Gabapentin for Substance Use Disorders
Is it Safe and Appropriate?

ABSTRACT
Gabapentin is effective for the treatment of alcohol dependence and can be used for treating anxiety, insomnia, headaches, and/or pain in patients who have comorbid substance use disorders (SUDs) or who are at high risk of substance abuse. Deaths from unintentional drug overdoses are increasing, are the leading cause of injury death in the United States, and are mostly attributable to prescription drugs, in particular opioid agents. Compared to other psychotropic drugs, gabapentin is not especially harmful or lethal. Gabapentin misuse is possible, similar to other medications not typically considered drugs of abuse, but it should be considered safe and appropriate for use in patients with all types of SUDs, including patients who take opioid drugs. [Journal of Psychosocial Nursing and Mental Health Services, 52(2), 13-16.]

Gabapentin (Neurontin®, Gralise®, Horizant®), a gamma-aminobutyric acid (GABA) analog drug, appears to be safe and efficacious for the treatment of alcohol dependence based on short-term controlled studies (Howland, 2013). Gabapentin is commonly used for treating anxiety, insomnia, headaches, and/or pain in patients who have comorbid substance use disorders (SUDs) or who are at high risk of substance abuse. Gabapentin is not a controlled drug, but its misuse has been described, as have withdrawal symptoms associated with abrupt discontinuation (Howland, 2014). Deaths from unintentional drug overdoses have been increasing during the past 20 years, and such overdoses are the leading cause of injury death in the United States (Paulozzi, 2012). The increase in drug poisoning has been driven by prescription drugs, in

Robert H. Howland, MD
particular prescription opioid drugs. Given the potential for misuse of gabapentin, is it safe or even appropriate to use gabapentin for the treatment of SUDs, including patients taking opioid drugs?

**IS GABAPENTIN LETHAL?**

In a letter, Smith, Higgins, Baldacchino, Kidd, and Bannister (2012) reported that gabapentin was being used by 5.2% of 251 patients who had been attending substance misuse services (in the Tayside region of Scotland in 2009) for at least 4 years. These patients were three times more likely to admit to nonmedical use of analgesic agents, although the term “analgesics” was not defined. Smith et al. (2012) also reported that of 1,400 postmortem examinations in Scotland in 2011, 48 included gabapentin in their toxicology report (with 36 also including morphine, methadone, or both). The authors then stated “like opiates, gabapentin is fatal in overdose; unlike opiates, there is no antidote and the long half-life instils [sic] the need for prolonged, intensive management of overdose” (p. 406). This statement, however, is not substantiated by the authors. Opioid agent-associated mortality is well established and increasingly common (Centers for Disease Control and Prevention, 2011), but there is no clear evidence that gabapentin itself is especially lethal in an overdose (Klein-Schwartz, Shepherd, Gorman, & Dahl, 2003; Middleton, 2011; Schauer & Varney, 2013). According to the U.S. product label, lethal doses of gabapentin were not found in animal studies and reports of acute overdoses in humans were not associated with death or disability. Because gabapentin is not hepatically metabolized and is excreted through the kidneys, hemodialysis can be performed if it were medically necessary following a gabapentin overdose (Bockbrader et al., 2010).

Most opioid drug overdoses involve more than a single drug. Gabapentin is commonly used to treat pain, and it is not surprising that gabapentin (and/or other concurrently prescribed analgesic drugs) might be found in toxicology reports. Moreover, gabapentin, griseofulvin (Gris Pez®, an antifungal drug), paracetamol (Tylenol®, acetaminophen), caffeine, diazepam (Valium®), benzocaine (Americaine®, a topical anesthetic), and phenacetin (an analgesic whose active metabolite is acetaminophen) have all been identified as “cutting agents” (used to dilute the purity of street drugs, including opioid drugs) (Scottish Crime and Drug Enforcement Agency, n.d.). These “cutting agents” would be detected in toxicology reports, and some of them are potentially harmful themselves in an overdose. In Scotland during the years 2010-2012, 2,493 deaths by poisoning were recorded (General Register Office for Scotland, n.d.). Gabapentin was listed in 84 (3.4%) of these deaths, but 83 involved multiple drugs and only one involved gabapentin alone. In 46 (55%) of these 84 deaths, gabapentin was not even considered to be a contributing factor in the cause of death.

