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Citizen Petition

Submitted to:

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Date: February 9, 2022

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 initiate the proceedings to place (a) gabapentin (2-[1-(aminomethyl) cyclohexyl] acetic acid), including its salts, (including the brand name products Gralise and Neurontin) and (b) gabapentin enacarbil (1-{[({(1RS)-1-[(2-methylpropanoyl)oxy] ethoxy}carbonyl)amino]methyl} cyclohexyl) acetic acid), including its salts, (including the brand name product Horizant) into schedule V of the CSA because the drugs have a marked potential for abuse with serious consequences that include psychological effects, physical dependence, seizures, suicide, and overdose death.

Gabapentin is approved by the FDA to treat specific forms of epilepsy and neuropathic pain.[1, 2] Gabapentin enacarbil, which is approved by the FDA for treatment of primary restless legs syndrome and postherpetic neuralgia, is a prodrug of gabapentin, and, accordingly, its therapeutic effects are attributable to gabapentin.[3] From 2011 to 2017, total prescriptions for

[1] Pfizer. Label: gabapentin (NEURONTIN). December 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020235s069,020882s050,021129s050lbl.pdf. Accessed January 12, 2022.
[2] Almatica Pharma. Label: gabapentin (GRALISE). April 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022544s026lbl.pdf. Accessed January 12, 2022.
[3] Arbor Pharmaceuticals. Label: gabapentin enacarbil (HORIZANT). April 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022399s010lbl.pdf. Accessed January 12, 2022.

gabapentin doubled to 64.8 million prescriptions per year.[4] Gabapentin is structurally similar to the naturally-occurring neurotransmitter gamma-aminobutyric acid (GABA) and the drug pregabalin, the latter of which has been a schedule V drug under the CSA since 2005.[5,6] The exact mechanisms by which gabapentin exerts its analgesic and antiepileptic effects are currently unknown.[7]

The FDA-approved product labeling for gabapentin and gabapentin enacarbil states that both drugs can cause several neurologic adverse reactions including dizziness, somnolence, and fatigue, and gabapentin labeling additionally notes that the drug is associated with increased risks of ataxia (incoordination) and nystagmus (involuntary rapid eye movement).[8, 9] The labeling also warns that gabapentin and gabapentin enacarbil may cause respiratory depression when used concomitantly with central nervous system (CNS) depressants, including opioids or in a setting of underlying respiratory impairment.

There is now extensive evidence documenting the abuse potential of gabapentin and increasing misuse, abuse, and dependence of the drug. For example, the DEA's Diversion Control Division's information sheet for gabapentin[10] notes the following:

(1) Like pregabalin, "sedative and/or psychedelic effects" may result from gabapentin use.

(2) Reports to the American Association of Poison Control Centers in 2016 related to gabapentin exceeded 72,000, up from just 5,889 four years earlier.

(3) A 2008 study in the Appalachian region of Kentucky found that 15% of adults reporting nonmedical use of pharmaceuticals said they used gabapentin to "get high."

(4) A 2013 study from the United Kingdom (U.K.) observed a lifetime prevalence of gabapentin misuse of 1.1% among 1,500 persons age 16 to 59 responding to an online survey.

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[4] Drug Enforcement Administration. Diversion Control Division. Drug & Chemical Evaluation Section. Gabapentin (Neurontin®). September 2019. https://www.deadiversion.usdoj.gov/drug_chem_info/gabapentin.pdf#search=gabapentin. Accessed February 6, 2022.
[5] *Ibid.*
[6] 70 FR 43633-43635.
[7] Drug Enforcement Administration. Diversion Control Division. Drug & Chemical Evaluation Section. Gabapentin (Neurontin®). September 2019. https://www.deadiversion.usdoj.gov/drug_chem_info/gabapentin.pdf#search=gabapentin. Accessed February 6, 2022.
[8] Pfizer. Label: gabapentin (NEURONTIN). December 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020235s069,020882s050,021129s050lbl.pdf. Accessed January 12, 2022.
[9] Arbor Pharmaceuticals. Label: gabapentin enacarbil (HORIZANT). April 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022399s010lbl.pdf. Accessed February 6, 2022.
[10] Drug Enforcement Administration. Diversion Control Division. Drug & Chemical Evaluation Section. Gabapentin (Neurontin®). September 2019. https://www.deadiversion.usdoj.gov/drug_chem_info/gabapentin.pdf#search=gabapentin. Accessed February 6, 2022.

(5) The National Forensic Laboratory Information System and the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) system have both observed hundreds to thousands of surveillance reports between 2002 and 2017 indicating that gabapentin is increasingly being diverted illegally across the U.S.

Despite the well-documented abuse and misuse of gabapentin and its strong similarity to pregabalin, already in schedule V, gabapentin is still dangerously unscheduled. Accordingly, surveillance and control activities that can reduce the dangers of gabapentin abuse and misuse are urgently needed. Such public health activities will only be properly addressed when gabapentin is added to schedule V. Importantly, as of November 2020, seven states already had classified gabapentin as a schedule V drug, while another 12 states had required gabapentin prescription monitoring.[11] In the U.K., both gabapentin and pregabalin have been scheduled as controlled substances since 2019.[12]

A. ACTION REQUESTED

Promptly initiate the proceedings to place (a) gabapentin (2-[1-(aminomethyl) cyclohexyl] acetic acid), including its salts, and all products containing gabapentin (including the brand name products Gralise and Neurontin) and (b) gabapentin enacarbil (1-{[({(1RS)-1-[(2-methylpropanoyl)oxy]ethoxy} carbonyl)amino]methyl} cyclohexyl) acetic acid), including its salts, (including the brand name product Horizant) into schedule V of the CSA.

B. STATEMENT OF GROUNDS

1. Background on the Controlled Substances Act[13,14]

The DEA schedule classifies select and uniquely dangerous drugs into five distinct categories from schedule I, which contain illegal substances such as heroin and LSD, to schedule V which contains drugs with relatively low (though still substantial) abuse potential, including low-dose narcotics (for example, Robitussin AC [codeine and guaifenesin]) and other non-narcotic medication (for example, Lomotil [diphenoxylate-atropine] and Lyrica [pregabalin]). Drugs are placed on a given schedule largely because of their abuse potential, the highest abuse potential pertaining to schedules I and II and the lowest abuse potential to schedule V.[15]

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[11] Campbell LS, Coomer TN, Jacob GK, Lenz RJ. Gabapentin controlled substance status. *J Am Pharm Assoc*. 2021;61(4):e218-e224.
[12] U.K. Care Quality Commission. Controlled drugs: pregabalin and gabapentin. April 22, 2021. https://www.cqc.org.uk/guidance-providers/adult-social-care/controlled-drugs-pregabalin-gabapentin. Accessed February 6, 2022.
[13] Drug Enforcement Administration. Drug scheduling. https://www.dea.gov/drug-information/drug-scheduling. Accessed February 6, 2022.
[14] 21 C.F.R. §§ 1306.12 and 1306.22.
[15] Drug Enforcement Agency. Drug scheduling. https://www.dea.gov/drug-information/drug-scheduling. Accessed February 6, 2022.

A drug can only be scheduled if it is hazardous and has abuse potential. The following are four abuse indicators cited by the DEA that warrant controls required by the scheduling of a given drug:

(1) There is evidence that individuals are taking the drug in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community.

(2) There is significant diversion of the drug from legitimate drug channels.

(3) Individuals are taking the drug on their own initiative rather than on the basis of medical advice from a practitioner.

(4) The drug is a new drug so related in its action to a drug or other substance already listed as having a potential for abuse to make it likely that the drug will have the same potential for abuse as such drugs, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.[16]

In determining the schedule into which a drug should be placed, the DEA must consider the following eight factors listed in Section 201(c) of the CSA [21 U.S.C. § 811(c)][17]:

(1) The drug's actual or relative potential for abuse;

(2) Scientific evidence of the drug's pharmacological effect, if known;

(3) The state of current scientific knowledge regarding the substance;

(4) The drug's history and current pattern of abuse;

(5) The scope, duration, and significance of abuse;

(6) What, if any, risk there is to public health;

(7) The drug's psychic or physiological dependence liability; and

(8) Whether the substance is an immediate precursor of a substance already controlled.

The DEA defines schedule V drugs as follows: [18]

[16] Drug Enforcement Agency. Drugs of Abuse: A DEA Resource Guide. 2020 Edition. https://www.getsmartaboutdrugs.gov/sites/getsmartaboutdrugs.com/files/publications/Drugs%20of%20Abuse%202020-Web%20Version-508%20compliant.pdf. Accessed February 6, 2022.
[17] *Ibid.*
[18] *Ibid.*

- The drug has a low potential for abuse relative to the drugs or other substances in schedule IV.

- The drug or other substance has a currently accepted medical use in treatment in the United States.

- Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule IV.

Scheduling further establishes federal authority to require manufacturers, distributors, and health care providers to distribute or prescribe a controlled drug using specific procedures that limit and trace the drug as it is produced, shipped, and prescribed to patients.[19]

Subsequent sections of this petition discuss why gabapentin should be classified in schedule V based on the DEA criteria described above.

2. Background on gabapentin

a. Description

Gabapentin, which is marketed under the brand names Gralise and Neurontin and in multiple generic formulations, is structurally related to the naturally occurring inhibitory neurotransmitter GABA but has no effect on GABA binding, uptake, or degradation.[20] Gabapentin enacarbil, which is marketed under the brand name Horizant, is a prodrug of gabapentin, and, therefore, its therapeutic effects are attributable to gabapentin.[21] Gabapentin is also very similar in structure to pregabalin, which is marketed under the brand name Lyrica (see Exhibit 1 below).

The exact mechanisms of action for gabapentin's analgesic and antiepileptic effects are unknown.[22] *In vitro* studies have shown that gabapentin binds with high affinity to the α2β subunit of voltage-activated calcium channels; however, the relationship of this binding to the therapeutic effects of gabapentin is unknown.[23]

In vitro studies show that gabapentin binds to areas of the rat brain including the neocortex and hippocampus;[24] the neocortex corresponds to anatomical regions involved in the most complex brain functions including sensory perception, emotional regulation, attention, and problem solving, and the hippocampus is specifically involved in learning and memory.

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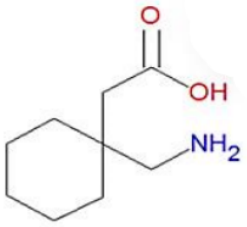
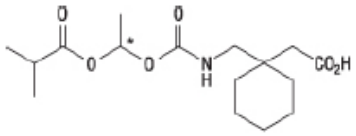
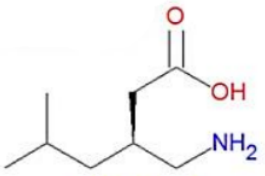
[19] *Ibid.*
[20] Pfizer. Label: gabapentin (NEURONTIN). December 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020235s069,020882s050,021129s050lbl.pdf. Accessed February 6, 2022.
[21] Arbor Pharmaceuticals. Label: gabapentin enacarbil (HORIZANT). April 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022399s010lbl.pdf. Accessed February 6, 2022.
[22] *Ibid.*
[23] *Ibid.*
[24] Almatica Pharma. Label: gabapentin (GRALISE). April 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022544s026lbl.pdf. Accessed February 6, 2022.

It is further hypothesized that gabapentin antagonizes thrombospondin binding to α2δ-1, a receptor involved in excitatory synapse formation, and that gabapentin may function therapeutically by blocking formation of new synapses.[25,26] Thrombospondin is a natural astrocyte-secreted protein that binds to the growth factor domain of the α2δ-1 neuronal cell surface receptor, which is involved in excitatory synapse formation. *In vitro* and i*n vivo* rodent studies support this synapse formation pathway and further show that gabapentin powerfully inhibits it.[27]

Exhibit 1. Chemical structure of gabapentin, gabapentin enacarbil, and pregabalin

Drug (Brands)	Gabapentin (Neurontin,[28] Gralise[29])	Gabapentin Enacarbil (Horizant)[30]	Pregabalin (Lyrica)[31]
Full Name	2-[1-(aminomethyl) cyclohexyl] acetic acid	1-{[({(1RS)-1-[(2-methylpropanoyl)oxy] ethoxy}carbonyl)amino]methyl} cyclohexyl) acetic acid	(s)-3-(aminomethyl)-5-methylhexanoic acid
Molecular Formula	$C_9H_{17}NO_2$	$C_{16}H_{27}NO_6$	$C_8H_{17}NO_2$
Molecular Weight	171.24	329.39	159.23
Chemical Structure[32]			

[25] *Ibid.*
[26] Eroglu C, Allen NJ, Susman MW, et al. The gabapentin receptor α2δ-1 is a neuronal thrombospondin receptor responsible for excitatory CNS synaptogenesis. *Cell*. 2009; 139(2):380-392.
[27] *Ibid.*
[28] Pfizer. Label: gabapentin (NEURONTIN). December 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020235s069,020882s050,021129s050lbl.pdf. Accessed February 6, 2022.
[29] Almatica Pharma. Label: gabapentin (GRALISE). April 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022544s026lbl.pdf. Accessed February 6, 2022.
[30] Arbor Pharmaceuticals. Label: gabapentin enacarbil (HORIZANT). April 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022399s010lbl.pdf. Accesses February 62, 2022.
[31] Pfizer. Label: pregabalin (LYRICA). April 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021446s040,%20022488s017lbl.pdf. Accessed February 6, 2022.
[32] Drug Enforcement Administration. Diversion Control Division. Drug & Chemical Evaluation Section. Gabapentin (Neurontin®). September 2019. https://www.deadiversion.usdoj.gov/drug_chem_info/gabapentin.pdf#search=gabapentin. Accessed February 6, 2022.

b. FDA-approved indications and dosages

Gabapentin was first approved by the FDA in 1993 under the brand name Neurontin as adjunctive therapy in the treatment of partial-onset seizures, with or without secondary generalization, in adults with epilepsy.[33] Neurontin is now also FDA-approved as adjunctive therapy in the treatment of partial-onset seizures in adult and pediatric patients 3 years and older with epilepsy and for postherpetic neuralgia (a painful, months-to-years–long condition that sometimes follows a shingles outbreak caused by the varicella zoster virus) in adults.[34]

The maximum recommended dose of Neurontin for treatment of postherpetic neuralgia is 600 milligrams (mg) three times daily (total daily dose of 1,800 mg).[35] The recommended maintenance dose of Neurontin for treatment of epilepsy with partial-onset seizures in adults is 300 to 600 mg three times daily; according to the product labeling, dosages up to 800 mg three times daily (total daily dose 2,400 mg) were tolerated in long-term clinical trials, and doses of 1,200 mg three times daily (total daily dose 3,600 mg) were tolerated in a small number of patients for a relatively short duration.[36]

Gabapentin also is marketed under the brand name Gralise, which is approved only for management of postherpetic neuralgia.[37] Importantly, the product labeling for Gralise states that "Gralise is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration."[38] Gralise is administered only once daily, at a maximum dose of 1,800 mg.

