



1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

Citizen Petition

Submitted to:

Uttam Dhillon
Acting Administrator
Drug Enforcement Administration
U.S. Department of Justice
8701 Morrissette Drive
Springfield, VA 22152

Norman E. Sharpless, M.D.
Acting Commissioner of Food and Drugs
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

The Honorable Alex M. Azar II
Secretary
U.S. Department of Health and Human Services
200 Independence Avenue SW
Washington, DC 20201

Date: November 6, 2019

On behalf of Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, the undersigned submit this petition under Section 201 of the Controlled Substances Act (CSA) (21 U.S.C. § 811) and under Drug Enforcement Administration (DEA) regulations at 21 C.F.R. § 1308 and Food and Drug Administration (FDA) regulations at 21 C.F.R. § 10.30 to request that the DEA Administrator and the Commissioner of Food and Drugs immediately initiate the proceedings for rescheduling 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol, its salts, its optical and geometric isomers, and salts of these isomers (including tramadol) from schedule IV to schedule II of the CSA because the drug has a high potential for abuse — with use potentially leading to severe psychological or physical dependence — and is considered dangerous.

Tramadol, a synthetic codeine analog, is an opioid agonist indicated in adults for management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. It was dangerously unscheduled for 20 years in the U.S. before finally being placed in schedule IV in 2014. Since then, new evidence has accumulated showing that tramadol is an increasingly overprescribed, addictive, potentially deadly narcotic that should be rescheduled to schedule II. Tramadol's current placement in schedule IV has generated a false perception of the drug's safety profile — particularly with respect to its potential for abuse, dependence, and addiction — among both prescribers and patients, which has contributed to the large increase in its prescribing following the DEA's 2014 rescheduling of hydrocodone combination products from schedule III to schedule II of the CSA. As currently scheduled, tramadol poses a public health risk and needs to undergo urgent reevaluation and prompt rescheduling from schedule IV to schedule II of the CSA.

A. ACTION REQUESTED

Immediately initiate the proceedings for rescheduling 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol, its salts, its optical and geometric isomers, and salts of these isomers (including tramadol) from schedule IV to schedule II of the CSA.

B. STATEMENT OF GROUNDS

1. Background on Schedules II, III, and IV of the Controlled Substances Act^{1,2}

a. Schedule II

Schedule II drugs, substances, or chemicals are defined as drugs with a high potential for abuse, with use potentially leading to severe psychological or physical dependence. These drugs are also considered dangerous. Examples of schedule II drugs include fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, and oxycodone.

Refills for drugs listed in schedule II are prohibited. However, an individual practitioner may issue multiple prescriptions authorizing a patient to receive a total of up to a 90-day supply of a schedule II drug provided the following conditions are met:

- (1) Each separate prescription is issued for a legitimate medical purpose by an individual practitioner acting in the usual course of professional practice;
- (2) The individual practitioner provides written instructions on each prescription (other than the first prescription, if the prescribing practitioner intends for that prescription to be filled immediately) indicating the earliest date on which a pharmacy may fill each prescription;
- (3) The individual practitioner concludes that providing the patient with multiple prescriptions in this manner does not create an undue risk of diversion or abuse;
- (4) The issuance of multiple prescriptions as described in this section is permissible under the applicable state laws; and
- (5) The individual practitioner complies fully with all other applicable requirements under the CSA and the CSA regulations as well as any additional requirements under state law.

b. Schedule III

Schedule III drugs, substances, or chemicals are defined as drugs with a moderate to low potential for physical and psychological dependence. These drugs' abuse potential is less than schedule I and schedule II drugs but more than schedule IV. Examples of schedule III opioid

¹ Drug Enforcement Administration. Drug scheduling. <https://www.dea.gov/drug-scheduling>. Accessed November 4, 2019.

² 21 C.F.R. §§ 1306.12 and 1306.22.

drugs include products containing 90 milligrams of codeine per dosing unit (acetaminophen with codeine), ketamine, and testosterone.

No prescription for a controlled substance listed in Schedule III may be filled or refilled more than six months after the date on which the prescription was issued, and no prescription for a controlled substance listed in Schedule III authorized to be refilled may be refilled more than five times.

c. Schedule IV

Schedule IV drugs, substances, or chemicals are defined as drugs with a low potential for abuse and low risk of dependence. Examples of schedule IV drugs include diazepam, tramadol, and zolpidem.

No prescription for a controlled substance listed in Schedule IV may be filled or refilled more than six months after the date on which the prescription was issued, and no prescription for a controlled substance listed in Schedule IV authorized to be refilled may be refilled more than five times.

2. Background on Tramadol

a. Description

Tramadol is a synthetic codeine analog and centrally acting opioid agonist, first synthesized by the German pharmaceutical company Chemie Grünenthal GmbH in 1962.³ The FDA-approved versions of the drug are formulated as the racemic mixture (\pm)-*cis*-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol.^{4,5} It is currently marketed in the U.S. only in oral tablet and capsule formulations that contain either tramadol alone (under brand names Conzip and Ultram and multiple generic versions) or combinations of tramadol and acetaminophen (under the brand name Ultracet and multiple generic versions).⁶ Orally administered tramadol is rapidly and almost completely absorbed. The drug is then rapidly distributed throughout the body, with approximately 20% plasma protein binding.⁷

Tramadol has a multimodal mechanism of action. The principal mode of action is through binding of the parent compound and its more potent metabolite, *O*-desmethyltramadol (M1), to the μ -opioid receptors.⁸ A secondary mode of action occurs through weak inhibition of reuptake of norepinephrine and serotonin — which enhances the inhibitory effects on pain transmission in

³ Science Museum. Brought to Life: Exploring the History of Medicine. Chemie Grünenthal GmbH. <http://broughttolife.sciencemuseum.org.uk/broughttolife/people/chemiegmbh>. Accessed November 4, 2019.

⁴ Janssen Pharmaceuticals. Label: tramadol hydrochloride (ULTRAM). October 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020281s0451b1.pdf. Accessed November 4, 2019.

⁵ Hereafter, the term “tramadol” will be used to refer to 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol, its salts, isomers, salts of isomers, and all isomeric configurations of possible forms.

⁶ Food and Drug Administration. Orange book: Approved drug products with therapeutic equivalence evaluations. <https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm>. Accessed November 4, 2019. Search term: “tramadol.”

⁷ Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokin*. 2004;43(13):879-923.

⁸ *Ibid.*

the spinal cord — by the parent compound tramadol.^{9,10} Both mechanisms contribute to tramadol's analgesic effects as well as to its adverse-effect profile.

Relative to other opioids, tramadol has been reported as a weak agonist of the μ -opioid receptor, binding to the human μ -opioid receptor with an affinity constant (K_i) of 2.4 micromolar (μM) in vitro.^{11,12} However, the (+)-enantiomer of its M1 metabolite shows a nearly 700-fold higher affinity ($K_i=3.4 \mu\text{M}$) for the human μ -opioid receptor in vitro than the parent compound.¹³

Tramadol is primarily metabolized in the liver by *O*- and *N*-demethylation, as well as conjugation reactions that form glucuronides and sulfates, and is mostly (approximately 90%) excreted by the kidneys.¹⁴ The conversion of tramadol through *O*-demethylation to its M1 metabolite is catalyzed by cytochrome P450 (CYP) 2D6.¹⁵ The gene that encodes the CYP2D6 enzyme show polymorphism, resulting in significant variability in the rate of drug metabolism across individuals. Individuals can be categorized into three tramadol-metabolizer phenotypes based on their CYP2D6 genotype: ultra-rapid metabolizers, extensive metabolizers, and poor metabolizers.¹⁶ This phenotypic variation impacts therapeutic response and the risk of toxicity.

