, and headache. Like other opioids, overdoses can result in respiratory depression and death. Another noted side effect of tramadol is serotonin syndrome (characterized by tremors, agitation, sweating/fevers, muscle rigidity, diarrhea, confusion, which can be life-threatening when severe), especially when combined with other serotoninergic drugs such as antidepressants, antiemetics (ondansetron), anti-migraine medication (triptans), and other opioid medications. Tramadol has also been noted to lower seizure thresholds, increasing the risk of seizure.

Drug Enforcement Agency (DEA) Scheduling of Tramadol

The Department of Health and Human Services (HHS) and the DEA began the process to schedule tramadol in 2007-2010 and considered eight factors outlined in 21 U.S.C. 811: (1) Its actual or relative potential for abuse; (2) scientific evidence of its pharmacological effect, if known; (3) the state of current scientific knowledge regarding the drug or other substance; (4) its history and current pattern of abuse; (5) the scope, duration, and significant of abuse; (6) what, if any, risk there is to the public health; (7) its psychic or physiological dependence liability; and (8) whether the substance is an immediate precursor of a substance already controlled. After consideration of comments, scientific and medical evaluation, recommendations by HHS and its own eight factor analysis, the DEA finalized the scheduling of tramadol from an uncontrolled drug to schedule IV on July 2, 2014.

Increasing Prevalence of Tramadol Use as a Continued Pattern

One point of concern is continued increase in tramadol use even after its classification as a schedule IV drug. Shortly after tramadol was designated a schedule IV drug in July 2014, hydrocodone was changed from schedule III to schedule II in October 2014 in an effort to curb opioid use. Multiple studies have found that when hydrocodone use dropped, commensurate increases in tramadol and other opioids resulted in a relatively unchanged number of total opioid prescriptions.[4,5] In a survey of pharmacists, over 80% agreed that prescriptions of tramadol "increased" or "significantly increased" following rescheduling of hydrocodone.[6]

Other indicators have shown that the use of tramadol is prevalent regardless of the rescheduling of hydrocodone. In a large study compiling all opioid prescriptions given in emergency department (ED) encounters at Veterans Health Administration (VA) sites between January 2009 and June 2015, an opioid medication was prescribed in 13.6% of visits, with tramadol as the second most commonly prescribed drug in the ED, behind

[4] Harrison ML, Walsh TL. The effect of a more strict 2014 DEA schedule designation for hydrocodone products on opioid prescription rates in the United States. Clin Toxicol (Phila). 2019 Feb 21:1-9.
[5] Tan WH, Feaman S, Milam L, Garber V, McAllister J, Blatnik JA, Brunt LM. Postoperative opioid prescribing practices and the impact of the hydrocodone schedule change. Surgery. 2018 Oct;164(4):879-886.
[6] Varisco TJ, Ogunsanya ME, Barner JC, Fleming ML. Pharmacists' perceptions regarding the impact of hydrocodone rescheduling on prescription volume, workflow management, and patient outcomes. J Am Pharm Assoc (2003). 2017 Mar - Apr;57(2S):S51-S62.

acetaminophen/hydrocodone.[7] Another study on opioid medication prescriptions at all national VA sites between 2000 and 2016 found that despite educational campaigns on opioid prescribing between 2010 and 2013, prescribing rates of tramadol and hydrocodone increased between 2011 and 2015.[8] Tramadol was the third most common prescribed opioid overall, a total of 2,150,889,394 prescriptions reported during this time period.[13]

Considerations since 2014 Rule

In the decision to schedule tramadol instead of leaving it unscheduled, its narcotic and reinforcing effects similar to morphine and other opioids such as analgesia, respiratory depression, miosis, cough suppression, and inhibition of bowel motility, were a main consideration. In the proposed determination to schedule tramadol, the DEA summarized that "individuals are taking tramadol in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community" as summarized from data from the Drug Abuse Warning Network (DAWN). ED visits from use of tramadol had been increasing continually from 2004 through 2010. In addition, data from the National Poison Data System (NPDS) indicated that human toxic exposures to tramadol had been increasing in 2009 to 2011, warranting its scheduling as a controlled substance. From our research, the use of tramadol has only increased beyond the volume observed in 2014, indicating that the schedule IV placement, particularly in light of hydrocodone rescheduling shortly afterwards, did not reign in the risks originally observed in 2014.

The decision to place tramadol into schedule IV rests primarily on the observation that much of the data regarding tramadol rang similar to that for propoxyphene (schedule IV). In particular, there is a similar withdrawal syndrome and dependence development as observed in animal models. Furthermore, statistics on the rate of ED visits for tramadol per prescriptions dispensed was similar to propoxyphene. One argument that must be made is that this number is reported as a "rate," which is adjusted for the much lower number of propoxyphene prescriptions overall, especially since the FDA's recommendation to withdraw propoxyphene from the US market in 2011. In addition, the number of times tramadol was seized by law enforcement in drug exhibits was similar to numbers for propoxyphene (schedule IV) in 2010, and less than numbers for hydrocodone (now schedule II), codeine (II, III, V), and buprenorphine (III). Again, it must be noted that the comparison to propoxyphene should be given less weight now than in the past, due to the discontinuation of propoxyphene in the US market and its rarity of use now. The prevalence of tramadol use now (in 2019) as compared to propoxyphene (used as the basis of recommendation to place in Schedule IV in 2014), resulting in greater numbers of exposures and toxicities, could serve as a basis for re-examining the schedule IV classification.

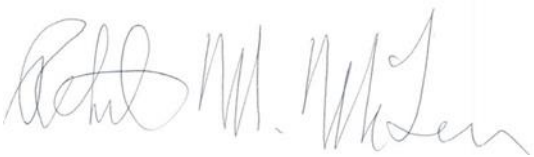
[7] Grasso MA, Dezman ZDW, Grasso CT, Jerrard DA. Opioid pain medication prescriptions obtained through emergency medical visits in the Veterans Health Administration. J Opioid Manag. 2017 Mar/Apr;13(2):77-84.
[8] Grasso MA, Grasso CT, Jerrard DA. Prescriptions Written for Opioid Pain Medication in the Veterans Health Administration Between 2000 and 2016. J Addict Med. 2017 Nov/Dec;11(6):483-488.

Conclusion

In summary, we believe that a re-examination of the 2014 placement of tramadol into schedule IV is warranted. Therefore, ACP requests that the DEA, HHS, and the FDA review tramadol's schedule IV classification and consider rescheduling the drug as the agency feels appropriate.

We appreciate your consideration on this matter. If you have additional questions regarding our policies or this letter, please do not hesitate to contact Hilary Daniel, Associate, Health Policy at hdaniel@acponline.org.

Sincerely,



Robert McLean, MD, MACP

President

CC: Drug Enforcement Agency