Gabapentin enacarbil was first approved by the FDA under the brand name Horizant in 2011 for treatment of moderate-to-severe primary restless legs syndrome in adults.[39] It was subsequently approved for treatment of postherpetic neuralgia in adults. The maximum recommended dosage of Horizant for restless legs syndrome is 600 mg once daily at about 5 p.m., and for postherpetic neuralgia 600 mg two times daily (total daily dosage of 1,200 mg).[40] "Horizant provides approximately dose-proportional and extended exposure to gabapentin over the range 300 to

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[33] Food and Drug Administration. Medical review(s), new drug application 21-216, supplement 15. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21-216.pdf_Neurontin_Medr_P1.pdf. Accessed February 6, 2022.
[34] Pfizer. Drug label: gabapentin (NEURONTIN). December 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020235s069,020882s050,021129s050lbl.pdf. Accessed February 6, 2022.
[35] Pfizer. Label: gabapentin (NEURONTIN). December 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020235s069,020882s050,021129s050lbl.pdf. Accessed February 6, 2022.
[36] *Ibid.*
[37] Almatica Pharma. Label: gabapentin (GRALISE). April 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022544s026lbl.pdf. Accessed February 6, 2022.
[38] *Ibid.*
[39] Arbor Pharmaceuticals. Label: gabapentin enacarbil (HORIZANT). April 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022399s010lbl.pdf. Accessed February 6, 2022.
[40] *Ibid.*

6,000 mg. [Gabapentin enacarbil] and gabapentin are not interchangeable because the same daily dose of each results in different plasma concentrations of gabapentin."[41]

Gabapentin and gabapentin enacarbil dosages must be decreased in patients with decreased kidney function.[42,43,44]

c. Scheduling

Gabapentin is presently unscheduled by the DEA. However, as of November 2020, seven states (Alabama, Kentucky, Michigan, North Dakota, Tennessee, Virginia, and West Virginia) already had designated gabapentin as a schedule V drug, while another 12 states had required gabapentin prescription monitoring.[45] A 2022 study by Grauer and Cramer found that in three states that designated gabapentin as a schedule V drug (Kentucky, Tennessee, and West Virginia), there was a reduction in the total days' supply of gabapentin prescribed per Medicare Part D enrollee compared with the total days' supply prescribed to such enrollees in ten control states that had no state-imposed restrictions on gabapentin and were in the top quartile of all states for opioid prescribing per capita.[46] In contrast, Grauer and Cramer also found that in nine states that only had implemented a prescription drug monitoring program (PDMP) for gabapentin (Kansas, Massachusetts, Minnesota, Nebraska, New Jersey, North Dakota, Ohio, Virginia, and Wyoming), there was little change in the total days' supply of gabapentin prescribed per Medicare Part D enrollee compared with the 39 control states that had no PDMP or scheduling for gabapentin during the period covered by this analysis (2013 to 2018).

In 2019, the U.K. formally classified both gabapentin and pregabalin, which are members of the family of drugs that inhibit GABA called "gabapentinoids," as Schedule 3 controlled substances under its Misuse of Drugs Regulations of 2001 and as class C controlled substances under its Misuse of Drugs Act of 1971.[47] As such, prescriptions for these drugs in the U.K. must clearly define the dose, are valid for a maximum of 28 days after the date on the prescription, and the maximum quantity prescribed should not exceed a 30-day supply.[48] It is notable that one of the stakeholders engaged in the U.K. scheduling decision was that country's Chief Inspector of

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[41] *Ibid.*
[42] Pfizer. Drug label: gabapentin (NEURONTIN). December 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020235s069,020882s050,021129s050lbl.pdf. Accessed February 6, 2022.
[43] Almatica Pharma. Label: gabapentin (GRALISE). April 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022544s026lbl.pdf. Accessed February 6, 2022.
[44] Arbor Pharmaceuticals. Label: gabapentin enacarbil (HORIZANT). April 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022399s010lbl.pdf. Accessed February 6, 2022.
[45] Campbell LS, Coomer TN, Jacob GK, Lenz RJ. Gabapentin controlled substance status. *J Am Pharm Assoc*. 2021;61(4):e218-e224.
[46] Grauer JS, Cramer JD. Association of state-imposed restrictions on gabapentin with changes in prescribing in Medicare. *J Gen Intern Med.* 2022 Jan 11. doi: 10.1007/s11606-021-07314-2. Epub ahead of print.
[47] U.K. Care Quality Commission. Controlled drugs: pregabalin and gabapentin. April 22, 2021. https://www.cqc.org.uk/guidance-providers/adult-social-care/controlled-drugs-pregabalin-gabapentin. Accessed February 6, 2022.
[48] *Ibid.*

Prisons, who had reported diversion of prescription gabapentinoids among "high security and vulnerable prisoner populations."[49]

3. Background on pregabalin

Pregabalin, which is marketed under the brand name Lyrica, was first approved by the FDA in 2004. It is currently approved for the following:

- Management of pain associated with diabetic peripheral neuropathy
- Management of postherpetic neuralgia
- Adjunctive therapy for the treatment of partial-onset seizures in patients one month of age or older
- Management of fibromyalgia
- Management of neuropathic pain associated with spinal cord injury.[50]

In 2005, the DEA placed pregabalin [(S)-3-(aminomethyl)-5-methylhexanoic acid], including its salts, and all products containing pregabalin into schedule V of the CSA.[51] As noted above, pregabalin has been classified as a controlled substance in the U.K. since 2019.

4. Gabapentin's hazards to human health

a. FDA-approved product labeling warnings, precautions, and adverse reactions

Comparing the FDA-approved labels for gabapentin (Neurontin, Gralise) and gabapentin enacarbil (Horizant) with the label for pregabalin (Lyrica) reveals extremely similar risk profiles across these gabapentinoids.[52,53,54,55] The FDA-approved product labeling for all four brand-name products lists increased risks of suicidal behavior and ideation and of respiratory depression as prominent warnings and precautions. Respiratory depression with use of both gabapentin and pregabalin is specifically linked to concomitant use of other CNS depressants such as opioids.

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[49] Gov. U.K. Home Office. A consultation on proposals to schedule pregabalin and gabapentin under the Misuse of Drugs Regulations 2001. Government response to the consultation. September 15, 2018.
[50] Pfizer. Label: pregabalin (LYRICA). April 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021446s040,%20022488s017lbl.pdf. Accessed February 6, 2022.
[51] 70 FR 43633-43635.
[52] Pfizer. Drug label: gabapentin (NEURONTIN). December 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020235s069,020882s050,021129s050lbl.pdf. Accessed February 6, 2022.
[53] Almatica Pharma. Label: gabapentin (GRALISE). April 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022544s026lbl.pdf. Accessed February 6, 2022.
[54] Arbor Pharmaceuticals. Label: gabapentin enacarbil (HORIZANT). April 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022399s010lbl.pdf. Accessed February 6, 2022.
[55] Pfizer. Label: pregabalin (LYRICA). April 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021446s040,%20022488s017lbl.pdf. February 6, 2022.

The warnings and precautions section of product labeling for all of the brand-name products except Gralise further states that the drugs can cause driving impairment, somnolence, sedation, and dizziness.

Neuropsychiatric reactions in children are a unique concern noted in the product labeling for Neurontin when the drug is used to treat seizures in children aged 3 to 12 years. These neuropsychiatric reactions included emotional lability, hostility and aggressive behaviors, thought disorders, changes in school performance, restlessness, and hyperactivity. The Neurontin label specifically reports that analysis of controlled clinical trial data involving children with epilepsy found that emotional lability was evident in 6% of gabapentin users and only 1.3% of placebo users. Similarly, subjects treated with gabapentin, compared with those who received a placebo, had a higher incidence of hostility (5.2% vs. 1.3%), hyperkinesia (4.7% vs. 2.9%), and thought disorders (1.7% vs. 0%).

Clinical trial results cited within the product labeling further revealed similar common adverse reactions (i.e., adverse reactions that occurred in at least 5% of subjects treated with gabapentin or pregabalin and at least twice the rate observed in placebo-group subjects). Those common adverse events included dizziness for all four brand-name drug products and somnolence in all products except Gralise. In clinical trials of gabapentin (Neurontin) for epilepsy in patients aged 12 years and older, the following adverse events were observed in at least 8% of gabapentin-group subjects and occurred at a minimum of twice the rate of those seen in placebo-group subjects: ataxia, fatigue, and nystagmus.

Finally, the labels for Neurontin, Gralise, Horizant (if the dosage exceeds 600 mg once daily), and Lyrica warn that rapid discontinuation of the drug may increase seizure frequency in patients with seizure disorders and advises that the dosage should be gradually reduced over a minimum of one week.

b. FDA Drug Safety Communication regarding respiratory depression, 2019

On December 19, 2019, the FDA issued a Drug Safety Communication regarding the risk of respiratory depression associated with the use of both gabapentin and pregabalin.[56] Specifically, the agency warned that gabapentin or pregabalin use can result in serious breathing difficulties among individuals who have respiratory-depression risk factors. Such risk factors include the use of other respiratory depressants (such as opioids, antidepressants, anxiolytics, and antihistamines) or the presence of conditions such as chronic obstructive pulmonary disease.

The FDA Drug Safety Communication was based on data from the FDA Adverse Event Reporting System (FAERS), clinical trials, observational studies, and animal studies.

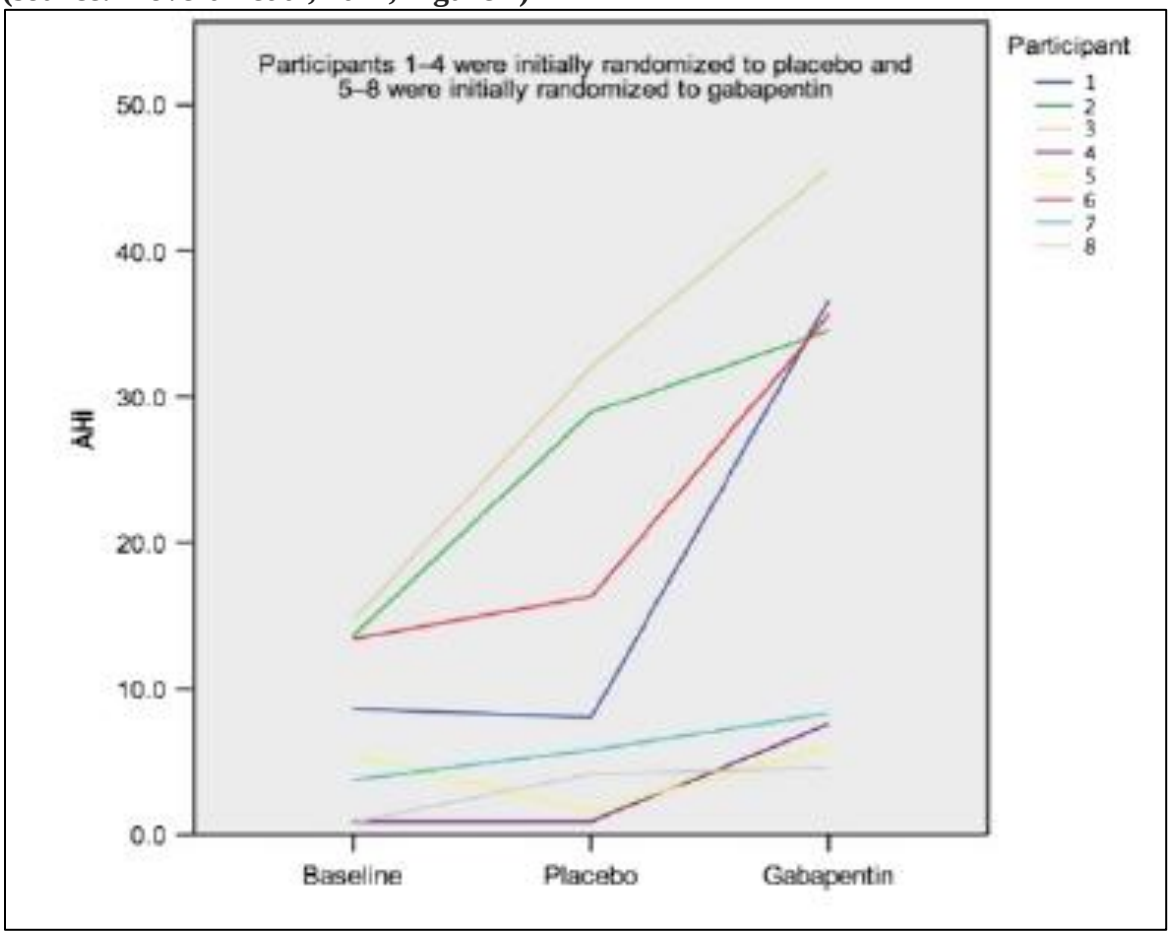
[56] Food and Drug Administration. Drug Safety Communication: FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR) when used with CNS depressants or in patients with lung problems. December 19, 2019. https://www.fda.gov/media/133681/download. Accessed February 6, 2022.