The prevalence of the ultra-rapid metabolizer phenotype is estimated to be 1-10% for whites (European, North American), 3-4% for African Americans, and 1-2% for East Asians (Chinese, Japanese, Korean), and may be greater than 10% for certain other racial/ethnic groups (Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, and Puerto Rican).¹⁷ The FDA-approved product labeling includes the following warning regarding the use of tramadol in such individuals:

These individuals convert tramadol into its active metabolite, *O*-desmethyltramadol (M1), more rapidly and completely than other people. This rapid conversion results in higher than expected serum M1 levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing)... Therefore, individuals who are ultra-rapid metabolizers should not use [tramadol].¹⁸

⁹ *Ibid.*

¹⁰ Janssen Pharmaceuticals. Label: tramadol hydrochloride (ULTRAM). October 2019.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020281s0451bl.pdf. Accessed November 4, 2019.

¹¹ Raffa RB, Friderichs E, Reimann W, et al. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. *J Pharmacol Exp Ther.* 1992;260(1):275-285.

¹² Gillen C, Haurand M, Kobelt DJ, Wnendt S. Affinity, potency and efficacy of tramadol and its metabolites at the cloned human μ -opioid receptor. *Naunyn Schmiedebergs Arch Pharmacol.* 2000;362(2):116-121.

¹³ *Ibid.*

¹⁴ Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet.* 2004;43(13):879-923.

¹⁵ *Ibid.*

¹⁶ van Schaik RH. 6. Dose adjustments based on pharmacogenetics of CYP450 enzymes. *EJIFCC.* 2008;19(1):42-47.

¹⁷ Janssen Pharmaceuticals. Label: tramadol hydrochloride (ULTRAM). October 2019.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020281s0451bl.pdf. Accessed November 4, 2019.

¹⁸ *Ibid.*

Approximately 7% of the population are poor metabolizers of tramadol.¹⁹ For these patients, tramadol may be less effective for treating pain than it is for extensive metabolizers.²⁰

Importantly, few people know whether they are ultra-rapid metabolizers of tramadol because CYP2D6 genotyping generally is not performed prior to prescribing tramadol to patients.

b. Approved Indication

The following is tramadol's FDA-approved indication:

ULTRAM is indicated in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use:

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses..., reserve ULTRAM for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]:

- Have not been tolerated or are not expected to be tolerated.
- Have not provided adequate analgesia or are not expected to provide adequate analgesia.²¹

Although this indication is nearly identical to the FDA-approved indication for schedule II opioids, such as oxycodone,²² tramadol continues to be prescribed more liberally than schedule II opioids in part because of the misperception conveyed by its schedule IV status that it is safer and the relatively lax prescribing restrictions for schedule IV drugs.

c. Boxed Warning

The FDA-approved product labeling for tramadol (Ultram) appropriately includes the following boxed warning that highlights the dangers of tramadol, which are nearly identical to the dangers of schedule II opioids, such as oxycodone (see Appendix for the boxed warning for oxycodone):

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; ULTRA-RAPID METABOLISM OF TRAMADOL AND OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTIONS WITH DRUGS AFFECTING

¹⁹ *Ibid.*

²⁰ van Schaik RH. 6. Dose adjustments based on pharmacogenetics of CYP450 enzymes. *EJIFCC*. 2008;19(1):42-47.

²¹ *Ibid.*

²² Purdue Pharma. Label: oxycodone (OXYCONTIN). October 2019.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022272s0431bl.pdf. Accessed November 4, 2019.

CYTOCHROME P450 ISOENZYMES; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

ADDICTION, ABUSE AND MISUSE

ULTRAM exposes patients and other users to the risks of opioid addiction, abuse and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing **ULTRAM**, and monitor all patients regularly for the development of these behaviors and conditions...

OPIOID ANALGESIC RISK EVALUATION AND MITIGATION STRATEGY (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products... Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

LIFE-THREATENING RESPIRATORY DEPRESSION

Serious, life-threatening, or fatal respiratory depression may occur with use of **ULTRAM**. Monitor for respiratory depression, especially during initiation of **ULTRAM** or following a dose increase...

ACCIDENTAL INGESTION

Accidental ingestion of **ULTRAM**, especially by children, can be fatal...

ULTRA-RAPID METABOLISM OF TRAMADOL AND OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN

Life-threatening respiratory depression and death have occurred in children who received tramadol. Some of the reported cases followed tonsillectomy and/or adenoidectomy; in at least one case, the child had evidence of being an ultra-rapid metabolizer of tramadol due to a CYP2D6 polymorphism... **ULTRAM** is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy... Avoid the use

of ULTRAM in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol...

NEONATAL OPIOID WITHDRAWAL SYNDROME

Prolonged use of ULTRAM during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available...

INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with ULTRAM requires careful consideration of the effects on the parent drug, tramadol, and the active metabolite, M1...

RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death...

- **Reserve concomitant prescribing of ULTRAM and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit treatment to the minimum effective dosages and durations.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.²³**

[Emphasis in original]

²³ Janssen Pharmaceuticals. Label: tramadol hydrochloride (ULTRAM). October 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020281s0451b1.pdf. Accessed November 4, 2019.

d. Additional Warnings for Tramadol

The FDA-approved product labeling for tramadol also warns about the following additional risks of serious, potentially life-threatening harm associated with tramadol use: serotonin syndrome, seizures, suicide, and severe hypotension (low blood pressure).²⁴ These warnings further highlight that tramadol is a dangerous drug.

3. Regulatory History of Tramadol Scheduling Under the Controlled Substances Act

Tramadol initially was approved by the FDA on March 3, 1995, for use as an opioid analgesic under the trade name of Ultram (new drug application 020-281) for the management of moderate to moderately severe pain.²⁵ At that time, tramadol was not scheduled under the CSA despite the FDA's recognition of μ -opioid receptor binding by tramadol and its M1 metabolite and the agency's conclusion that tramadol's adverse event profile was similar to that of an opioid.²⁶ Prior to tramadol's approval, the FDA's Drug Abuse Advisory Committee in 1994 predicted a low abuse rate and recommended against scheduling tramadol, a recommendation the FDA accepted.²⁷

The subsequent accumulation of overwhelming evidence of tramadol's dangers as a non-controlled opioid — including evidence of dependence, addiction, abuse, and diversion — prompted the submission in 2005 of five citizen petitions to the FDA asking the agency to recommend to the DEA that tramadol be scheduled under the CSA.²⁸ Two of the petitions specifically requested that tramadol be scheduled as a schedule III drug, and two other petitions, although not making such a specific request, stated that “all available data would support the scheduling of tramadol at the level of schedule III.”²⁹ Each of the latter two petitions was submitted by physicians who were board certified in internal medicine and addiction medicine.³⁰ Both physician petitioners reported seeing many cases of tramadol abuse and dependence since the drug's introduction into the market in the U.S. Both also cited extensive evidence, including drug abuse surveillance data and results of experimental animal and clinical studies published in

²⁴ *Ibid.*

²⁵ Food and Drug Administration. Approval letter for NDA 20-281. March 3, 1995.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/020281Orig1s000rev.pdf. Accessed November 4, 2019. PDF pages 4-7.

²⁶ Food and Drug Administration. Review documents for NDA 20-281.

https://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/020281Orig1s000rev.pdf. Accessed November 4, 2019. PDF pages 327-328, 332, and 340.

²⁷ Food and Drug Administration. Transcript of the April 28, 1998, meeting of the Drug Abuse Advisory Committee. <https://wayback.archive-it.org/7993/20170404125905/https://www.fda.gov/ohrms/dockets/ac/98/transcpt/3411t2.pdf>.

Accessed November 4, 2019. PDF pages 11, 38-39, and 100.

²⁸ Food and Drug Administration. Final response to citizen petitions FDA-2005-P-0425, FDA-2005-P-0054, FDA-2005-P-0058, FDA-2005-P-0191 and FDA-2005-P-0055. March 22, 2016.

<https://www.regulations.gov/document?D=FDA-2005-P-0191-0006>. Accessed November 4, 2019.

²⁹ *Ibid.*

³⁰ Skipper GE. Citizen petition to the FDA regarding scheduling of tramadol under the Controlled Substances Act. October 24, 2005. https://www.citizen.org/wp-content/uploads/051024_Citizen-Petition-on-Tramadol_Skipper.pdf.