Complete listings of all suspected adverse drug reactions (ADRs) reported to the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom are compiled in Drug Analysis Prints (DAPs), which can be easily accessed on the MHRA website (MHRA, n.d.). The DAP for gabapentin (covering the years 1993 to September 2013) indicates that only 44 fatal adverse reactions were reported during these 20 years, although no information is given about the clinical circumstances, concurrent medications used, or determination of causality.

According to U.S. data in 2011 from the National Poison Data System (NPDS), the substance categories most frequently involved in fatal and non-fatal exposures were analgesic drugs (including opioid drugs) (ranked 1), sedative/hypnotic/antipsychotic drugs (ranked 4), antidepressant drugs (ranked 6), antihistamine drugs (ranked 9), and stimulants/street drugs (ranked 15) (Bronstein, Spyker, Cantilena, Rumack, & Darr, 2012). The anticonvulsant drugs category (including gabapentin) was ranked 19. In the NPDS database, 2,765 human drug exposures resulting in death were documented and 1,995 of these fatalities were judged to be related to the drug(s) involved. When deaths were sorted according to the substance most likely responsible for the death (referred to as "cause rank"), analgesic drugs was highest, followed by antidepressant drugs, cardiovascular drugs, sedative/hypnotic/antipsychotic drugs, and stimulants/street drugs. Gabapentin was involved in 34 (1.7%) of the 1,995 fatalities. All 34 cases involved multiple drugs, and gabapentin was never judged to have a cause rank of 1 (deemed most likely responsible for the death). Gabapentin was the only drug exposure in two non-fatal cases.

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None of these data provide much support for the idea that gabapentin is especially harmful or lethal. Why not? Gabapentin is excreted through the kidneys, is not hepatically metabolized, and is not toxic to the heart, liver, or kidneys (Bockbrader et al., 2010; Davy et al., 2013). Also, the amount of gabapentin reaching the central nervous system (CNS) after an overdose might be restricted. Gabapentin oral bioavailability (absorption) is not dose proportional. In other words, as the dose increases, bioavailability decreases. The L-amino acid transport system (LAT), located in the intestinal tract and also expressed in the blood-brain barrier (BBB), is responsible for the absorption of gabapentin from the gut and its transport across the BBB into the CNS (Dickens et al., 2013). Because the LAT is saturable, the proportion of gabapentin that can be transported from the gut and then across the BBB is limited, potentially protecting the brain from acutely elevated concentrations following an oral overdose. Even if gabapentin is taken intranasally or intravenously (bypassing the gut), transport across the BBB would be limited by the saturable LAT.

**ABUSE LIABILITY OF GABAPENTIN AND OTHER PSYCHOTROPIC MEDICATIONS**

Determining the abuse liability of a drug is primarily done by assessing its subjective and reinforcing effects. Subjective ratings of drug “liking” depend on net self-report ratings of positive and negative effects. A drug serves as a reinforcer if the behavior leading to its consumption increases in probability over time. Good concordance usually is found between the reinforcing and subjective effects of drugs, but many variables will influence drug-taking behavior and the subjective effects of drugs, making it difficult to definitively establish abuse liability (Comer et al., 2008). Although there is some evidence of gabapentin abuse, I believe the magnitude of the abuse risk is small and the abuse risk is not comparable to that seen with typical drugs of abuse. Because the intestinal absorption and BBB transport of gabapentin are not dose-proportional, there might be a physiological limit to the ability to develop rapid “intoxicating” brain concentrations of gabapentin, except perhaps in a small minority of individuals. By contrast, the GABA analog drug pregabalin (Lyrica®) has nonsaturable absorption and a steeper dose-response relationship than gabapentin (Bockbrader et al., 2010). Unlike gabapentin, pregabalin is a scheduled drug according to U.S. Drug Enforcement Agency (DEA) criteria. Studies involving alcohol (Bisaga & Evans, 2006; Myrick, Anton, Voronin, Wang, & Henderson, 2007) or opioid drugs (Gilron et al., 2005; Keskinbora, Pekel, & Aydinli, 2007) did not find that their use was associated with enhanced intoxicating or euphoric effects when used in combination with gabapentin, although the opioid drug studies were conducted in pain patients rather than SUD patients.