The FDA's review of FAERS data from January 1, 2012 to October 26, 2017 identified 49 cases of respiratory depression in patients taking gabapentin (15 cases) or pregabalin (34 cases). Twelve cases resulted in death, all of which coincided with least one risk factor for developing respiratory depression or concomitant use of a CNS depressant. Because FAERS relies on voluntary passive surveillance, these numbers significantly underestimate the preventable respiratory morbidity and mortality that occurred because of respiratory depression caused by use or misuse of gabapentin and pregabalin.

The FDA Drug Safety Communication cited one small double-blind, placebo-controlled randomized trial that showed that exposure to only a single dose of gabapentin prior to sleep resulted in a significant increase in apnea-hypopnea episodes and hypoxic events during sleep compared with exposure to a placebo.[57] The trial, published by Piovezan et al in 2017, enrolled eight healthy, older (aged 60 to 89 years, mean=71 years), non-obese men in a crossover study in which four were randomized to first receive a single 300-mg dose of gabapentin at bedtime and the other four received a placebo at bedtime. After a one-week washout period, the subjects crossed over to the other intervention arm. The primary outcome measures were the number of apnea-hypopnea episodes per hour of total sleep time (the apnea-hypopnea index [AHI]) and the number of episodes of oxygen desaturation per hour of total sleep time (oxygenation desaturation index) during the night of sleep immediately following administration of gabapentin or placebo. Both measures showed substantial and potentially harmful gabapentin effects. The AHI was 22.4 ± 6.1 episodes/hour for gabapentin versus 12.2 ± 4.3 episodes/hour for placebo ($p \leq 0.05$). The oxygenation desaturation index was 20.6 ± 5.8 episodes/hour for gabapentin versus 10.8 ± 3.9 episodes/hour for placebo ($p \leq 0.05$). The trial authors concluded that "gabapentin worsened sleep breathing acutely compared to placebo."[58] Exhibit 2 below, excerpted from Piovezan et al, 2017, shows the subject-by-subject AHI results.

[57] Piovezan RD, Kase C, Moizinho R, et al. Gabapentin acutely increases the apnea-hypopnea index in older men: data from a randomized, double-blind, placebo-controlled study. *J Sleep Res.* 2017;26(2):166-170.
[58] *Ibid.*

Exhibit 2. Individual apnea–hypopnea index from the baseline to the study interventions. (source: Piovezan et al, 2017, Figure 2)



The FDA's Drug Safety Communication also cited a series of three observational studies conducted by researchers at the Mayo Clinic showing that preoperative exposure to gabapentin is associated with an increased risk of postoperative respiratory depression. For example, Weingarten et al at the Mayo Clinic retrospectively reviewed medical records for 11,970 patients who underwent joint arthroplasty with multimodal analgesia from 2008 to 2012.[59] Of these patients, 2,836 experienced postoperative respiratory depression. Using multivariate analysis, the researchers found that administration of high-dose gabapentin (>300 mg), compared with no gabapentin use preoperatively, was associated with a higher incidence of postoperative respiratory depression in patients who received general anesthesia (odds ratio [OR]=1.47; 95% confidence interval [CI]: 1.26-1.70) or peripheral nerve blockade (OR=1.60; 95% CI: 1.27-2.02). A subsequent, similarly designed study conducted at the Mayo Clinic by Cavalcante et al involving 8,567 patients undergoing major laparoscopic procedures from January 2010 to July

[59] Weingarten TN, Jacob AK, Njathi CW, et al. Multimodal analgesic protocol and postanesthesia respiratory depression during phase I recovery after total joint arthroplasty. *Reg Anesth Pain Med*. 2015;40(4):330-336.

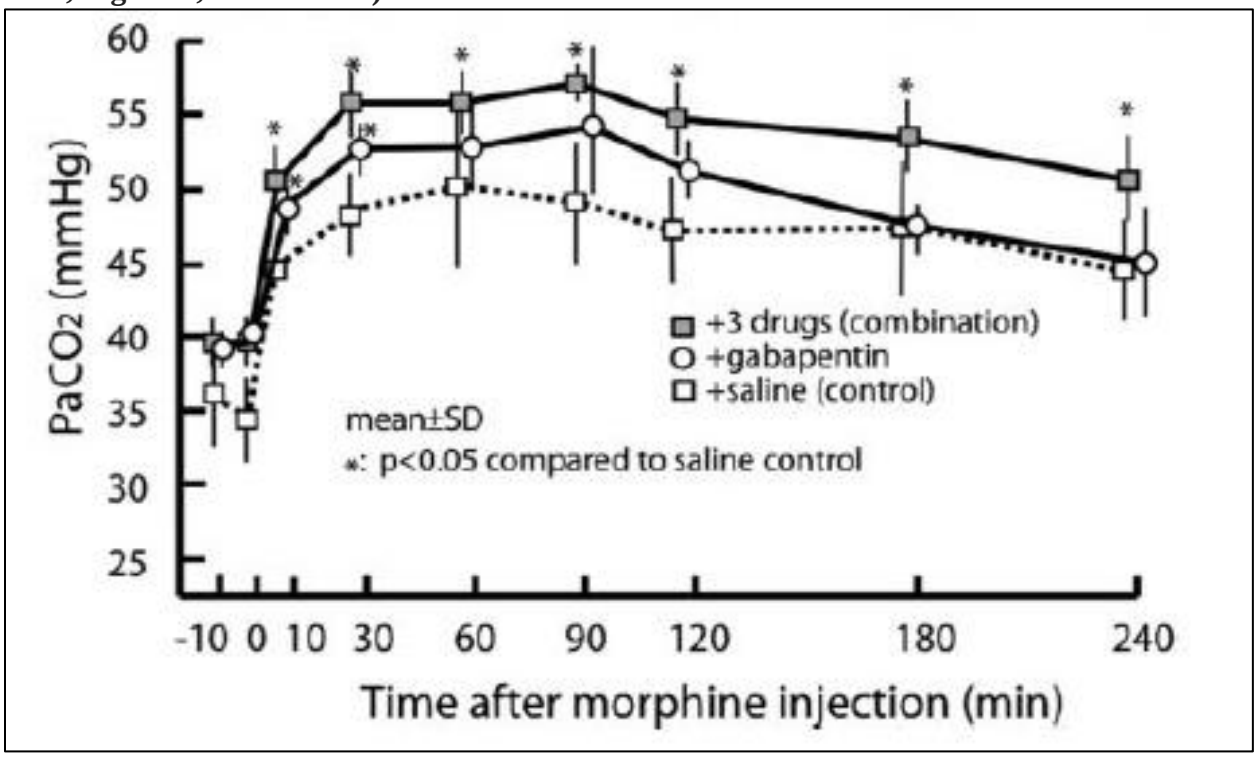
2014 found preoperative gabapentin use again was associated with a higher incidence of postoperative respiratory depression (OR=1.47; 95% CI: 1.22-1.76).[60]

The third Mayo Clinic study by Deljou et al assessed the association between chronic (home) use and preoperative or postoperative administration of either gabapentin or pregabalin and the risk of severe oversedation or respiratory depression as inferred from the use of naloxone.[61] The researchers retrospectively identified 128 surgical patients who had undergone general anesthesia from 2011 to 2016 and were administered naloxone within 48 hours of the surgery, and then compared them to 256 matched control patients who did not require naloxone rescue during the same postsurgery interval. Controls were matched to cases on age, sex, exact type of surgical procedure, and date of surgery within two years. Using multivariate regression models, the researchers found that home use combined with postoperative use of gabapentinoids (compared with no use) was associated with a markedly increased risk of postoperative need for naloxone rescue (OR=6.30; 95% CI: 2.38-16.66). The researchers concluded that the most important result of their study "was that gabapentinoid therapy and its continuation into the postoperative period were associated with over-narcotization requiring naloxone administration."[62]

Finally, the FDA Drug Safety Communication cited three animal studies demonstrating the respiratory depression risks associated with gabapentinoid use. In one of these studies that was published in 2008, Kozer et al showed that rabbits administered a single intravenous dose of morphine (5 mg/kg) after four daily subcutaneous injections of gabapentin (25 mg/kg) had greater CO_2 retention at 10 and 30 minutes after the morphine injection than rabbits administered a single intravenous dose of morphine after four daily subcutaneous injections of normal saline (see Exhibit 3 below, excerpted from Kozer et al, 2008).[63]

[60] Cavalcante AN, Sprung J, Schroeder DR, Weingarten TN. Multimodal analgesic therapy with gabapentin and its association with postoperative respiratory depression. *Anesth Analg*. 2017;125(1):141-146.
[61] Deljou A, Hedrick SJ, Portner ER, et al. Pattern of perioperative gabapentinoid use and risk for postoperative naloxone administration. *Br J Anaesth*. 2018;120(4):798-806.
[62] *Ibid*.
[63] Kozer E, Levichek Z, Hoshino N, et al. The effect of amitriptyline, gabapentin, and carbamazepine on morphine-induced hypercarbia in rabbits. *Anesth Analg*. 2008;107(4):1216-22.

Exhibit 3. Arterial blood CO_2 levels at various time points after morphine injection in rabbits (N=6 per group) pretreated with four daily doses of gabapentin or normal saline (or a combination of amitriptyline, carbamazepine and gabapentin) (source: Kozer et al., 2008, Figure 1, bottom half)



c. Further evidence linking perioperative coadministration of gabapentinoids and opioids to respiratory depression

Adding to the previously discussed clinical evidence presented in the FDA's December 2019 Drug Safety Communication regarding the risk of respiratory depression associated with the perioperative use of either gabapentin or pregabalin, Bykov et al conducted a retrospective cohort study that was published in 2020 to evaluate the association between perioperative coadministration of gabapentinoids (either gabapentin or pregabalin) and opioids with inpatient opioid-related adverse events in surgical patients.[64] They analyzed data from a large research database that contained data on approximately 20% of annual hospital admissions in the U.S. From this database, the researchers identified a cohort of 5.5 million adults who underwent major surgery from 2007 to 2017, of whom 892,484 were administered a gabapentinoid (61.2% received gabapentin) with an opioid. The primary outcome was opioid overdose (defined as use of naloxone) prior to discharge (with a maximum follow-up of 30 days). The researchers identified 441 overdose events overall corresponding to an absolute risk of 1.4 events per 10,000 patients with gabapentinoid exposure and 0.7 events per 10,000 patients receiving opioids alone. Propensity matching using a qualifying subsample of more than 3.7 million patients (3.0 million

[64] Bykov K, Bateman BT, Franklin JM et al. Association of gabapentinoids with the risk of opioid-related adverse events in surgical patients in the United States. *JAMA Netw Open*. 2020;3(12):e2031647.

opioids only, 0.73 million opioids plus a gabapentinoid), with statistical adjustment for demographic, case severity, and other variables, yielded an adjusted hazard ratio for overdose of 1.95 (95% CI: 1.49-2.55). Post-hoc analyses further did not observe a significant difference between gabapentin exposure (adjusted hazard ratio=1.84; 95% CI: 1.35-2.51) and pregabalin exposure (adjusted hazard ratio=2.49; 95% CI: 1.70-3.65).

d. Off-label use of gabapentin

In 2019, Zhou et al published a cross-sectional study using data from the National Ambulatory Medical Care Survey (NAMCS) that examined the trends of patient and prescriber characteristics and the diagnoses associated with U.S. ambulatory care visits involving gabapentinoids (gabapentin or pregabalin for adult visits) from 2003 to 2016.[65] The overall weighted estimate of the number of ambulatory visits involving gabapentinoids during the study period was 260.1 million (with 208.9 million visits for gabapentin and 53.7 million visits for pregabalin). The researchers observed that gabapentinoid-involved visits increased from 9.1 per 1,000 visits in 2003 to 34.9 in 2016 for U.S. adults age 18-64 years (a nearly a fourfold increase). Additionally, they found that across the 208.9 million visits that involved gabapentin, the drug was prescribed by primary care physicians in 45.8% of those visits, whereas psychiatrists and neurologists were the prescribing physicians in only 5.5% and 8.4% of visits, respectively. Finally, the NAMCS data revealed that 98.3% of all gabapentin prescriptions were for indications not approved by the FDA (an unapproved use was defined as a visit involving gabapentin without an FDA-approved indication for the drug among the first three physician-reported diagnoses). By comparison, the proportion of all pregabalin prescriptions for unapproved indications was slightly lower at 89.9%, presumably, in part, because pregabalin is currently placed in schedule V.