Accessed November 4, 2019; Ovson EA. Citizen petition to the FDA regarding scheduling of tramadol under the Controlled Substances Act. November 1, 2005. <https://www.regulations.gov/document?D=FDA-2005-P-0191-0004>. Accessed November 4, 2019.

the scientific medical literature, demonstrating the high abuse potential of tramadol. One of the physician petitioners also cited his own published study showing that in Alabama and Michigan from 1994 to 2002, tramadol was the third most frequently abused drug by physicians, ranking ahead of fentanyl and oxycodone, among others.³¹

In response to the 2005 citizen petitions, the DEA and the Department of Health and Human Services (HHS) gathered data on tramadol and conducted a scientific and medical evaluation to determine whether the drug should be added as a controlled substance, and if so, in which schedule. The HHS recommended to the DEA that tramadol be added to schedule IV of the CSA. On November 4, 2013, the DEA published a notice of proposed rulemaking in the *Federal Register* that proposed placing tramadol into schedule IV of the CSA.³² Key data and conclusions in support of this proposal included the following:

- Since tramadol entered the market in 1995, abuse of the drug “by a wide spectrum of individuals of different ages, alone and in combination with other psychoactive substances,” had occurred.
- Individuals were taking tramadol in amounts sufficient to create a hazard to their health, to the safety of other individuals, and to the community.
- Tramadol abuse was associated with serious adverse events including death, drug dependence, drug withdrawal symptoms, seizures, serotonin syndrome, and other serious medical problems.
- Data from the National Forensic Laboratory Information System and the System to Retrieve Information from Drug Evidence databases provided evidence of a significant increase in diversion of tramadol from legitimate drug channels from 2000 to 2012.
- Data from the National Survey on Drug Use and Health (NSDUH) showed that the estimated number of individuals who had used tramadol products nonmedically at least once in their lifetime increased from 994,000 in 2002 to 2,614,000 in 2011, a nearly threefold increase.
- In 2007 and 2008, more prescriptions had been written for tramadol than any other opioid except for hydrocodone combination products (schedule III) and oxycodone (schedule II).
- Fifteen years of post-marketing epidemiologic abuse-related data from scientific literature as well as the Adverse Event Reporting System provided clear evidence of tramadol dependence, abuse, and addiction in the U.S.
- Case reports revealed that tramadol was abused to obtain euphoria and for its sedating effects; it caused cravings, drug-seeking behaviors, tolerance, doctor-shopping, and even self-injury in efforts to obtain more prescriptions for the drug.
- Data from the Drug Abuse Warning Network database showed that the number of tramadol-related deaths increased from 45 cases in 1997 to 88 cases in 2002.
- An HHS review of reports of tramadol-associated deaths from the Florida Department of Law Enforcement (FDLE) found that the number of deaths involving tramadol increased

³¹ Skipper GE, Fletcher C, Rocha-Judd R, Brase D. Tramadol abuse and dependence among physicians. *JAMA*. 2004;292(15):1818-1819.

³² Department of Justice, Drug Enforcement Administration. Schedules of controlled substances: Placement of tramadol into schedule IV; notice of proposed rulemaking. November 4, 2013. 78 FR 65923-65932.

from 106 in 2003 to 235 in 2008. Furthermore, the FDLE data showed that between 2005 and 2008, there were more tramadol-related deaths than heroin-related deaths.

On July 2, 2014, the DEA issued a final rule placing tramadol into schedule IV of the CSA.³³ The decision to place the drug in schedule IV was based on the following questionable DEA findings:

- (1) Tramadol has a low potential for abuse relative to the drugs or substances in schedule III. The abuse potential of tramadol is comparable to the schedule IV controlled substance propoxyphene;
- (2) Tramadol has a currently accepted medical use in treatment in the U.S. Tramadol and other tramadol-containing products are approved for marketing by the FDA to manage moderate to moderately severe pain; and
- (3) Abuse of tramadol may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule III.

4. Public Health Basis for Rescheduling Tramadol from Schedule IV to Schedule II of the Controlled Substances Act

a. Recent Trends in Tramadol Prescribing

From 1999 to 2010, both the number of opioid prescriptions and the number of deaths due to opioid overdoses in the U.S. increased overall by approximately 400%. During this period, hydrocodone combination products — which at the time were listed in schedule III of the CSA, in contrast to non-combination hydrocodone products, which were listed in schedule II — had become the most frequently prescribed opioids in the U.S. and were viewed as a major driver of the opioid overdose epidemic.³⁴ On August 22, 2014, in an effort to combat these trends, the DEA issued a final rule rescheduling hydrocodone combination products from schedule III to schedule II of the CSA.³⁵ This change, which came into effect on October 6, 2014, eliminated refills for these products and capped the aggregate amount of medication potentially dispensed per patient visit at a 90-day supply. Of note, the state of New York had passed regulations rescheduling hydrocodone products in February 2013.

To assess the effect of the rescheduling of hydrocodone combination products on subsequent opioid prescribing trends, Harrison and Walsh sought to conduct a longitudinal study of the annual rates of opioid prescriptions before and after the rescheduling in the 10 most populous states based on 2010 Census data (California, Texas, New York, Florida, Illinois, Pennsylvania,

³³ Department of Justice, Drug Enforcement Administration. Schedules of controlled substances: Placement of tramadol into schedule IV; final rule. July 2, 2014. 79 FR 37623-37630.

³⁴ 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;57(11):1064-1072.

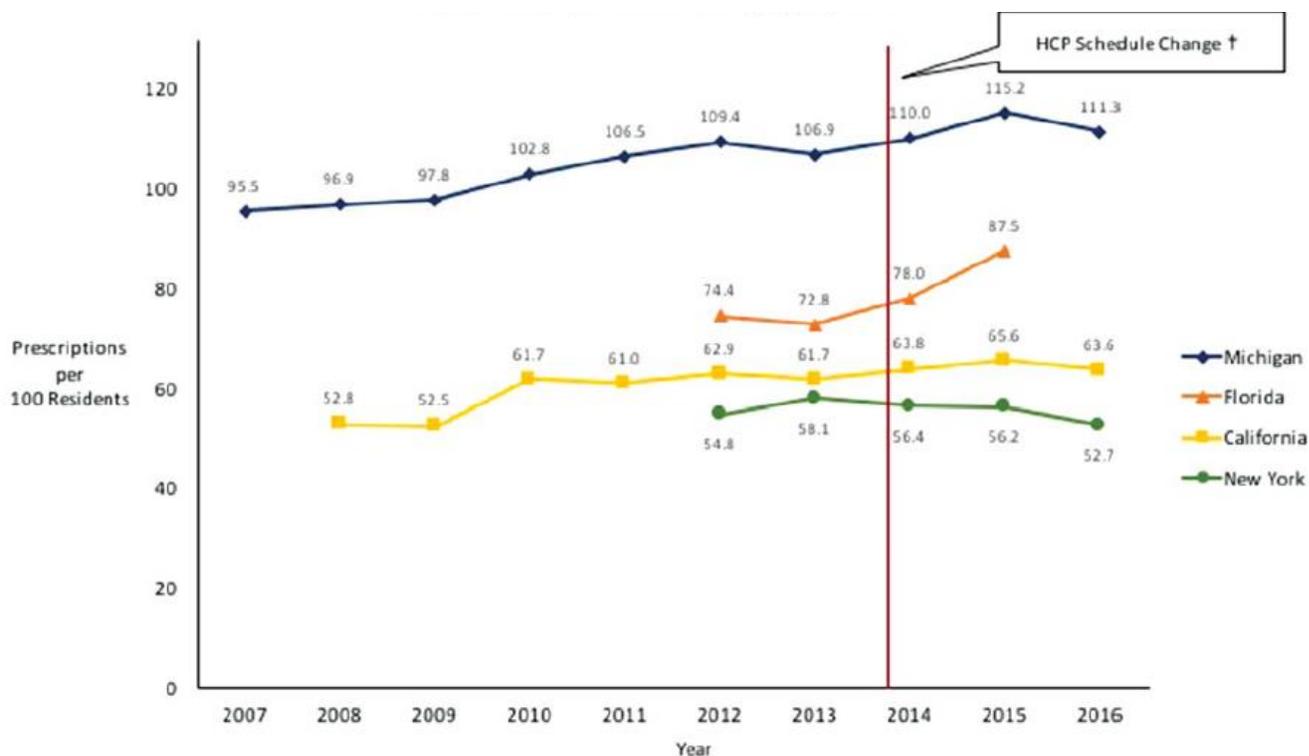
³⁵ Department of Justice, Drug Enforcement Administration. Schedules of controlled substances: Rescheduling of hydrocodone combination products from schedule III to schedule II; final rule. August 22, 2014. 79 FR 49661-49682.