The risk of gabapentin misuse may be greater in chronic severe SUD populations and in correctional institutional populations, but such misuse is certainly not unique to gabapentin. Del Paggio (2005) described experiences with psychotropic medication abuse in correctional facilities. He noted that this is a problem not only for gabapentin, but also for atypical antipsychotic drugs quetiapine (Seroquel®) and olanzapine (Zyprexa®), anticholinergic drugs benzpropine (Cogentin®) and trihexyphenidyl (Artane®), tricyclic antidepressant drugs (e.g., amitriptyline [Elavil®], nortriptyline [Pamelor®]), and desipramine [Norpramin®], and antidepressant drug bupropion (Wellbutrin®). The misuse, abuse, and/or diversion of antihistamine, anticholinergic, antidepressant, and antipsychotic drugs have been reported by others (Dilsaver, 1988; Haddad, 1999; Hilliard, Barloon, Farley, Penn, & Koranek, 2013; Sansone & Sansone, 2010; Thomas, Nallur, Jones, & Deslandes, 2009).

Readers might wonder why such a variety of drugs that are not scheduled according to DEA criteria can still be misused, even though the majority of patients taking these drugs do not abuse them. Obviously, these drugs all affect the CNS and have potential behavioral effects. Individuals frequently self-administer psychoactive drugs to experience their positive effects, but with prolonged use many of these effects may wane or the drugs may begin to produce deleterious effects (Duka, Crombag, & Stephens, 2011). Associative learning mechanisms may explain how drug-associated cues become able to trigger or modulate drug-seeking behavior. Pavlov’s dogs learned to salivate when presented with stimuli that had become associated with food. Similarly, conditioned drug-seeking behaviors might lead to the use and misuse of psychotropic drugs not typically considered drugs of abuse. Such drug-seeking and drug-misuse behaviors (e.g., involving gabapentin) might occur when drugs of abuse are not readily accessible or when they seem to have “lost their magic” for users. Despite reports of misuse, the subjective liking effects and reinforcing effects of gabapentin and other psychotropic drugs is likely to differ qualitatively and quantitatively from those effects of typical drugs of abuse.

**CONCLUSION**

In my opinion, gabapentin should be considered safe and appropriate for use in patients with all types of SUDs, including patients who take opioid drugs. For treating comorbid anxiety or insomnia in such patients, I believe gabapentin would be a much safer choice than benzodiazepine drugs (Lintzeris & Nielsen, 2009) and probably safer than antidepressant or antipsychotic drugs, based on drug safety data from the NPDS (Bronstein et al., 2012) and the Drug Abuse Warning Network (Howland, 2014; Substance Abuse and Mental Health Services Administration, n.d.). Medication prescribers should not be overly sanguine about the misuse
potential or safety of any drug. Vigilant monitoring for evidence of prescription drug misuse, not just with gabapentin, should be routine for all drugs in all patients. Signs of misuse include patients who come to appointments (especially initial appointments) asking for certain drugs by name; frequent claims of lost or stolen prescriptions; frequent requests for early prescription renewals; patients frequently taking extra drug doses or requesting to be put on higher drug doses; insured patients paying out of pocket for prescriptions; patients using multiple pharmacies or frequently changing pharmacies; patients seeing multiple physicians; and patients who have negative urine drug screens (suggesting that prescribed drugs are not being taken and might have been diverted). Nurses often are in the best position to detect prescription misuse and many nurses may have prescription privileges as well.

REFERENCES


Dr. Howland is Associate Professor of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, Pittsburgh, Pennsylvania. The author has disclosed no potential conflicts of interest, financial or otherwise.

Address correspondence to Robert H. Howland, MD, Associate Professor of Psychiatry, University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinic, 3811 O’Hara Street, Pittsburgh, PA 15213; e-mail: HowlandRH@upmc.edu.