Importantly, opportunities for misuse, abuse, and diversion of gabapentin have increased because the drug now is prescribed for numerous off-label indications, including the following:

- Alcohol use disorder or alcohol withdrawal
- Chronic cough
- Fibromyalgia
- Hiccups
- Postoperative pain
- Pruritus, chronic
- Social anxiety disorder
- Vasomotor symptoms tied to menopause[66]

[65] Zhou L, Bhattacharjee S, Kwoh CK, et al. Trends, patient and prescriber characteristics in gabapentinoid use in a sample of United States ambulatory care visits from 2003 to 2016. *J Clin Med*. 2019;29:9(1):83.
[66] Gabapentin: Drug Information. *UpToDate*. Topic 8483 Version 445.0. www.uptodate.com. Accessed July 17, 2020.

e. Increasing evidence of gabapentin harms including misuse, abuse, and diversion.

The next several subsections provide evidence directly addressing the first three of the four indicators cited by DEA documentation that abuse concerns warrant the controls conveyed with the scheduling of a given drug. Specifically, we present summaries of representative recent systematic reviews and primary research studies that provide evidence for each of the following: (1) Individuals are taking gabapentin in amounts sufficient to create a hazard to their health or to the safety of other individuals or to the community, (2) there is significant diversion of gabapentin from legitimate drug channels, and (3) individuals are using gabapentin on their own initiative rather than on the basis of medical advice from a health care practitioner.

i. Systematic reviews documenting misuse, abuse, and addiction potential of gabapentin

Five recent systematic reviews provided evidence of the harms associated with gabapentin abuse, misuse, and diversion. These reviews also offer additional details about the physiological harms of gabapentin use that were summarized above in the section about current FDA product labels and warnings for gabapentin and pregabalin (section 4.a). These harms include serious neurologic and psychiatric adverse effects, respiratory depression, and death. The five systematic reviews are summarized in chronological order of publication.

Smith et al, Addiction, *2016*

The first systematic review, published by Smith et al. in 2016, identified 23 case studies and 11 epidemiological reports offering empirical information about the misuse or abuse of gabapentin.[67] The authors defined *misuse* as the use of a drug in a manner or for a purpose other than those indicated, including, but not limited to, taking another person's medication, unprescribed or nonrecommended route of administration, or a higher dosage than prescribed, and *abuse* as persistent use of a drug despite negative consequences. Twenty-three of the 34 case studies and reports included in the review came from the U.S., with others presenting data from the U.K. (n=4), Germany (n=1), Finland (n=1), India (n=1), South Africa (n=1), and France (n=1). One report analyzed websites in English, German, Spanish, Italian, Dutch, Norwegian, Finnish, and Swedish and another analyzed websites from unspecified countries.

Smith et al identified only one study (Kapil et al, described in more detail below) that provided an estimate of 1.1% for the lifetime prevalence of gabapentin abuse in the general population in the U.K.

Smith et al further deduced from the reviewed literature that gabapentin was primarily misused for recreational purposes, self-medication, or intentional self-harm and was used alone or in combination with other substances, especially opioids, benzodiazepines, or alcohol. They observed that by the early 2000s off-label use of gabapentin ranged from 83–95% of prescribed gabapentin and accounted for over 90% of all legitimate gabapentin sales. Consistent with the

[67] Smith RV, Havens JR, Walsh SL. Gabapentin misuse, abuse, and diversion: A systematic review. *Addiction*. 2016;111(7):1160-1174.

concerns about diversion and misuse of gabapentin being tied to such excessive prescribing, Smith et al reported that epidemiological studies from the U.S. and the U.K. estimated that in 40–65% of cases involving gabapentin abuse, the drug was obtained via prescription.

Evoy et al, Drugs, *2017*

Evoy et al in 2017 published a systematic review providing evidence that among individuals with substance use disorders, rates of gabapentinoid (gabapentin or pregabalin) abuse or misuse are much higher than in the general population.[68] They found that across seven studies published from 2013 to 2016, including three conducted in the U.S, 15% to 22% of patients with opioid use disorder abused gabapentin, while pregabalin abuse varied widely from 3% to 68%. Evoy et al noted that premarket clinical trials demonstrated that pregabalin produced euphoria, but this effect was not seen in premarket clinical trials for gabapentin. However, postmarket reports have noted that gabapentin produces euphoric effects in abusers of the drug at high doses.

*Bonnet and Scherbau*m, European Neuropsychopharmacology, *2017*

Bonnet and Scherbaum in 2017 published a systematic review that estimated and characterized the addiction risks of gabapentinoids.[69] The review included 106 studies, including studies on rewarding behavior of gabapentinoids (n=17; some of which were animal studies), clinical studies on gabapentinoid abuse and dependence (n=14), case studies on gabapentinoid abuse and dependence (n=38), and studies on gabapentinoid-related overdoses and fatalities (n=37). The authors concluded that although they did not find convincing evidence of a "vigorous addictive power of gabapentinoids," both gabapentin and pregabalin do pose an addiction risk for patients with current or past substance abuse. They also determined that pregabalin appeared to be somewhat more addictive than gabapentin regarding the magnitude of behavioral dependence symptoms, transitions from prescription to self-administration, and the durability of the self-administrations.

Bonnet and Scherbaum summarized their findings with a tabulation showing that pregabalin and gabapentin have characteristics suggesting very weak to moderate abuse potential, markedly less than those for opioids, alcohol, benzodiazepines, and cannabis (see Exhibit 4, excerpted from Bonnet and Scherbaum, 2017). While Exhibit 4 indicates that the addiction risk of gabapentin and pregabalin are both weak to moderate overall, these two gabapentinoids are quite similar when they are evaluated in comparison with other substances known to have high addictive properties.

[68] Evoy KE, Morrison MD, Saklad SR. Abuse and misuse of pregabalin and gabapentin. *Drugs*. 2017;77(4):403-426.
[69] Bonnet U, Scherbaum N. How addictive are gabapentin and pregabalin? A systematic review. *Eur Neuropsychopharmacol*. 2017;27(12):1185-1215.

Exhibit 4. Addictive risks of gabapentinoids and traditional substances of abuse: a comparative appraisal (source: Bonnet and Scherbaum, 2017, Table 4)

Characteristics/substances of abuse	Opioids	Alcohol	Gabapentin	Pregabalin	Benzodia zepines	Cannabis
Self-administration behavior (animals) "Wanting"[a]	*****	****	none	*(only on "overdose")	***	**
Physical dependence (tolerance, withdrawal symptoms)	*****	****	***	***	****	**
Behavioral = psychological dependence (craving, loss of control, addictive behavior) "Wanting"[d]	*****	*****	(*)(only in patients with history of SUD)	*(especially in patients with history of SUD)	****	***
Severity of addiction[b]	*****	****	*	**	****	***
Transitions from prescription to self-administration Wanting"[a]	*****	n/a	*	**	**	(**)[c]
Relapsing behavior/durability "Wanting"[a]	*****	*****	*	**	****	****
Voluntary treatment-seeking behavior "Wanting"[a]	*****	*****	none	none	***	***
Overdose toxicity	*****	***	*	**	****	*
Social hazards (independent on co-use of other substances of abuse) "Wanting"[a]	*****	*****	n/a[d]	n/a[d]	***	***
Rapid euphorization "Liking"[a]	*****(especially intravenous)	****	**(especially on overdose)	****(especially on overdose)	****(especially on overdose)	***
Easy to obtain	****	*****	****	****	****	****
Legal control of prescription/dispensing	*****(most countries)	(**)[e]	none	*(Norway, USA)	**(e.g. flunitrazepam in Germany)	*****(most countries)

The addictive power is expressed in **"Wanting"**.

Notes:

Abbreviations: SUD = substance use disorder.

= no effects, * = very weak effects, ** = weak effects, *** = moderate effects, **** = strong effects, ***** = very strong effects. The estimation of the addictive power toxicity and safety of the gabapentinoids is based upon the present review. The estimation of the addictive power and safety of traditional drugs of abuse is based upon comprehensive reviews (e.g. Morgan, 1990; Coupey, 1997; Karoly et al., 2015; Korpi et al., 2015; Volkow and Morales, 2015; Brett and Murnion, 2015; Weaver; 2015; Bluth and Pincus, 2016; Quednow and Herdener, 2016) and the authors' expertise in the treatment of drug- and alcohol addiction (e.g. Bonnet et al., 1999; Bonnet and Gastpar, 1999; Bonnet, 2011; Bonnet et al., 2015; Scherbaum, 2016).

[a]according to Berridge and Robinson, 2016

[b]according to the mean number of fulfilled operationalized dependence-criteria (ICD-10; DSM-IV),

[c]strong overlap between medicinal and recreational cannabis users (Pacula et al., 2016).

[d]no relevant information in the literature,

[e]considering predominantly Muslim countries, laws about young people and drinking alcohol,

Hägg et al, Drug Safety, *2020*

Hägg et al in 2020 published a narrative review of 41 studies published between 2010 and 2020 regarding gabapentinoids — including pharmacovigilance studies, register-based studies, surveys, clinical toxicology studies, and forensic toxicology studies — that provided evidence of misuse (defined as any type of inappropriate use of a medicinal drug, irrespective of whether there is any dependency involved; such misuse might be accidental or even unrecognized by the patient), abuse (defined as an active and recognized nonmedical use of a substance, in most cases linked to dependence/addiction and often involving higher doses than normal), dependence, addiction (defined as a neuropsychiatric disorder characterized by a recurring desire to continue taking the drug despite harmful consequences), or overdose of gabapentinoids in humans.[70] The authors of the review concluded that (a) both gabapentin and pregabalin are being abused and misused, particularly by those with a history of drug abuse; (b) individuals with an opioid use disorder seem to be more prone to abuse gabapentinoids than those with other substance use disorders; (c) intoxications with gabapentinoids are characterized by an intake of other psychoactive substances; and (d) there seems to be an increasing number of fatalities over the last several years linked to gabapentinoids, mainly pregabalin. Hägg et al further noted that "available evidence suggests that abuse and misuse are more frequent in users of pregabalin compared with gabapentin."[71]

Evoy et al, Drugs, *2021*

Evoy et al published an updated systematic review of gabapentinoid misuse and abuse in 2021.[72] The review included 55 studies (29 from North America, 17 Europe, 6 Asia, and 3 Australia). Twenty (36.4%) studied gabapentin only, 18 (32.7%) pregabalin only, and 17 (30.9%) both gabapentin and pregabalin. The 2021 review corroborated findings from the same group's earlier 2017 systematic review[73] that gabapentin and pregabalin are increasingly being abused or misused to self-medicate and can produce rewarding effects alone but often are used concomitantly with other drugs, and that opioid use disorder is the greatest risk factor for abuse of both gabapentin and pregabalin. The review referenced single case reports and more extensive case-series reports showing that both gabapentin and pregabalin are similarly used to produce feelings of euphoria, relaxation, or disassociation. Most concerning was the finding of increased evidence of associated patient harm, including increased hospital utilization and opioid-related overdose risk. Of note, Evoy et al[74] identified seven recently published case reports or

[70] Hägg S, Jönsson AK, Ahlner J. Current evidence on abuse and misuse of gabapentinoids. *Drug Saf*. 2020;43(12):1235-1254.
[71] *Ibid.*
[72] Evoy KE, Sadrameli S, Contreras J et al. Abuse and misuse of pregabalin and gabapentin: A systematic review update. *Drugs*. 2021;81(1):125-156.
[73] Evoy KE, Morrison MD, Saklad SR. Abuse and misuse of pregabalin and gabapentin. *Drugs*. 2017;77(4):403-426.
[74] Evoy KE, Sadrameli S, Contreras J et al. Abuse and misuse of pregabalin and gabapentin: A systematic review update. *Drugs*. 2021;81(1):125-156.

series[75,76,77,78,79,80,81] that indicate that gabapentin use and misuse can lead to physical dependence and withdrawal symptoms upon sudden discontinuation of the drug.

ii. A case series linking gabapentin use and misuse by pregnant women to physical dependence and withdrawal symptoms in newborns

Withdrawal symptoms are a hallmark of the physical dependence that can result from the use of addictive substances. In 2017, Loudin et al published a case series that reviewed the clinical experience of 19 newborn infants whose umbilical cord samples tested positive for opioids and whose mothers disclosed the nonprescription use of gabapentin during pregnancy at doses ranging from 600 to 12,500 mg/day.[82] Nine of these infants were managed with methadone alone, but 10 required additional therapy with gabapentin. Fifteen of these infants demonstrated alarming withdrawal symptoms including tongue thrusting, wandering eye movements while awake, back arching, and continuous extremity movements. Among the 10 infants weaned with tapering doses of methadone and gabapentin, gabapentin therapy lasted a mean of 47 days (range: 30–73 days).