Ohio, Michigan, Georgia, and North Carolina), which represent the four geographic regions of the U.S. (Northeast, South, Midwest, and West).³⁶

Only four of the ten states collected and were willing to provide Harrison and Walsh with yearly data on opioid prescriptions for the period of interest: California (for 2008 to 2016), Florida (for 2012 to 2015), Michigan (for 2007 to 2016), and New York (for 2012 to 2016). For these four states, the researchers calculated the rates of total opioid prescriptions per 100 residents for each year for which data were available. They also calculated for three states (California, Michigan, and New York) the rates of prescribing per 100 residents for each of the following opioid products for each year for which data were available: codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, and tramadol.

The major results of Harrison and Walsh's study are present in Figures 1 to 4 below that are excerpted from their 2019 paper published in *Clinical Toxicology*.

Figure 1: Total opioid prescription rates per 100 people in California, Florida, Michigan, and New York.



³⁶ 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;57(11):1064-1072.

Figure 2. California opioid prescription rates per 100 people, by drug.

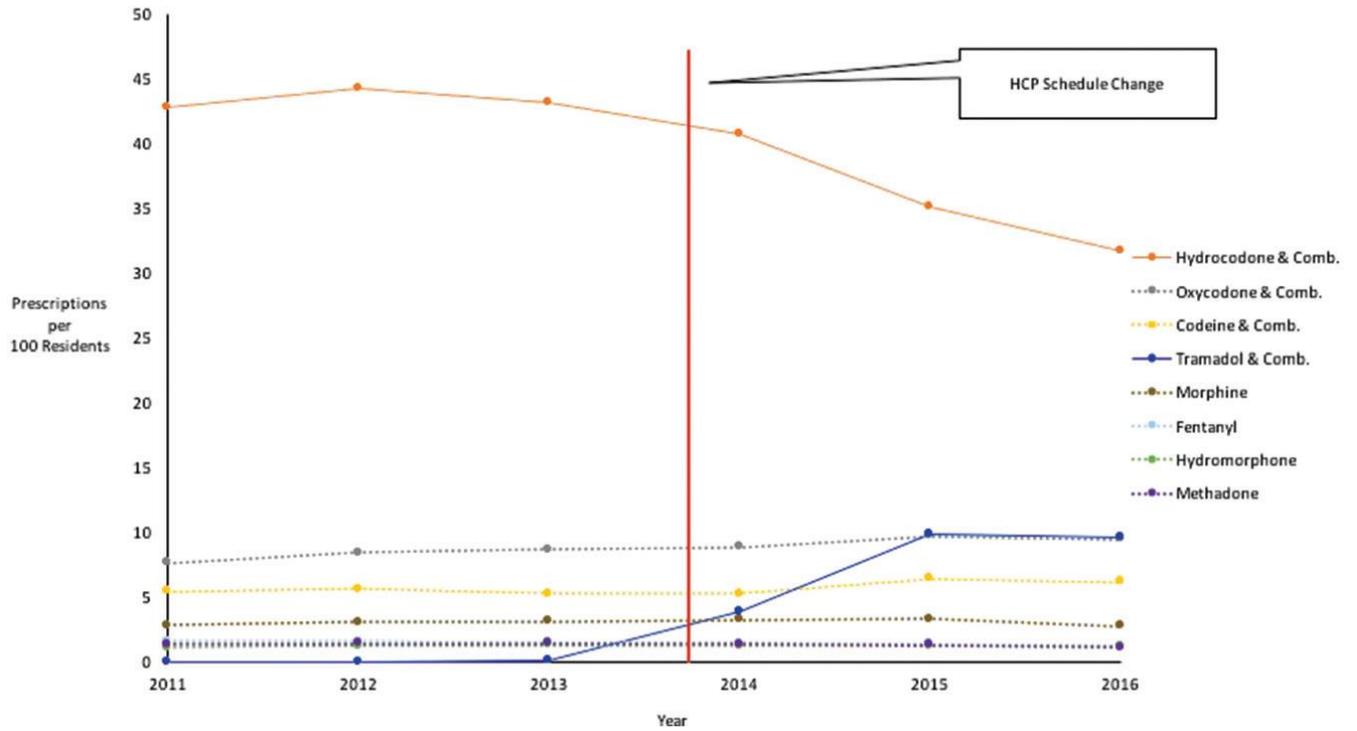


Figure 3. Michigan opioid prescription rates per 100 people, by drug.