Other evidence of withdrawal symptoms with gabapentin is presented in subsections vii, viii, and ix below.

iii. Increased risk of hospitalizations and emergency department visits linked to overdoses, overuse, or misuse of gabapentin, with or without concomitant opioid overuse

In 2014, Wills et al published results of a retrospective cross-sectional chart review of cases of overdoses of newer anticonvulsants using data from a searchable database maintained by the Virginia Poison Control Center, which provides toxicology consultations in the Central Virginia

[75] Vickers Smith R, Boland EM et al. A qualitative analysis of gabapentin misuse and diversion among people who use drugs in Appalachian Kentucky. *Psychol Addict Behav*. 2018;32(1):115-121.
[76] Banker K, Ruekert L, Hasan S. Compulsive gabapentin abuse despite lack of desirable effects: a case report. *J Subst Use*. 2017;22(6):661-663.
[77] Khalid Z, Hennen MA, Aldana-Bernier L. Gabapentin abuse by nasal insufflation: a case report. *J Clin Psychopharmacol*. 2019;39(1):89-91.
[78] Martinez GM, Olabisi J, Ruekert L, Hasan S. A call for caution in prescribing gabapentin to individuals with concurrent polysubstance abuse: a case report. *J Psychiatr Pract.* 2019;25(4):308-312.
[79] Loudin S, Murray S, Prunty L et al. An atypical withdrawal syndrome in neonates prenatally exposed to gabapentin and opioids. *J Pediatr*. 2017;181:286-288.
[80] Buttram ME, Kurtz SP. Descriptions of gabapentin misuse and associated behaviors among a sample of opioid (mis)users in South Florida. *J Psychoactive Drugs*. 2021;53(1):47-54.
[81] Huybrechts KF, Bateman BT, Desai RJ, et al. Risk of neonatal drug withdrawal after intrauterine co-exposure to opioids and psychotropic medications: cohort study. *BMJ*. 2017;358:j3326.
[82] Loudin S, Murray S, Prunty L et al. An atypical withdrawal syndrome in neonates prenatally exposed to gabapentin and opioids. *J Pediatr*. 2017;181:286-288.

region and has an annual call volume of approximately 27,000.[83] The researchers examined all poisoning events in adults related to the use of new anticonvulsant drugs that also were serious enough to result in a hospitalization during the years 2002 to 2011. The following eight drugs were considered: gabapentin, lamotrigine, levetiracetam, tiagabine, topiramate, zonisamide, pregabalin, and oxcarbazepine. The researchers excluded 50 cases that involved coingestion of another drug, leaving 347 adult cases for analysis. Among those 347 adult hospitalization cases, gabapentin was by far the most common overdose agent (n=116, 33%). The next most common overdose drug was lamotrigine (n=67, 19%), and pregabalin was seen in only 23 cases (7%).

Peckham et al in 2018 published results of a retrospective cohort study conducted in the U.S. that assessed patient harm — defined as use of inpatient hospital (IPH) or emergency department (ED) services use— associated with overuse of gabapentin with or without concomitant overuse of opioids.[84] Using the Truven Health MarketScan Commercial Claims and Encounters database, the researchers drew a sample of nearly 800,000 insured patients aged 16 through 64 years for calendar years 2013 through 2015 who were long-term users (≥120 days of use during the 12-month cohort identification period) of gabapentin alone (n=44,152), at least one prescription opioid (n=736,835), or both gabapentin and at least one prescription opioid (n=15,343). The study found that sustained overuse (≥3,600 mg/day for ≥9 of 12 months) of gabapentin alone, compared with no overuse of gabapentin alone, significantly increased the adjusted odds ratio for all-cause use of IPH services (OR=1.37; 95% CI: 1.06–1.77), drug-related use of IPH services (OR=1.44; 95% CI: 1.01 to 2.05) and use of IPH or ED services for altered mental status (e.g., euphoria, anxiety) (OR=1.86; 95% CI: 1.32–2.62). Concomitant use of gabapentin and an opioid, even without evidence of overuse, approximately doubled the odds of all-cause use of IPH services (OR=1.99; 95% CI: 1.84–2.15) and increased the risk of drug-related use of IPH services by 65% (OR=1.65; 95% CI: 1.46–1.85). Finally, sustained overuse of both gabapentin and opioids quadrupled the odds of all-cause use of IPH services (OR=4.08; 95% CI: 2.58–6.46) and more than quadrupled the odds of potentially drug-related use of IPH services (OR=4.72; 95% CI: 2.67–8.37) — suggesting that a dangerous interaction occurs with concomitant use of gabapentin and an opioid.

In a separate commentary published in 2018, Peckham et al called for federal reclassification of gabapentin as a controlled substance, noting that the abuse potential of the drug had been well-documented with clear evidence that it is highly sought after for use in potentiating opioids.[85] They emphasized that when gabapentin is combined with opioids, the risk of respiratory depression and opioid-related mortality increases significantly.

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[83] Wills B, Reynolds P, Chu E et al. Clinical outcomes in newer anticonvulsant overdose: a poison center observational study. *J Med Tocixol*. 2014;10(3):254-260.

[84] Peckham AM, Fairman KA, Sclar DA. All-cause and drug-related medical events associated with overuse of gabapentin and/or opioid medications: A retrospective cohort analysis of a commercially insured US population. *Drug Saf*. 2018;41(2):213-228.

[85] Peckham AM, Ananickal MJ, Sclar DA. Gabapentin use, abuse, and the US opioid epidemic: the case for reclassification as a controlled substance and the need for pharmacovigilance. Risk Manag Healthc Policy. 2018 Aug 17;11:109-116.

iv. Evidence of increasing incidence of poisonings linked to gabapentin misuse or abuse

Faryar et al in 2019 published results of a retrospective cross-sectional review of data on poisonings reported to the Kentucky Poison Control Center from 2012 to 2015 involving individuals aged 16 or older.[86] They found 424 gabapentin-only poisonings and 1,321 poisonings involving gabapentin plus one or more other drugs. The number of reported gabapentin-only exposures increased from 39 in 2012 to 160 in 2015, and the number of reported multidrug exposures involving gabapentin increased from 165 in 2012 to 440 in 2015. For the gabapentin-only exposures, the median gabapentin dose ingested was 6,000 mg, and the mean dose ingested was 13,087 mg. For the multidrug poisonings, 32% involved opioids, and 35% involved benzodiazepines. Intensive care unit admission occurred in 23% of the gabapentin-only exposures and 49% of the multidrug exposures, and 1% resulted in death. Although 992 (57%) of these poisonings were "suspected suicides," 406 (23%) were instead categorized as "misuse/abuse."

v. Drug-related fatalities linked to gabapentin

Ojanperä et al in 2016 published a study that analyzed drug-related fatal poisonings in Finland in 2005, 2009, and 2013.[87] The researchers examined forensic toxicology reports for such cases and calculated the fatal toxicity index (FTI) of medicinal drugs, which is the absolute number of deadly poisonings caused by a particular drug divided by its consumption (defined by summing all dispensed daily doses [DDD]) (FTI is reported as number of deaths per million DDD), for each of the three study years. In Finland during the study years, forensic pathologists were responsible for determining whether drugs were involved in a death and, if so, which drug was the most important causal agent. The numbers of postmortem toxicology cases investigated in Finland in 2005, 2009, and 2013 were 6,210, 6,892, and 6,568, respectively, which represented approximately 13% to 14% of all deaths in Finland during those years. Of those cases, the number of fatal drug poisonings was 501, 636, and 476, respectively, in those years. Review of these fatal overdose toxicology reports yielded a list of 70 drugs prescribed in Finland where the FTI was greater than or equal to 0.1 deaths per million DDD. Most (n=55, 79%) of the 70 drugs identified act on the CNS. In a ranking of these drugs by FTI based on pooled data from all three study years, pregabalin ranked 20th with an FTI of 1.92 deaths per million DDD, and gabapentin ranked 30th with an FTI of 0.91 deaths per million DDD. Many of the highest individual FTIs in general were opioids, including the following:

- Methadone (ranked 1st with an FTI of 42.65)
- Dextropropoxyphene (ranked 2nd with an FIT of 31.84)
- Oxycodone (ranked 6th with an FTI of 6.76)
- Tramadol (ranked 9th with an FTI of 5.69)

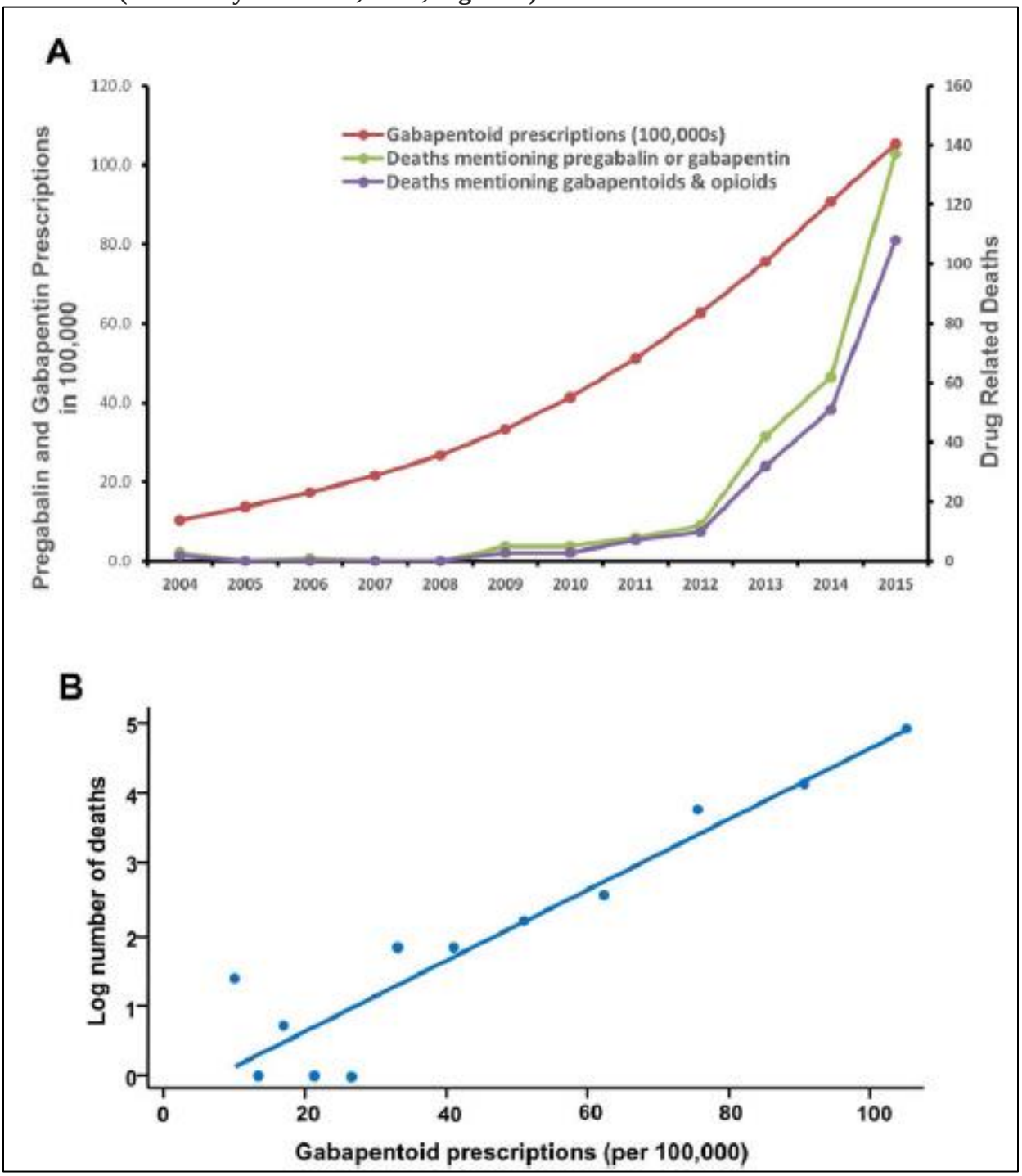
[86] Faryar KA, Webb AN, Bhandari B, et al. Trending gabapentin exposures in Kentucky after legislation requiring use of the state prescription drug monitoring program for all opioid prescriptions. *Clin Toxicol*. 2019;57(6):398-403.
[87] Ojanperä I, Kriikku P, Vuori E. Fatal toxicity index of medicinal drugs based on a comprehensive toxicology database. *Int J Legal Med*. 2016;130(5):1209-1216.

- Morphine (ranked 10th with an FTI of 5.24)
- Fentanyl (ranked 17th with an FTI of 2.05)
- Codeine (ranked 19th with an FTI of 1.97)

Lyndon et al examined trends in drug-related deaths involving gabapentinoid prescribing in England and Wales from 2004 to 2015 using a database developed by the Office of National Statistics in the U.K.[88] They found that prescriptions for gabapentin and pregabalin increased approximately 24% per year during the study period, from 1 million in 2004 to 10.5 million in 2015 (see Exhibit 5, Panel A, excerpted from Lydon et al, 2017). During this same time period, there were dramatic increases in drug-related deaths involving gabapentin or pregabalin (from less than one per year before 2009 to 137 in 2015), 79% of which also involved opioids. Use of a simple log-linear regression further revealed a strong correlation (coefficient=0.965) between the annual number of prescriptions for gabapentinoids and the log of the annual number of drug-related deaths per 100,000 involving these specific drugs (See Exhibit 5, Panel B, excerpted from Lyndon et al, 2017). For each increase of 100,000 in gabapentinoid prescriptions, the number of deaths increased by approximately 5%. This study did not analyze these trends separately for gabapentin or pregabalin. Such findings were likely influential in the U.K. scheduling of both gabapentin and pregabalin as controlled substances in 2019.

[88] Lyndon A, Audrey S, Wells C, et al. Risk to heroin users of poly-drug use of pregabalin or gabapentin. *Addiction*. 2017; 112(9):1580-1589.

Exhibit 5. Number of pregabalin and gabapentin prescriptions and number of deaths per annum in which pregabalin and gabapentin were mentioned on the death certificate from 2004 – 2015 (source: Lyndon et al, 2017, Figure 1)



Expanded postmortem surveillance in recent years has increased the detection of gabapentin overdoses in some U.S. jurisdictions. For example, in July 2014, Kentucky added the substance to its routine postmortem toxicology screening panel.[89] According to data published by Hargrove et al in 2018, prior to this change in Kentucky's screening panel, gabapentin was detected in 5.4 death cases per month, whereas the rate of gabapentin detection jumped to 25.9 death cases per month following the change.[90] Such trends led Evoy et al, in their 2021 systematic review discussed above, to conclude that gabapentinoid involvement in overdose deaths is "significantly underestimated," and further that misuse of this class of medications "represents an alarming trend that has continued to grow and cause significant patient harm."[91]

Among 4,169 overdose deaths with postmortem toxicology result reports from five U.S. jurisdictions (northeast Tennessee, Maricopa County in Arizona, Kentucky, North Carolina, and West Virginia) in 2015, 931 (22%) of decedents tested positive for gabapentin (of note, in northeast Tennessee postmortem screening for gabapentin was performed only when gabapentin use was suspected or known to be involved, likely leading to an underestimate of gabapentin-related deaths in that jurisdiction).[92] Among the 3,360 drug-overdose decedents who tested positive for opioids, 880 (26%) also tested positive for gabapentin. Conversely, among the 931 decedents who tested positive for gabapentin, 876 (94%) also tested positive for opioids.

Faryar et al in 2019 reported that in 2015 the Kentucky Drug Overdose Fatality Surveillance System detected 1,295 overdose deaths and further observed that 36% involved gabapentin, second as a single drug form only to morphine which was found in 44% of those postmortem toxicology events.[93]

A prospective postmortem toxicology cohort study conducted by Nahar et al in the U.K. from 2016 to 2017 examined the prevalence of toxicology test results that were positive for gabapentin, pregabalin, and other drugs in a cohort of 3,750 decedents.[94] The researchers found that toxicology tests were positive for gabapentin in 118 decedents (3.1%) and for pregabalin in 229 decedents (6.1%). In comparison, toxicology test results were positive for the schedule IV opioid tramadol in 120 decedents (3.2%). For postmortem cases linked to use of either gabapentin or pregabalin, the toxicology testing was positive for another drug or alcohol for most decedents (89% for gabapentin, 99% for pregabalin), most commonly a nonheroin opioid drug

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[89] Hargrove SL, Bunn TL, Slavova S et al. Establishment of a comprehensive drug overdose fatality surveillance system in Kentucky to inform drug overdose prevention policies, interventions and best practices. *Inj Prev.* 2018;24(1):60-67.
[90] *Ibid*.
[91] Evoy KE, Sadrameli S, Contreras J et al. Abuse and misuse of pregabalin and gabapentin: A systematic review update. *Drugs*. 2021;81(1):125-156.
[92] Slavova S, Miller A, Bunn TL, et al. Prevalence of gabapentin in drug overdose postmortem toxicology testing results. *Drug Alcohol Depend*. 2018 May 1;186:80-85.
[93] Faryar KA, Webb AN, Bhandari B, et al. Trending gabapentin exposures in Kentucky after legislation requiring use of the state prescription drug monitoring program for all opioid prescriptions. *Clin Toxicol*. 2019;57(6):398-403.
[94] Nahar LK, Murphy KG, Paterson S. Misuse and mortality related to gabapentin and pregabalin are being under-estimated: a two-year post-mortem population study. *J Anal Toxicol*. 2019;43(7):564-570.

(60% and 65%, respectively) or an antidepressant (53% and 64%, respectively). Moreover, the study determined that routine (i.e., outside of this study's protocol) screening policies did not include screening for gabapentin and pregabalin and thus would have underestimated the exposures to these gabapentinoids by 58% and 54%, respectively. The researchers concluded that their study provided robust quantitative evidence that both gabapentin and pregabalin are widely used with opioids, increasing the possible risk of toxicity due to respiratory depression and also supporting the U.K. government's 2019 decision to reclassify both as controlled drugs.

A retrospective review, published by Tharp et al in 2019, of postmortem cases from the western region of Virginia from 2014 to 2017 found 104 people who had tested positive for gabapentin in postmortem blood samples (a substantial number given that in 2016 this region experienced a total of 471 opioid overdose deaths).[95] Moreover, the responsible pathologist determined that gabapentin, alone or in combination with other drugs, was a direct cause of death in 49 of these cases (47% of the total decedents) and a contributing cause of death in 11 other cases (11% of the total decedents).

Most recently, O'Donnell et al in December 2021 published a report in the *Morbidity and Mortality Weekly Report* on drug-overdose deaths in the U.S. involving illicitly manufactured fentanyl from July 2019 to December 2020 in 29 states and the District of Columbia. They found that across all regions of the U.S. (Northeast, Midwest, South, and West) gabapentin was co-involved in 2.7–5.2% of all illicitly manufactured fentanyl overdose deaths.[96]

vi. Data on diversion of gabapentin in the U.S.

Buttram et al in 2017 published a retrospective analysis of case reports of gabapentin diversion from the Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System (Denver Health and Hospital Authority, Colorado), a national prescription-drug surveillance system, from 2002 to 2015.[97] A total of 407 cases of gabapentin diversion were reported in 41 states during the study period. The researchers found that the gabapentin diversion rate steadily increased from zero cases in the first two quarters of 2002 to a high of 0.027 cases per 100,000 people in the fourth quarter of 2015 (see Exhibit 6, excerpted from Buttram et al, 2017), a rate that was comparable to the diversion rate seen for Oxycontin-branded oxycodone in 2015 (0.021 per 100,000).

Buttram et al also deployed an email-based, self-administered questionnaire about new drug trends to 241 drug-diversion reporting agencies in April 2016 and received responses from 73

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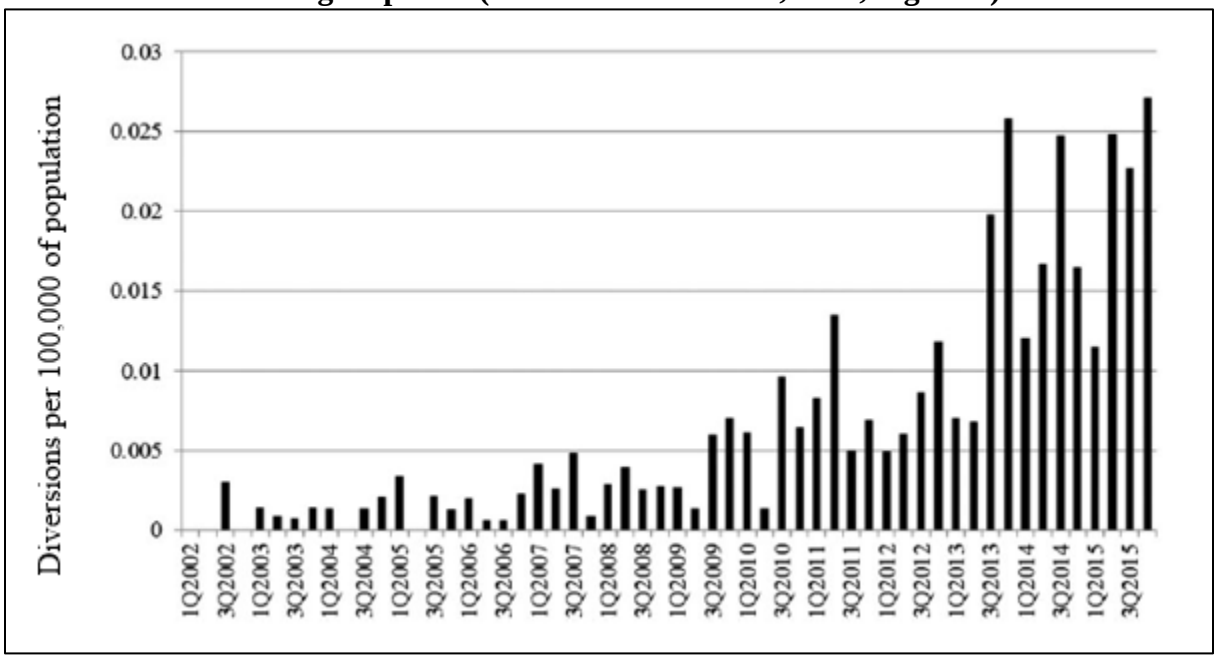
[95] Tharp AM, Hobron K, Wright T. Gabapentin-related deaths: Patterns of abuse and postmortem levels. *J Forensic Sci*. 2019;64(4):1105-1111.
[96] O'Donnell J, Tanz LJ, Gladden RM, et al. Trends in and characteristics of drug overdose deaths involving illicitly manufactured fentanyls - United States, 2019-2020. *MMWR Morb Mortal Wkly Rep*. 2021;70(50):1740-1746.
[97] Buttram ME, Kurtz SP, Dart RC, Margolin ZR. Law enforcement-derived data on gabapentin diversion and misuse, 2002-2015: diversion rates and qualitative research findings. *Pharmacoepidemiol Drug Saf.* 2017;26(9):1083-1086.

agencies (30% response rate).[98] Twenty-one agencies from Alabama, California, Georgia, Idaho, Indiana, Kentucky, Louisiana, Maine, Michigan, North Carolina, Ohio, Oregon, and Tennessee described their experience with gabapentin diversion or misuse in their jurisdictions. Five agencies noted that gabapentin demand was related to misuse or abuse of opioids. Among 13 responding agencies that described gabapentin diversion cases, individual respondents noted that the drug had been "reported stolen," obtained by "doctor shopping," trafficked via the internet, and connected to a street value of $10 per pill.

Exhibit 6. Diversion of gabapentin (source: Buttram et al, 2017, Figure 1)



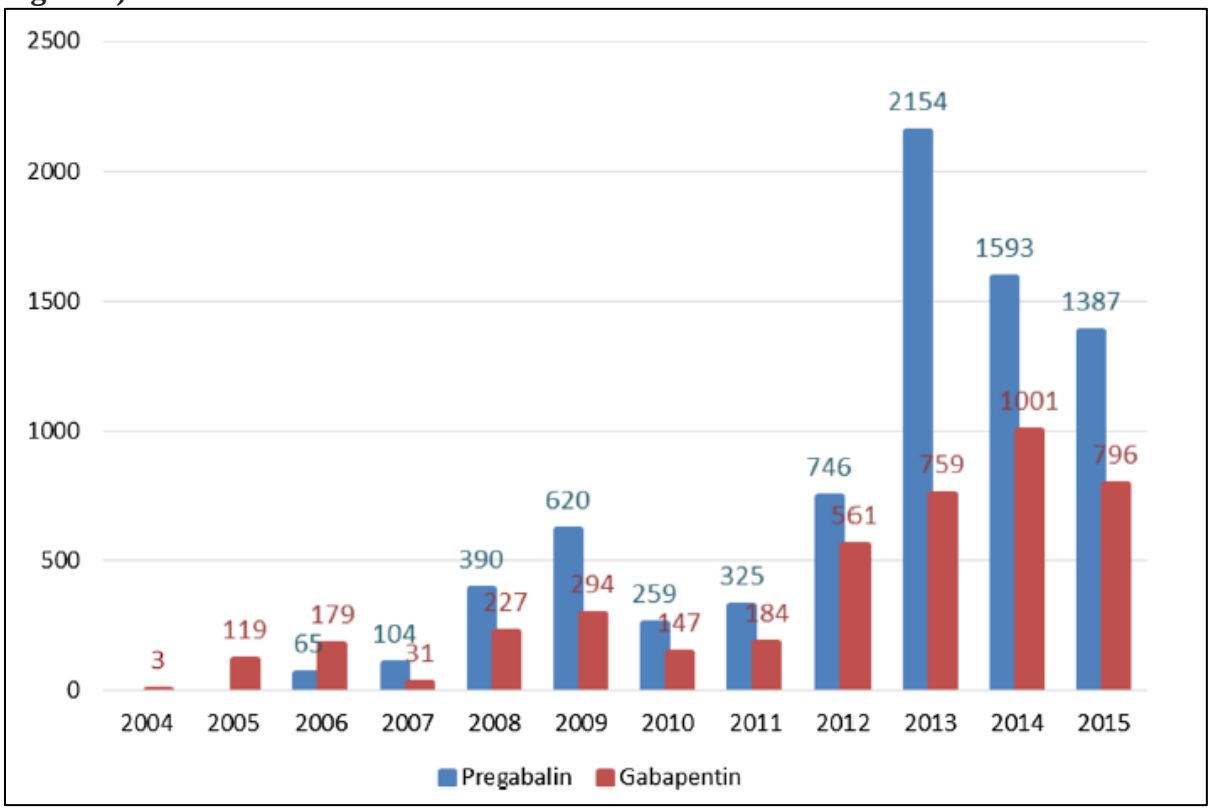
Piper et al in 2018 published an analysis of all arrests reported to the Maine Diversion Alert Program in 2016 (n=2,368) to identify the illegal and prescription pharmaceuticals implicated in these arrests.[99] Gabapentin was implicated in 41 arrests (1.7%), ranking 13th among all implicated drugs and first among all unscheduled prescription drugs. In contrast, pregabalin was tied to only three arrests (0.13%). Moreover, the absolute count of arrests involving gabapentin exceeded those for several schedule I through IV drugs, including hashish (n=22, 0.93%), methylenedioxymethamphetamine/methylenedioxyamphetamine (n=22, 0.93%), methylphenidate (n=18, 0.76%), methadone (n=15, 0.63%), lorazepam (n=15, 0.63%), and morphine (n=14. 0.59%). These results, though unadjusted for prevalence of use, suggest that in Maine gabapentin has been more of a diversion problem than many other currently scheduled drugs.