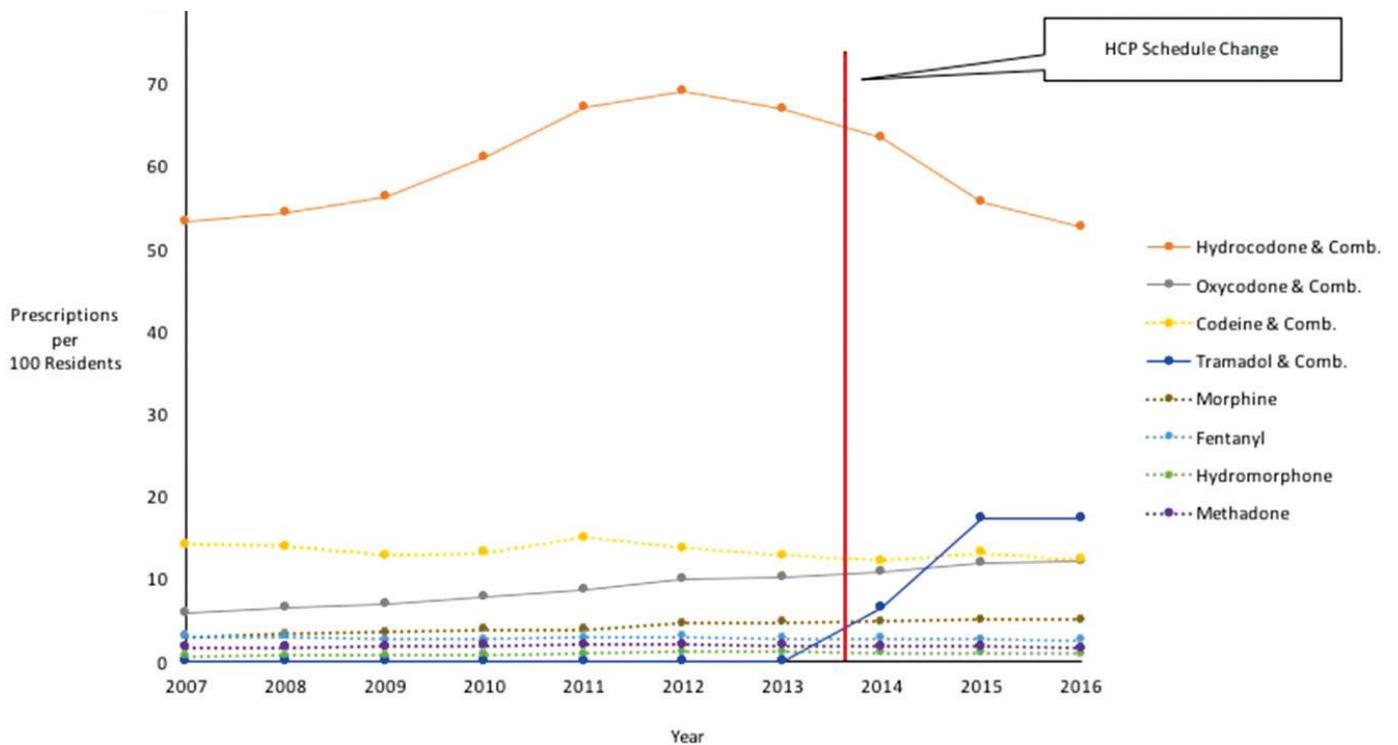
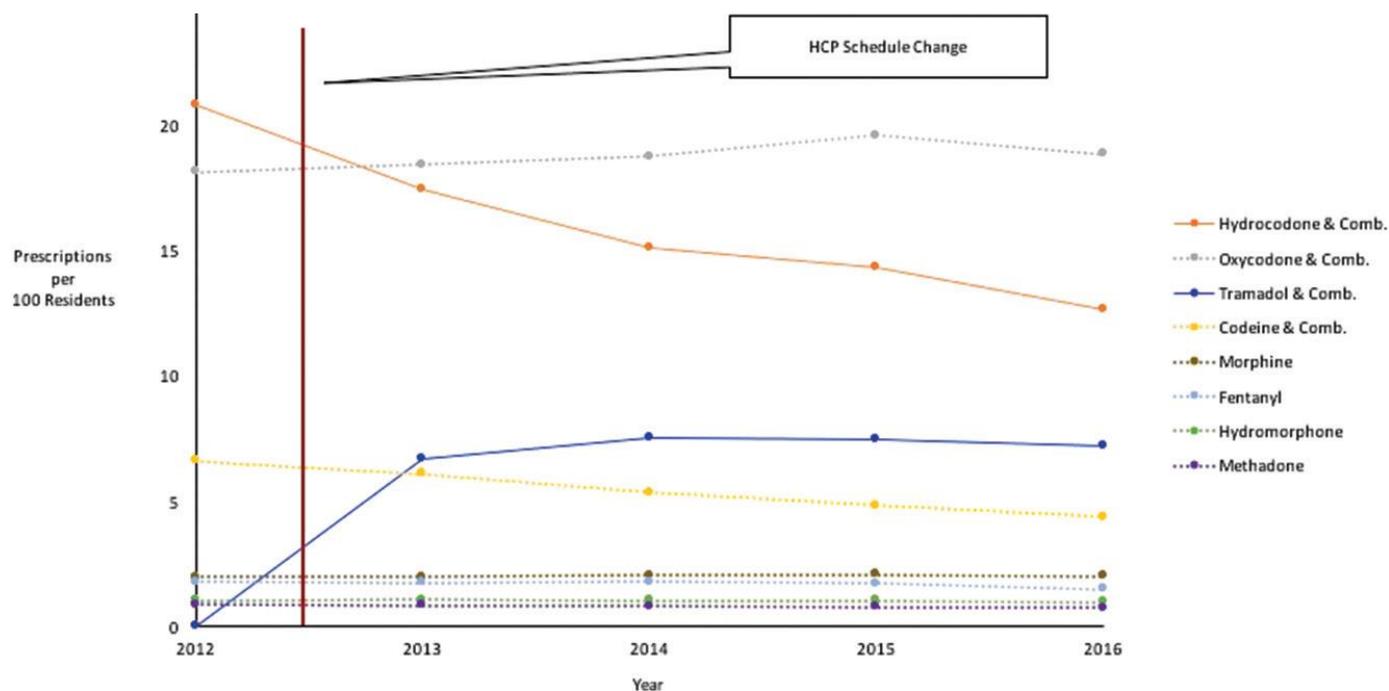


Figure 4. New York opioid prescription rates per 100 people, by drug.

The following were Harrison and Walsh's key findings:

- The rates of total opioid prescribing per 100 residents were relatively stable or increased slightly until the year 2015, when the rates peaked in three of the four states (California, Florida, and Michigan; see Figure 1).
- Following the rescheduling of hydrocodone combination products in 2014 for California and Michigan and in 2013 for New York, the rates of prescribing of all hydrocodone products per 100 residents declined substantially in all three states (see Figures 2 to 4).
- However, the decline in the rates of hydrocodone product prescribing following the rescheduling of hydrocodone combination products was largely offset by a dramatic increase in the rates of prescribing of tramadol products per 100 residents in California, Michigan, and New York (see Figures 2 to 4 and Table 1). For Michigan and New York, the net increase in the rate of tramadol prescribing per 100 residents after the rescheduling of hydrocodone combination products exceeded the net decrement in the rate of hydrocodone product prescribing per 100 residents. Notably, tramadol went from the least frequently prescribed opioid before the scheduling change to the most commonly prescribed non-hydrocodone opioid in California and Michigan, and to the second most commonly prescribed non-hydrocodone opioid in New York, trailing behind only oxycodone.

Table 1. Rate of prescribing hydrocodone and tramadol products per 100 people before and after the rescheduling of hydrocodone combination products. (Source, Harrison and Walsh, 2019³⁷)

State/Opioid	Prescribing Rate 2 Years Before	Prescribing Rate 1 Year Before	Prescribing Rate 1 Year After	Prescribing Rate 2 Years After
California				
Hydrocodone	44.3	43.2	35.0	31.7
Tramadol	0.0	0.2	9.9	9.7
Michigan				
Hydrocodone	69.1	66.8	55.6	52.7
Tramadol	0.0	0.1	17.3	17.4
New York				
Hydrocodone	-	20.8	15.1	14.3
Tramadol	-	0.0	7.6	7.5

Harrison and Walsh concluded that additional measures were needed to rein in opioid prescribing.

Finally, according to IMS Health, 43.6 million tramadol prescriptions were dispensed in the U.S. in 2016, 41.0 million were dispensed in 2017, and approximately 16.0 million were dispensed for the first half of 2018.³⁸

These data indicate that tramadol has become one of the most commonly prescribed opioids in the U.S. since the DEA rescheduled hydrocodone combination products from schedule III to schedule II of the CSA.

b. Recent Trends in Misuse of Tramadol

The Substance Abuse and Mental Health Services Administration each year conducts a comprehensive nationwide survey known as the National Survey on Drug Use and Health.³⁹ The survey enrolls people aged 12 or older and provides up-to-date information on tobacco, alcohol, and drug use, among other health-related issues, in the U.S. Among the data collected by the survey are data on the use and misuse of opioids. For the purposes of the surveys conducted since 2015, misuse was defined as use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor.⁴⁰

³⁷ *Ibid.*

³⁸ Drug Enforcement Administration. Tramadol (trade names: Ultram®, Ultracet®). October 2018. https://www.dea diversion.usdoj.gov/drug_chem_info/tramadol.pdf. Accessed November 4, 2019.

³⁹ National Survey on Drug Use and Health. About the survey. https://nsduhweb.rti.org/respweb/about_nsduh.html. Accessed November 4, 2019.

⁴⁰ Hughes A, Williams MR, Lipari RN, et al. Prescription drug use and misuse in the United States: Results from the 2015 National Survey on Drug Use and Health. September 2016. <https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR2-2015/NSDUH-FFR2-2015.htm>. Accessed November 4, 2019.

The NSDUH survey revealed that the estimated numbers of people aged 12 and older in the U.S. who misused tramadol in 2016, 2017, and 2018 were approximately 1.6, 1.8, and 1.5 million, respectively, which exceeded the estimated numbers of people who misused many schedule II opioids, including morphine, fentanyl, oxycodone, Demerol (meperidine), and hydromorphone (see Table 2). Moreover, for the interval of 2016 through 2018, the proportion of people using tramadol who misused the drug exceeded the corresponding proportions of people who misused Demerol and morphine and was approximately two-thirds as high as the corresponding proportions of people who misused fentanyl, hydrocodone, and oxycodone. The year-to-year decrease in tramadol misuse in 2018 paralleled decreases in the misuse of all other opioids.