[98] *Ibid*.
[99] Piper BJ, Suarez MJ, Piserchio JP, et al. Illicit and prescription drug misuse as reported to the Maine Diversion Alert Program. *Forensic Sci Int.* 2018 Apr;285:65-71.

vii. Pharmacosurveillance data regarding gabapentin misuse, abuse, dependence, and withdrawal

Chiappini and Schifano in 2016 published an analysis of data from the European Medicines Agency's EudraVigilance database of electronic reports of suspected adverse drug reactions to identify and assess cases of gabapentinoid misuse, abuse, or dependence.[100] From 2004 to 2015, there were 4,301 spontaneous adverse events for gabapentin and 7,639 for pregabalin that involved misuse, abuse, or dependence. These events represented 4.8% and 6.6% of all adverse events reported to the EudraVigilance database for each drug, respectively. The number of these reports generally increased consistently from year to year (see Exhibit 7, excerpted from Chiappini and Schifano, 2016). Among these reports there were 86 fatalities for gabapentin and 27 for pregabalin. Such surveillance data suggest that both drugs were associated with substantial morbidity related to misuse, abuse, and dependence.

Exhibit 7. Number of gabapentinoid misuse/abuse/dependence adverse drug reactions per year reported to the EudraVigilance database (source: Chiappini and Schifano, 2016, Figure 1)



[100] Chiappini S, Schifano F. A decade of gabapentinoid misuse: an analysis of the European Medicines Agency's 'suspected adverse drug reactions' database. *CNS Drugs*. 2016;30(7):647-654.

A 2019 analysis, by Evoy et al, of FDA Adverse Event Reporting System (FAERS) data from reports submitted from October 2012 through December 2016 identified 10,038 adverse-event reports for gabapentin, including 576 specifically related to abuse, misuse, dependence, or overdose, 106 (18.4%) of which were fatal.[101] In comparison, only 571 total adverse events were reported during that same time period for pregabalin, including 58 related to abuse, misuse, dependence, or overdose, 24 (41.4%) of which were fatal. Beyond the 106 deaths, the most common adverse events related to gabapentin were abuse (n = 159; 27.6%), overdose (n=142; 24.7%), intentional product misuse (n=122; 21.2%), drug withdrawal syndrome (n=94; 16.3%), euphoric mood (n=48; 8.3%), and intentional overdose (n=47; 8.2%).

In 2019, the Institute for Safe Medication Practices (ISMP) published an analysis of adverse-event reports for gabapentin and pregabalin that had been submitted to the FAERS database for the 12-month period ending in September 2018.[102] ISMP researchers identified the following important safety signals:

- **Withdrawal symptoms/dependence:** More than 1,200 reports described withdrawal syndromes, drug abuse, intentional misuse, or overdose.
- **Mental impairment**: Patients complained of memory loss, memory impairment, confusion, dizziness, and falls.
- **Drug ineffective.** The signal that the drugs were ineffective or aggravated the condition included many cases that indicated unapproved use.
- **Overdose deaths**. Hundreds of reports of intentional and accidental overdose and death were received but typically involved combinations with many other potentially addictive drugs, notably opioids and anti-anxiety agents.

The ISMP reported proportional reporting ratios (PRR) for selected adverse events in the FAERS database related to gabapentin or pregabalin use (see Exhibit 8, excerpted from the ISMP report, 2019). Notably, the ISMP researchers found that, based on the PRR results for events of interest, the overall safety profiles of gabapentin and pregabalin were similar. Notable differences between the two drugs were (a) gabapentin was much more likely to be associated with reports that it was ineffective when used for an off-label indication (PRR 51.54 for gabapentin versus 5.24 for pregabalin), and (b) pregabalin was more likely to have withdrawal and rebound effects reported (PRR 12.09 for pregabalin versus 2.59 for gabapentin). ISMP researchers concluded that the "FDA should consider reclassifying gabapentin as a scheduled drug — as is pregabalin — and consider other measures to reduce a pattern of unsafe use."[103]

[101] Evoy KE, Covvey JR, Peckham AM et al. Reports of gabapentin and pregabalin abuse, misuse, dependence, or overdose: An analysis of the Food And Drug Administration Adverse Events Reporting System (FAERS). *Res Social Adm Pharm.* 2019;15(8):953-958.
[102] Institute for Safe Medication Practices, *QuarterWatch*, March 27, 2019.
[103] *Ibid.*

Exhibit 8. Selected adverse drug events reported for pregabalin and gabapentin to the FAERS database for 12-month period ending in September 2018 (source: ISMP, 2019, Table 3)

	Pregabalin		Gabapentin	
	N	PRR	N	PRR
Total reports*	7,756		5,936	
Dependence - withdrawal**				
Substance related addictive disorders (HLT)	186	2.47	153	2.66
Withdrawal - rebound effects (HLT)	505	12.09	87	2.59
Overdoses (HLT)	326	2.64	185	1.96
Cognitive impairment				
Mental impairment (HLT)	115	2.45	99	2.77
Memory loss (HLT)	245	3.10	131	2.17
Confusion - disorientation (HLT)	139	2.11	125	2.50
Lack of effect				
Drug ineffective for unapproved use (PT)	112	5.24	702	51.54
Drug ineffective (PT)	912	1.64	828	2.09
Self-harm				
Suicidal/self injurious behavior (HLT)***	161	1.94	326	4.41
*12 months ending 2018 Q3. HLT = High Level Term. PT = Preferred Term. PRR = Proportional Reporting Ratio				
**One report may contain > 1 term. ***Cases may include duplicate reporting from literature				

Vickers-Smith et al in 2020 published a pharmacovigilance study analyzing FAERS data from 2005 to 2015.[104] The purpose of the study was to determine whether there were pharmacovigilance signals for abuse or misuse of gabapentin. Among nearly 6 million unique adverse-event reports, the researchers identified 99,977 reports for gabapentin, 97,813 for pregabalin, and 73,977 for duloxetine. They used loglinear modeling to estimate odds ratios for the co-occurrence of a report of abuse-related and abuse-specific adverse events for gabapentin and pregabalin, using duloxetine as a negative control reference. Duloxetine was deemed a suitable referent because it is a psychotropic medication (an antidepressant) and it also is used to treat neuropathic pain. Compared directly to duloxetine adverse-event reports, both gabapentin

[104] Vickers-Smith R, Sun J, Charnigo RJ, et al. Gabapentin drug misuse signals: A pharmacovigilance assessment using the FDA adverse event reporting system. *Drug Alcohol Depend*. 2020 Jan 1;206:107709.

and pregabalin showed higher odds ratio estimates for reports of abuse-related and abuse-specific adverse events. Specifically, the following adverse event signals were significantly more evident with gabapentin use than with duloxetine use (odds ratios 2.36 to 6.55): drug-withdrawal syndrome, euphoric mood, auditory hallucinations, drug abuser, ataxia, and delusions. Moreover, these odds ratio point estimates were nominally larger for gabapentin than for pregabalin for all these reported adverse events except delusions (see Exhibit 9, excerpted from Vickers-Smith et al, 2020). Vickers-Smith et al concluded that prescribers should be aware of gabapentin's abuse liability and the effects that may accompany its misuse.

Exhibit 9. Loglinear odds ratio estimates for the co-occurrence of a report of an abuse-specific adverse event (AE) and a possible indicator of an abuse AE by drug. (source: Vickers-Smith et al, 2020, Table 4)

Interaction	Gabapentin OR (95% CI)	Pregabalin OR (95% CI)	Duloxetine
AS-AE * Drug withdrawal syndrome	**6.55 (5.24 - 8.19)**	**3.08 (2.44 - 3.87)**	REF
AS-AE * Euphoric mood	**5.45 (2.70 - 12.26)**	**2.47 (1.27 - 5.42)**	REF
AS-AE * Auditory hallucination	**4.57 (1.79 - 14.04)**	**4.28 (1.61 - 13.46)**	REF
AS-AE * Drug abuser	**3.01 (1.26 - 7.82)**	2.45 (0.81 - 7.78)	REF
AS-AE * Ataxia	**2.85 (1.26 - 7.68)**	1.34 (0.55 - 3.79)	REF
AS-AE * Delusion	**2.36 (1.10 - 5.49)**	**3.33 (1.48 - 8.06)**	REF
AS-AE * Drug tolerance	2.25 (0.93 - 6.06)	1.90 (0.79 - 5.10)	REF
AS-AE * Feeling drunk	2.05 (0.61 - 9.25)	1.61 (0.53 - 6.92)	REF
AS-AE * Aggression	**1.98 (1.35 - 2.92)**	**2.47 (1.68 - 3.66)**	REF
AS-AE * Psychotic disorder	**1.96 (1.14 - 3.48)**	0.77 (0.37 - 1.57)	REF
AS-AE * Feeling of relaxation	1.95 (0.07 - 54.16)	3.78 (0.54 - 76.08)	REF
AS-AE * Drug tolerance increased	1.72 (0.31 - 10.93)	0.60 (0.10 - 3.79)	REF
AS-AE * Thinking abnormal	1.52 (0.96 - 2.47)	1.03 (0.61 - 1.73)	REF
AS-AE * Mood altered	1.37 (0.75 - 2.57)	1.47 (0.80 - 2.74)	REF
AS-AE * Feeling abnormal	**1.31 (1.02 - 1.69)**	1.26 (0.99 - 1.61)	REF
AS-AE * Delirium	1.24 (0.76 - 2.10)	0.64 (0.35 - 1.16)	REF
AS-AE * Somnolence	1.24 (0.99 - 1.55)	0.91 (0.73 - 1.14)	REF
AS-AE * Confusional state	1.20 (0.94 - 1.55)	0.82 (0.62 - 1.08)	REF
AS-AE * Dizziness	1.19 (0.94 - 1.50)	1.05 (0.83 - 1.32)	REF
AS-AE * Visual hallucination	1.16 (0.50 - 2.92)	1.29 (0.54 - 3.29)	REF
AS-AE * Mixed hallucinations	1.15 (0.24 - 6.16)	2.90 (0.82 - 13.63)	REF
AS-AE * Hallucination	1.08 (0.74 - 1.58)	0.90 (0.60 - 1.36)	REF
AS-AE * Disorientation	1.02 (0.63 - 1.67)	0.93 (0.56 - 1.55)	REF
AS-AE * Fall	0.94 (0.73 - 1.22)	0.90 (0.68 - 1.19)	REF
AS-AE * Off-label use	0.93 (0.70 - 1.22)	**1.46 (1.11 - 1.92)**	REF
AS-AE * Incoherent	0.90 (0.37 - 2.32)	0.47 (0.15 - 1.41)	REF
AS-AE * Gait disturbance	0.73 (0.51 - 1.05)	0.82 (0.58 - 1.18)	REF
AS-AE * Elevated mood	–	2.98 (0.34 - 64.10)	REF
AS-AE * Dissociation	–	0.38 (0.02 - 3.01)	REF

AE: adverse event; OR: odds ratio; 95 % CI: 95 % confidence interval; AS-AE: abuse-specific adverse event; REF: referent group.
Note: Missing results correspond to occasions where no events were reported.
Boldface indicates a significant result at $p < .05$.

viii. Individual user surveys or focus groups documenting misuse of gabapentin

Kapil et al in 2014 published results of a 2013 online survey of 1,500 individuals aged 16 to 59 in the U.K. to determine the prevalence, frequency, and sources of misuse of any of three GABA

analogues (baclofen, gabapentin, and pregabalin).[105] The survey respondents indicated a lifetime prevalence of misuse of any of these three GABA analogues of 2.4% and a lifetime prevalence of gabapentin and pregabalin misuse of 1.1% and 0.5%, respectively.