Table 2. Estimated misuse of pain reliever subtypes in past year among past year any users of pain relievers, aged 12 or older: numbers in thousands of people misusing each drug (percentages of all users of the drug who were misusing the drug), 2016 to 2018. (Source: Detailed tables from the 2017 and 2018 National Survey on Drug Use and Health^{41,42})

Opioid Product	2016	2017	2018
Hydrocodone	6,924 (12.6)	6,262 (12.0)	5,502 (11.5)
Oxycodone	3,905 (14.1)	3,735 (14.0)	3,374 (12.8)
Tramadol	1,591 (8.4)	1,753 (9.5)	1,455 (8.1)
Codeine	2,767 (10.4)	2,832 (10.5)	2,393 (9.4)
Morphine	536 (7.9)	501 (8.0)	486 (7.9)
Fentanyl	228 (12.4)	245 (12.0)	269 (12.7)
Buprenorphine	712 (31.6)	766 (31.7)	718 (28.3)
Oxycodone	302 (27.6)	332 (36.2)	237 (28.4)
Demerol	95 (6.9)	116 (9.6)	54 (4.5)
Hydromorphone	239 (11.3)	244 (12.6)	229 (13.0)
Methadone	346 (25.5)	261 (19.5)	256 (23.5)

c. Increased Mortality Risk with Tramadol Use

New research published since tramadol was placed in schedule IV of the CSA in 2014 has established a clear association between tramadol use and an increased mortality risk.

Jeong et al. conducted the first population-based epidemiological study exploring the association between tramadol use and mortality.⁴³ Using a novel study design, they analyzed retrospective data from the South Korea National Health Insurance Service-National Sample Cohort, which included data from more than one million patients from 2002 to 2013. They identified 19,443 patients who received at least one tramadol prescription prior to death between January 1, 2004,

⁴¹ Substance Abuse and Mental Health Services Administration. Reports and detailed tables from the 2017 National Survey on Drug Use and Health. <https://www.samhsa.gov/data/nsduh/reports-detailed-tables-2017-NSDUH>. Accessed November 4, 2019.

⁴² Substance Abuse and Mental Health Services Administration. Reports and detailed tables from the 2018 National Survey on Drug Use and Health. <https://www.samhsa.gov/data/nsduh/reports-detailed-tables-2018-NSDUH>. Accessed November 4, 2019.

⁴³ Jeong S, Tchoe HJ, Li J, Shin JY. All-cause mortality associated with tramadol use: A case-crossover study. *Drug Safety*. 2019;42(6):785-796.

and December 31, 2013 (45.3% female, 51.5% older than 75, 24.2% aged 65-74, 24.1% aged 20-64, and 0.2% younger than 20). The number of patients exposed to tramadol in the hazard period (defined as 30 days before death) was compared with the number of patients exposed to tramadol in the control period (the period prior to but with the same length as the hazard period). The hazard period was defined as the 30-, 45-, and 60-day periods before death. Jeong et al. used a hazard period of 30 days in their main analyses. Three consecutive control periods having the same duration as the hazard period were drawn for each patient included in the study. A 10-day washout period was introduced between the end of the control period and the start of the hazard period to reduce the likelihood of overlapping prescriptions.

Using the 30-day hazard period, Jeong et al. found an adjusted odds ratio for mortality risk of 1.77 (95% confidence interval [CI] 1.67-1.87) for tramadol exposure when adjusted for concomitant medications, surgeries, and acute respiratory conditions. The adjusted odds ratios for oral and parenteral forms of tramadol were 1.33 (95% CI 1.24-1.43) and 1.99 (95% CI 1.87-2.11), respectively. An elevated odds ratio for mortality associated with tramadol exposure was seen in males, females, patients of all age groups, and patients with various comorbidities, including cardiovascular disease, respiratory disease, renal disease, hepatic disease, and cancer. Zeng et al. conducted a sequential, propensity score-matched cohort study using an electronic medical records database for general practitioners in the U.K. that contains health information on approximately 11 million patients.⁴⁴ They assessed the all-cause mortality risk in osteoarthritis patients aged 50 years or older within one year after an initial tramadol prescription (n=44,451), compared with five other analgesic medications: naproxen (n=12,397), diclofenac (n=6,512), celecoxib (n=5674), etoricoxib (n=2,946), or codeine (n=16,992). The researchers matched patients prescribed tramadol with patients in each of the other comparison groups for a variety of demographic, social, lifestyle, and medical factors, including age, sex, body size, drinking habits, smoking status, duration of osteoarthritis, and other comorbidities. The patients had a mean age of 70 and 61% were women. Not surprisingly, the proportion of patients who were prescribed tramadol increased from 3% in 2000 to 11% in 2013 and 10% in 2015.

Zeng et al. found that after 12 months of follow-up, the mortality rate was higher for tramadol users than for users of naproxen (hazard ratio [HR] 1.71; 95% CI 1.41-2.07), diclofenac (HR 1.88; 95% CI 1.51-2.25), celecoxib (HR 1.70; 95% CI 1.33-2.17) and etoricoxib (HR, 2.04; 95% CI 1.37-3.03). No statistically significant difference in all-cause mortality was observed between users of tramadol and codeine (HR 0.94; 95% CI 0.83-1.05).

d. Significant Risk of Long-Term Opioid Use Following an Initial Prescription for Tramadol

Chronic opioid use is often a consequence of opioid use that began with a prescription for acute pain. Such chronic use of an opioid after an acute pain episode can be an important indicator of opioid dependence and addiction.

Two recently published studies have examined the risk of long-term opioid use following an initial prescription for tramadol compared with other opioids. Both demonstrated that the risk of

⁴⁴ Zeng C, Dubreuil M, LaRochelle MR, et al. Association of tramadol with all-cause mortality among patients with osteoarthritis. *JAMA*. 2019;321(10):969-982

long-term opioid use following an initial opioid prescription was greater with tramadol than with short-acting schedule II opioids, including short-acting hydrocodone and oxycodone.

The first study by Shah et al., which was published in 2017 in *Morbidity and Mortality Weekly Report*, involved an analysis of a random 10% sample of patient records from 2006 to 2015 in a large commercial health plan database from managed care plans that is representative of the U.S. commercially insured population.⁴⁵ The researchers selected records for adult patients who had at least one opioid prescription from June 1, 2006, to September 1, 2015, and six or more months of continuous enrollment without an opioid prescription before their first opioid prescription. They excluded patients with a diagnosis of any cancer (except nonmelanoma skin cancer) or substance abuse disorder in the six months prior to their first opioid prescription, as well as those whose first opioid prescription was for any buprenorphine formulation indicated for treatment of substance abuse.

Shah et al. followed patients from their first prescription until loss of enrollment, discontinuation of opioids (≥ 180 days without opioid use), or study completion date. They calculated the duration of use, number of prescriptions, cumulative dose (in morphine milligram equivalents [MMEs]), number of days' supply, and average daily dose in MMEs for the first episode of opioid use (defined as continuous use of opioids with a gap of no greater than 30 days). The first opioid prescription was categorized into six mutually exclusive groups: (1) long-acting opioids, (2) short-acting oxycodone, (3) short-acting hydrocodone, (4) other short-acting schedule II opioids, (5) schedule III and IV opioids and nalbuphine, and (6) tramadol.

Shah et al. included a total of 1,294,247 patients in their study, including 33,548 who continued opioid therapy for one year or more. The probability of long-term opioid use at one and three years was highest among patients who initiated treatment with long-acting opioids (27.3% at one year; 20.5% at three years). Strikingly, the probability of long-term opioid use at one and three years among all categories of short-acting opioids was highest among those patients who initiated treatment with tramadol (13.7% at one year; 6.8% at three years), exceeding the probabilities for short-acting hydrocodone (5.1% and 2.4%, respectively), short-acting oxycodone (4.7% and 2.3%, respectively), other short-acting schedule II opioids (8.9% and 5.3%, respectively), and schedule III and IV opioids and nalbuphine (5.0% and 2.2%, respectively).

The second recent and more rigorous study that examined the risk of long-term opioid use following an initial prescription for tramadol compared with other opioids was conducted by Thiels et al. and published in the *BMJ* in 2019.⁴⁶ Their aim was to determine the risk of transitioning from acute to prolonged opioid use in opioid-naïve patients treated with tramadol for postoperative pain. The study involved a retrospective analysis of de-identified claims data from OptumLabs Data Warehouse, which includes data for commercial and Medicare Advantage enrollees in a large, private U.S. health plan, from January 1, 2009, to June 30, 2018, with last surgery on December 31, 2017, for opioid-naïve patients undergoing one of 20 commonly

⁴⁵ Shah A, Hayes CJ, Martin BC. Characteristics of initial prescription episodes and likelihood of long-term opioid use — United States, 2006–2015. *MMWR Morb Mortal Wkly Rep.* 2017;66(10):265-269.

⁴⁶ Thiels CA, Habermann EB, Hooten WM, Jeffery MM. Chronic use of tramadol after acute pain episode: cohort study. *BMJ.* 2019;365:11849.

performed elective surgical procedures spanning multiple specialties, including general surgery, orthopedic surgery, colorectal surgery, urologic surgery, thoracic surgery, and gynecological surgery.

To minimize confounding that could result from clinical complexity, Thiels et al. excluded patients who had taken opioids before surgery (defined as filling a prescription for opioids in the preceding six months); been in treatment for opioid use disorder (defined as using buprenorphine or methadone in the 90 days after surgery); undergone multiple unrelated procedures on the same day; had an inpatient stay exceeding seven days; been admitted earlier than one day prior to the surgical procedure; had cancer and undergone a noncancer surgery; received hospice care; or been discharged to a skilled nursing facility within a day of surgery. Patients also had to have 90 days of insurance enrollment after surgery to ensure that the patients survived surgery when evaluated for postoperative opioid use.

Thiels et al. classified discharge prescriptions into one of five mutually exclusive and collectively exhaustive categories: (1) no opioid prescription, (2) any long-acting opioid (with or without any short-acting opioid, including tramadol), (3) tramadol only, (4) a short-acting opioid other than tramadol (served as the reference group), and (5) tramadol with another short-acting opioid. Active ingredient doses were converted to MMEs.

The researchers found that of the 444,764 patients that met the inclusion criteria and had at least 180 days of follow-up, 357,884 had a discharge prescription for one or more opioids. The most common type of discharge prescription was one or more short-acting opioids other than tramadol (n=333,289, 74.9%), whereas 13,519 patients (3%) received tramadol alone, and 5,457 (1.2%) received tramadol with another short-acting opioid. Tramadol was the third most frequently prescribed opioid in the study, ranking behind hydrocodone and short-acting oxycodone.

To assess prolonged use, Thiels et al. performed logistic regression at the individual level of the cohort with at least 180 days of follow-up. They selected three definitions of prolonged opioid use a priori that had been used in the medical literature:

- (1) Additional opioid use after surgery: at least one opioid fill 90 to 180 days after surgery;
- (2) Persistent opioid use after surgery: any span of opioid use starting in the 180 days after surgery and lasting at least 90 days; and
- (3) CONSORT definition of long-term opioid therapy, which was developed by the Consortium to Study Opioid Risks and Trends for studying long-term opioid therapy in patients being treated for chronic noncancer pain: an opioid-use episode starting in the 180 days after surgery that spans at least 90 days and includes either 10 or more opioid fills or 120 or more days' supply of opioids).

The researchers' logistic regression models were adjusted for surgery year, sex, race/ethnicity, type of surgery, beneficiary type (commercially insured, Medicare Advantage aged ≥ 65 , Medicare Advantage disabled), census division, age, discharge prescription volume (total MME),

binary variables for each Elixhauser comorbidity, and whether the person received any long-acting opioids at discharge.

Thiels et al. found that among all patients with at least 180 days of post-surgery follow-up, 31,431 (7.1%) had additional opioid use after surgery, 4,457 (1.0%) had persistent opioid use after surgery, and 2,027 (0.46%) met the stringent CONSORT definition of long-term opioid use (Table 3). The unadjusted risk of prolonged opioid use in patients who received discharge prescriptions for tramadol and for tramadol with another short-acting opioid exceeded that of patients who received discharge prescriptions for other short-acting opioids under each of the three definitions of prolonged opioid use.

Table 3. Risk of unadjusted prolonged opioid use (three definitions) for patients who received short-acting opioids excluding tramadol, tramadol only, tramadol and another short-acting opioid, any long-acting opioid, or no opioids at discharge (cohort with 180 days follow-up). Values are numbers (percentages). Reproduced from Thiels et al., 2019.⁴⁷

Definition	All patients (n=444,764)	No opioid fill (n=86,880)	Tramadol only (n=13,519)	Other short-acting opioid (n=333,289)	Tramadol + other short-acting opioid (n=5,457)	Any long-acting opioid (n=5,619)
Additional opioid use after surgery*	31,431 (7.07)	3,849 (4.43)	1,066 (7.89)	25,388 (7.62)	543 (9.95)	585 (10.41)
Persistent opioid use after surgery†	4,457 (1.00)	314 (0.36)	194 (1.44)	3,559 (1.07)	149 (2.73)	241 (4.29)
CONSORT definition of chronic opioid use‡	2,027 (0.46)	175 (0.20)	78 (0.58)	1,573 (0.47)	71 (1.30)	130 (2.31)

*At least one opioid fill 90-180 days after surgery.

†Any span of opioid use starting in the 180 days after surgery and lasting ≥ 90 days.

‡Opioid use episode starting in the 180 days after surgery that spans ≥ 90 days and includes either ≥ 10 opioid fills or ≥ 120 days' supply of opioids.

Most notably, Thiels et al. found that receipt of a tramadol prescription (alone or with another short-acting opioid) at discharge following surgery was associated with an increased adjusted risk of prolonged opioid use under each of three definitions compared with patients who received a short-acting opioid other than tramadol (see Table 4).

⁴⁷ *Ibid.*

Table 4. Adjusted risk ratios* (95% confidence intervals) and p values† for persistent opioid use (three definitions) in patients who received tramadol only, tramadol and another short-acting opioid, or any long-acting opioids (reference group: short-acting opioids excluding tramadol). Reproduced from Thiels et al., 2019.⁴⁸

Opioid type	Additional opioid use after surgery‡	Persistent opioid use after surgery§	CONSORT definition of opioid dependence¶
Other short-acting	Reference	Reference	Reference
Tramadol only	1.06 (1.00-1.13); p=0.049	1.47 (1.25-1.69); p<0.001	1.41 (1.08-1.75); p=0.013
Tramadol + short-acting	1.05 (0.96-1.14); p=0.261	1.04 (0.86-1.21); p=0.685	1.40 (1.05-1.74); p=0.022
Any long-acting	0.95 (0.87-1.03); p=0.218	1.18 (1.02-1.35); p=0.029	1.69 (1.36-2.02); p<0.001

*Risk ratios calculated as ratio of predictive margins after logistic regression including covariates of year, surgery, female sex, beneficiary type, race/ethnicity, census division, age category, categorical measurement of morphine milligram equivalents at discharge, and flags for each of Elixhauser comorbidities; see appendix F for full regression output.

†P values from hypothesis test that risk ratio does not equal 1.

‡At least one opioid fill 90-180 days after surgery.

§Any span of opioid use starting in the 180 days after surgery and lasting ≥ 90 days.

¶Opioid use episode starting in the 180 days after surgery that spans ≥ 90 days and includes either ≥ 10 opioid fills or ≥ 120 days' supply of opioids.

Relative to patients prescribed other short-acting opioids at discharge following surgery, patients prescribed tramadol had a 6% increased risk of additional opioid use (risk ratio 95% CI 1.00-1.13; risk difference 0.5 percentage points; p=0.049), a 47% increased risk of persistent opioid use (1.25 to 1.69; 0.5 percentage points; p<0.001); and a 41% increased adjusted risk of CONSORT-defined chronic opioid use (1.08 to 1.75; 0.2 percentage points; p=0.013).