Wilens et al in 2015 published a prospective survey study involving 196 of 199 consecutive patients admitted to a Massachusetts inpatient detoxification facility in 2013 (surveys from three patients were excluded for missing data).[106] The aim of this project was to examine the extent to which opioid-dependent patients seeking detoxification were using and misusing specific psychotropic agents. Most patients (n=162, 83%) were admitted for opioid detoxification (the other 34 patients were admitted for alcohol detoxification). Among the opioid-detoxification–only patients, 22% reported having received gabapentin prescriptions and 2% reported having received pregabalin prescriptions. Misuse of gabapentin or pregabalin (defined as excessively high dosing or use without a prescription) was reported by 22% and 7%, respectively, of the opioid detoxification patients.

A recent qualitative study of gabapentin misuse published by Smith et al in 2018 relied on responses from a convenience sample of 32 jailed or community-dwelling adults in rural Kentucky.[107] Most subjects were female (84.4%) and Caucasian (87.5%), and all reported recent nonmedical use of gabapentin. These 32 individuals, who already were involved in other cohort studies about drug use more broadly, participated in 30- to 60-minute focus groups that were recorded in 2015 and subsequently analyzed for themes about gabapentin misuse. The study authors reported that "Several participants described a gabapentin high as being similar to an opioid high; one likened the high from snorting gabapentin to that of a 'shot of cocaine.'" They further noted that "a considerable number of respondents recounted painful gabapentin withdrawal experiences, which they described as being similar to, but not as long lasting as, opioid or depressant (e.g., alcohol, alprazolam) withdrawal."[108] Such observational data led the researchers to conclude that gabapentin has abuse potential and that "a reexamination of the need for scheduling is warranted."[109]

ix. Additional evidence of misuse and abuse of gabapentin

In 2017, Tamburello et al published a retrospective chart review study of New Jersey Department of Corrections (DOC) records that found gabapentin to be the most misused authorized medication among adults in that system.[110] The authors of this study obtained a

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[105] Kapil V, Green JL, Le Lait MC et al. Misuse of the γ-aminobutyric acid analogues baclofen, gabapentin and pregabalin in the UK. *Br J Clin Pharmacol*. 2014;78(1):190-191.
[106] Wilens T, Zuauf C, Ryland D et al. Prescription medication misuse among opioid dependent patients seeking inpatient detoxification. *Am J Addict.* 2015;24(2):173-177.
[107] Vickers Smith R, Boland EM, Young AM et al. A qualitative analysis of gabapentin misuse and diversion among people who use drugs in Appalachian Kentucky. *Psychol Addict Behav*. 2018;32(1):115-121.
[108] *Ibid.*
[109] *Ibid.*
[110] Tamburello AC, Kathpal A, Reeves R. Characteristics of inmates who misuse prescription medication. *J Correct Health Care*. 2017;23(4):449-458.

random sample of 300 cases of adult inmates who had received a charge for misuse of authorized medications from the New Jersey Department of Corrections from 2003 to 2013. Thirteen cases were excluded because the location of the misuse offense was outside of the prison system or could not be identified or the substance in question was illegal, reducing the final study sample to 287 cases. Among the 287 cases reviewed, 177 (61.7%) identified the specific misused drug(s). Gabapentin was found to be the cited drug in 38 (14%) of the cases, more than any other single drug. The second and third most cited misused drugs were diphenhydramine (n=22, 8.3%) and clonidine (n=17, 6.4%), respectively. The precise nature of the misuse charge was not characterized by this study, but it was noted that such misuse plausibly includes feigning illness to self-administer or otherwise abuse medications (e.g., malingering) and diversion-for-profit (reselling) behaviors. Moreover, this research observed that in at least 13.6% of the studied cases the medication had not been prescribed to the cited inmate — thereby indicating the drug had been diverted from another individual.

In 2018, Driot et al published results of a retrospective cohort study of new users of pregabalin (n=8,692), gabapentin (n=1,963), or the antidepressant duloxetine (3,214) from June 2006 to December 2014 using a general health insurance database containing data from a randomly selected nationally representative sample of the French population.[111] The researchers found that misuse, defined by higher than maximal daily doses (600 mg for pregabalin, 3,600 mg for gabapentin, and 120 mg for duloxetine), was more common with pregabalin and duloxetine (12.8% and 9.7%, respectively) than with gabapentin (6.6%), with adjusted results indicating that such misuse was only significantly different between pregabalin and duloxetine, not between gabapentin and duloxetine. As duloxetine was selected as a comparator psychoactive substance also approved for neuropathic pain but with relatively low abuse potential, Driot et al's results might be taken to mean pregabalin has markedly more abuse potential than gabapentin. Other analyses from this same study, however, found that after the first episode of misuse, gabapentin and pregabalin yielded similar rates of developing a "primary addiction" — defined as hospitalization with a diagnosis of a substance use disorder or a prescription for a drug to treat a substance use disorder — (11.6% and 10.7%, respectively), thereby supporting the hypothesis that once misuse of either drug emerges, they similarly increase the risk of more serious dependence. Overall, the results of Driot et al suggested both gabapentinoids have abuse potential, though the results for gabapentin are less certain with data from France than for data from other countries, including the U.S. and the U.K., which show that gabapentin is more prevalent as an abused agent. Driot et al speculated that such geographic variability could be explained partly by country-specific differences in health professionals' awareness regarding the abuse potential of these drugs (due to pregabalin being initially scheduled in the U.S. but not in Europe) and differences in the level of use, which in France is very low for gabapentin compared with pregabalin. Regarding the latter factor, they noted that because the incident use of pregabalin in France was four times greater than that observed with gabapentin, the likelihood

[111] Driot D, Jouanjus E, Oustric S, et al. Patterns of gabapentin and pregabalin use and misuse: Results of a population-based cohort study in France. *Br J Clin Pharmacol*. 2018;85(6):1260-1269.

that vulnerable persons will be exposed to misuse or to other adverse outcomes is higher for pregabalin.

A Belgian cross-sectional study published by Van Baelen et al in 2018 of over 151,000 patients during the years 2008 to 2014 observed that 2.7% (649/30,256) of those treated for substance use disorders used gabapentin, compared with 0.7% (872/121,270) of those who did not receive such specialized treatment.[112] Notably, the relative number of gabapentin users per year increased steadily from 0.03% in 2008 to 1.1% in 2014 among patients receiving treatment for substance use disorder and, during the same time span, from 0.02% to 0.32% among those who did not receive such treatment. Ten percent of gabapentin users in each group purchased at least one prescription exceeding 3,600 mg/day — twice the recommended maximum dosage for treating postherpetic neuralgia — thereby suggesting misuse or abuse. It should further be noted that gabapentin therapy is not an FDA- or European Medicines Agency-approved treatment for substance use disorder.

Stein et al in 2020 published results of a prospective survey study of 401 of 472 patients admitted to a Massachusetts inpatient opioid-withdrawal center from May 2018 to March 2019 (65 of the 472 patients refused study participation or were discharged before surveys could be performed, and six were excluded for missing data).[113] The objective of the study was to examine predictors of ever using gabapentin among persons seeking treatment for opioid use and to assess how gabapentin was obtained (legally or otherwise). Among all respondents, 264 (66%) reported a history of gabapentin use. Among these gabapentin users, 162 (61%) reported using gabapentin to "get high," 104 (39%) said they used it to "increase heroin effects," and 35 (13%) reported using gabapentin because they were addicted to the drug. The source of the gabapentin used was nonprescribed in 124 patients (47%), prescribed only in 54 (20%), and both in 86 (33%). Among the 210 patients who reported using nonprescribed gabapentin, 153 (58%) said they used it to "get high," whereas among the 54 users who only used gabapentin that had been prescribed, nine (17%) reported using the drug to "get high." The researchers concluded that gabapentin is a medication with substantial abuse potential in populations with opioid use disorder.

In 2021, Buttram and Kurtz published results of an interview study involving 49 adults in South Florida, who reported both use of illicit opioids or misuse of prescription opioids during the preceding year and misuse of gabapentin during the preceding 90 days.[114] Participants were recruited through flyers and advertisements placed in public spaces and a local weekly publication. In addition to gabapentin misuse, substance use among the sample was varied, with a majority of participants reporting past 90-day (mis)use of prescription opioids (81.6%),

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[112] Van Baelen L, De Ridder K, Antoine J, Gremeaux L. Utilization of gabapentin by people in treatment for substance use disorders in Belgium (2011-2014): a cross-sectional study. *Arch Public Health*. 2018 Mar 19;76:17.
[113] Stein MD, Kenney SR, Anderson BJ et al. Prescribed and non-prescribed gabapentin use among persons seeking inpatient opioid detoxification. *J of Subst Abuse Treat.* 2020 Mar; 110:37-41.
[114] Buttram ME, Kurtz SP. Descriptions of gabapentin misuse and associated behaviors among a sample of opioid (mis)users in South Florida. *J Psychoactive Drugs*. 2021;53(1):47-54.

benzodiazepines (77.6%), heroin (61.2%), marijuana (61.2%), and binge drinking (55.1%). Twenty-eight participants (57%) had received at least one prescription for gabapentin prior to their misuse, and of those, 25% reported having misused the drug *before* receiving their first prescription for the drug. The primary reasons for these prescriptions, as reported by the study participants, were often for off-label indications, including the alleviation of withdrawal symptoms (25%) or mental distress (18%). Most users swallowed gabapentin pills whole (n=42, 86%), whereas five (10.2%) snorted the drug, three (6.1%) chewed it, and two (4.1%) injected it. Negative consequences of using the drug included physical (n=12, 24.5%) and psychological problems (n=4, 8.2%) and withdrawal symptoms (n=3, 6.1%). The majority of users reported that they sourced gabapentin via illicit means: sharing/trading with others (n=24, 49.0%), dealer/street buy (n=10, 20.4%), or theft (n=2, 4.1%). Many participants reported that gabapentin produced feelings reminiscent of alcohol intoxication or opioid-induced euphoria (although euphoria was milder than that experienced with opioids), whereas others reported that it alleviated pain or produced no noticeable effect.

It is no doubt the case that the above-described studies and results pertaining to concomitant misuse of gabapentinoids and opioids are illustrative of the recent evidence that Evoy and colleagues relied on to conclude in their 2021 systematic review that "The most concerning finding was increased evidence of associated patient harm, including increased hospital utilization and opioid-related overdose mortality risk."[115]

5. Discussion and Conclusions

Accordingly, the DEA and the FDA should promptly initiate proceedings to place all forms of gabapentin and gabapentin enacarbil into schedule V because the evidence presented in this petition clearly fulfills the following DEA criteria for such scheduling:

(1) There is evidence that individuals are taking gabapentin in amounts sufficient to create a hazard to their health and to the community.

(2) There is significant diversion of gabapentin from legitimate drug channels.

(3) Individuals are taking gabapentin on their own initiative rather than on the basis of medical advice from a practitioner.

More specifically, there is substantial evidence from many observational studies and directly from gabapentin labeling that the drug causes a wide range of CNS-related adverse effects, including dizziness, seizures, suicidal ideation, physical and psychological dependence, hospitalization, respiratory depression, and overdose death (especially in combination with opioids).

[115] Evoy KE, Sadrameli S, Contreras J et al. Abuse and misuse of pregabalin and gabapentin: A systematic review update. *Drugs*. 2021;81(1):125-156.

There is also substantial evidence of widespread misuse of the drug plausibly fueled, in part, by extraordinary levels of off-label prescribing, which some have estimated accounts for more than 90% of gabapentin prescriptions in the U.S. Moreover, there are numerous reports indicating that gabapentin is widely used and diverted on the street to induce "highs" or to otherwise self-medicate. Both gabapentin and pregabalin have been empirically linked to the opioid overdose epidemic as drugs that potentiate the activity of these oftentimes deadly analgesics.

And finally, the similarities between gabapentin and pregabalin (a U.S. schedule V drug since 2005) are extensive, ranging from their chemical structure and bioactivity to their approved indications and off-label uses, as well as their legal and illicit use patterns in the U.S. and elsewhere.

Placing gabapentin on schedule V along with pregabalin, as was simultaneously done in 2019 in the U.K. and since 2017 by several states in the U.S., would allow for better tracking of gabapentin's use and misuse, and for prescription-education and prescription-limitation requirements that could mitigate the risks of addiction, overdose, and death, which too often occur with gabapentin use.

In summary, gabapentin is a drug with a substantial potential for and extensive evidence of misuse and abuse, with use potentially leading to severe psychological or physical dependence and overdose death, particularly when used in combination with opioids. We therefore request that the DEA Administrator and the Commissioner of Food and Drugs promptly initiate the proceedings to place (a) gabapentin (2-[1-(aminomethyl) cyclohexyl] acetic acid), including its salts, (including the brand name products Gralise and Neurontin) and (b) gabapentin enacarbil (1-{[({(1RS)-1-[(2-methylpropanoyl)oxy] ethoxy}carbonyl)amino]methyl} cyclohexyl) acetic acid), including its salts, (including the brand name product Horizant) into schedule V of the CSA. Placement in Schedule V is appropriate because (a) these drugs have a lower potential for abuse relative to the drugs or other substances in schedule IV, (b) these drugs have currently accepted medical uses in treatment in the U.S., and (c) abuse of these drugs may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule IV.

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.

We look forward to your timely action on this petition. Thank you for your attention to this important public health issue.

Sincerely,

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