Thiels et al. concluded the following:

We found that tramadol, a drug that is scheduled at a lower risk level than other common short acting opioids (schedule IV versus schedule II for hydrocodone and oxycodone), has a similar or somewhat greater risk of prolonged opioid use after surgery. Although all factors related to the safety of a drug must be considered, from the standpoint of opioid dependence, the Drug Enforcement Administration and FDA should consider rescheduling tramadol to a level that better reflects its risks of prolonged use.⁴⁹

5. Discussion and Conclusions

In October 2017, the HHS declared that the opioid overdose epidemic was a public health emergency.⁵⁰ According to the Centers for Disease Control and Prevention, nearly 400,000

⁴⁸ *Ibid.*

⁴⁹ *Ibid.*

⁵⁰ U.S. Department of Health and Human Services. HHS Acting Secretary declares public health emergency to address national opioid crisis. October 26, 2017. <https://www.hhs.gov/about/news/2017/10/26/hhs-acting-secretary-declares-public-health-emergency-address-national-opioid-crisis.html>. Accessed November 4, 2019.

people in the U.S. died from an opioid-related overdose from 1999 to 2017.⁵¹ As the opioid overdose epidemic continues, there is a constant need to reassess the factors responsible for this crisis. The inappropriate scheduling of tramadol in schedule IV of the CSA likely is one of the many factors contributing to this ongoing epidemic.

The DEA, FDA, and HHS have an ongoing responsibility to reexamine whether opioids are being regulated appropriately, particularly when new information signals the need to change the indications, labeling, warnings, and scheduling of currently marketed opioids. In a 2017 report commissioned by the FDA, the National Academies of Sciences, Engineering, and Medicine issued detailed recommendations for creating a new opioid regulatory framework that incorporates public health considerations into all opioid-related regulatory decisions, including those related to initial scheduling and rescheduling.⁵²

As outlined in this petition, since the DEA's 2014 decision to place tramadol in schedule IV, there have been several important developments that provide more than sufficient justification for rescheduling the drug from schedule IV to schedule II to better protect public health, including the following:

- (1) The FDA-approved product labeling for tramadol has been revised to include an indication and boxed warnings about the risks of addiction, abuse, misuse, and life-threatening respiratory depression that are nearly identical to the indications and boxed warnings found in the product labeling for schedule II short-acting opioids, such as oxycodone.
- (2) There now is clear recognition that patients who have a CYP2D6 genotype that makes them ultra-rapid metabolizers of tramadol into the M1 metabolite, which has a several-hundred-fold greater affinity for μ -opioid receptor in vitro than the parent compound, are at significantly increased risk of having life-threatening or fatal respiratory depression even at the FDA-approved dosage. A substantial proportion of the population has this ultra-rapid metabolizer phenotype, including 1-10% of whites, 3-4% of African Americans, 1-2% of East Asians, and greater than 10% of certain other racial/ethnic groups (Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, and Puerto Rican). The FDA-approved product labeling now warns that individuals who are ultra-rapid metabolizers should not use tramadol. However, few people know whether they are ultra-rapid metabolizers of tramadol because CYP2D6 genotyping generally is not performed prior to prescribing tramadol to patients.
- (3) Since the DEA rescheduled hydrocodone combination products from schedule III to schedule II of the CSA, tramadol has become one of the most commonly prescribed opioids in the U.S. For example, tramadol went from the least frequently prescribed opioid before the scheduling change to the most commonly prescribed non-hydrocodone

⁵¹ Scholl L, Seth P, Kariisa M, et al. Drug and opioid-involved overdose deaths — United States, 2013–2017. *MMWR Morb Mortal Wkly Rep.* 2019;67(5152):1419-1427.

⁵² National Academies of Science, Engineering and Medicine. *Pain management and the opioid epidemic: Balancing societal and individual benefits and risks of prescription opioid use.* 2017. Washington, DC: The National Academies Press. doi: <https://doi.org/10.17226/24781>.

opioid in California and Michigan, and to the second most commonly prescribed non-hydrocodone opioid in New York, trailing behind only oxycodone.

- (4) The NSDUH survey revealed that the estimated numbers of people aged 12 and older in the U.S. who misused tramadol in 2016, 2017, and 2018 were approximately 1.6, 1.8, and 1.5 million, respectively, which exceeded the estimated numbers of people who misused many schedule II opioids, including morphine, fentanyl, oxymorphone, Demerol (meperidine), and hydromorphone. Moreover, for the interval of 2016 through 2018, the proportion of people using tramadol who misused the drug exceeded the corresponding proportions of people who misused Demerol and morphine and was approximately two-thirds as high as the corresponding proportions of people who misused fentanyl, hydrocodone, and oxycodone.
- (5) New research published since tramadol was placed in schedule IV of the CSA in 2014 has established a clear association between tramadol use and an increased mortality risk.
- (6) Recently published studies demonstrated that the risk of long-term opioid use following an initial opioid prescription — particularly for use in treating pain after surgery, one of the most common uses of tramadol — was greater with tramadol than with short-acting schedule II opioids, including short-acting hydrocodone and oxycodone.

The widespread but clearly false assumption that tramadol is safer; is less likely to cause misuse, dependence, and addiction; and has a better safety profile than schedule II and schedule III opioids is due primarily to its inappropriate placement in schedule IV. There is overwhelming evidence that tramadol is overprescribed and, like many schedule II opioids, addictive and potentially deadly. The dangerous misperception of tramadol's safety has led to reckless overprescribing during the past several years of the opioid epidemic.

In summary, tramadol is a drug with a high potential for abuse, with use potentially leading to severe psychological or physical dependence, and given the warnings in the current FDA-approved product labeling, it is clearly considered dangerous. We therefore request that the DEA Administrator and the Commissioner of Food and Drugs immediately initiate the proceedings for rescheduling 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol, its salts, its optical and geometric isomers, and salts of these isomers (including tramadol) from schedule IV to schedule II of the CSA.

C. ENVIRONMENTAL IMPACT

We claim categorical exclusion under 21 C.F.R. § 25.31(a) from the environmental assessment requirement. An assessment is not required because the requested action would not increase the use of the active moiety that is the subject of this petition.

D. ECONOMIC IMPACT

Will be submitted upon request.

E. CERTIFICATIONS

The undersigned certify that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.



Delaram J. Taghipour, M.D.
Resident, General Preventive Medicine
Johns Hopkins Bloomberg School of Public Health
delam.taghipour@jhu.edu



Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group
mcarome@citizen.org



Sidney M. Wolfe, M.D.
Founder and Senior Adviser
Public Citizen's Health Research Group
swolfe@citizen.org

Appendix
Boxed Warning for Oxycontin⁵³

WARNING: ADDICTION, ABUSE AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

OXYCONTIN® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing OXYCONTIN and monitor all patients regularly for the development of these behaviors and conditions [see Warnings and Precautions (5.1)].

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS):

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products [see Warnings and Precautions (5.2)]. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- **complete a REMS-compliant education program,**
- **counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,**
- **emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and**
- **consider other tools to improve patient, household, and community safety.**

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of OXYCONTIN. Monitor for respiratory depression, especially during initiation of OXYCONTIN or following a dose increase. Instruct patients to swallow OXYCONTIN tablets whole; crushing, chewing, or dissolving OXYCONTIN tablets can cause rapid release and absorption of a potentially fatal dose of oxycodone [see Warnings and Precautions (5.3)].

Accidental Ingestion

Accidental ingestion of even one dose of OXYCONTIN, especially by children, can result in a fatal overdose of oxycodone [see Warnings and Precautions (5.3)].

⁵³ Purdue Pharma. Label: oxycodone (OXYCONTIN). October 2019.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022272s0431bl.pdf. Accessed November 4, 2019.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of OXYCONTIN during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see Warnings and Precautions (5.4)].

Cytochrome P450 3A4 Interaction

The concomitant use of OXYCONTIN with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving OXYCONTIN and any CYP3A4 inhibitor or inducer [see Warnings and Precautions (5.5), Drug Interactions (7), Clinical Pharmacology (12.3)].

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see Warnings and Precautions (5.6), Drug Interactions (7)].

- **Reserve concomitant prescribing of OXYCONTIN and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

[Emphasis in original]