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Review

Illicit gamma-hydroxybutyrate (GHB) and pharmaceutical sodium oxybate (Xyrem®): Differences in characteristics and misuse

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ABSTRACT

There are distinct differences in the accessibility, purity, dosing, and misuse associated with illicit gamma-hydroxybutyrate (GHB) compared to pharmaceutical sodium oxybate. Gamma-hydroxybutyrate sodium and sodium oxybate are the chemical and drug names, respectively, for the pharmaceutical product Xyrem® (sodium oxybate) oral solution. However, the acronym GHB is also used to refer to illicit formulations that are used for non-medical purposes. This review highlights important differences between illicit GHB and sodium oxybate with regard to their relative abuse liability, which includes the likelihood and consequences of abuse. Data are summarized from the scientific literature; from national surveillance systems in the U.S., Europe, and Australia (for illicit GHB); and from clinical trials and post-marketing surveillance with sodium oxybate (Xyrem). In the U.S., the prevalence of illicit GHB use, abuse, intoxication, and overdose has declined from 2000, the year that GHB was scheduled, to the present and is lower than that of most other licit and illicit drugs. Abuse and misuse of the pharmaceutical product, sodium oxybate, has been rare over the 5 years since its introduction to the market, which is likely due in part to the risk management program associated with this product. Differences in the accessibility, purity, dosing, and misuse of illicit GHB and sodium oxybate suggest that risks associated with illicit GHB are greater than those associated with the pharmaceutical product sodium oxybate.

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1. Introduction

Gamma-hydroxybutyric acid is an endogenous compound and putative neurotransmitter that differs from the primary inhibitory neurotransmitter gamma-aminobutyric acid (GABA) by the substitution of a hydroxyl group in place of the amino group of the GABA molecule (Maitre, 1997; Pardi and Black, 2006). Sodium gamma-hydroxybutyrate or sodium 4-hydroxybutyrate (GHB) is the International Union of Pure and Applied Chemistry chemical name for the sodium salt of gamma-hydroxybutyric acid, whereas sodium oxybate is the international drug name for the identical compound (Hillebrand et al., 2008). Sodium oxybate is marketed as Xyrem® in the U.S., Canada, and Europe by Jazz Pharmaceuticals, Valeant Pharmaceuticals International, and UCB, respectively. It is approved for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy in the U.S., for the treatment of narcolepsy with cataplexy in adult patients in Europe, and for the treatment of cataplexy with narcolepsy in Canada. Sodium oxybate is approved in Germany as an anesthetic, Somsanit® (Dr. F. Köhler Chemie), and is approved in Austria and Italy for the treatment of opioid and alcohol withdrawal as Alcover® (Laboratorio Farmaceutico; Hillebrand et al., 2008). Clinical development programs are also under way to study the clinical efficacy and safety of sodium oxybate for the treatment of conditions such as fibromyalgia (Russell et al., 2009) and essential tremor (Frucht et al., 2005). For the purposes of this report, *sodium oxybate* will be used to refer to the government-approved drug or pharmaceutical product. *GHB* will be used to refer to endogenous gamma-hydroxybutyric acid and chemical grade gamma-hydroxybutyrate. *Illicit GHB* will be used to refer to illicitly manufactured gamma-hydroxybutyric acid or gamma-hydroxybutyrate and street drug products that are purported to be GHB and might contain GHB or other compounds of unknown dose and purity.

GHB was legally manufactured and widely available as a nutritional supplement (to induce sleep or increase muscle mass) in the 1980s until reports of abuse as a "club drug" (a drug used in a club or party setting for its euphoric effects; e.g., Sumnall et al., 2008) and "date-rape drug" (a drug used for drug-facilitated sexual assault; e.g., Chin et al., 1992) led to the scheduling of GHB as a controlled substance. As of March 2000, GHB and sodium oxybate were placed in a unique bifurcated Federal schedule in the U.S.: GHB for non-medical use is Schedule I, the most restrictive schedule of the Controlled Substances Act (2008). When used as prescribed for medical purposes (e.g., the treatment of narcolepsy), it is a Schedule III substance.

In March 2001, the Commission on Narcotic Drugs of the United Nations, at the recommendation of the World Health Organization, added GHB to Schedule IV of the 1971 Convention on Psychotropic Substances, with GHB subject to scheduling or control in all Member States of the European Union. Some Member States (e.g., Italy, Latvia, and Sweden) subsequently also placed controls on one or both of the GHB precursors gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD; Hillebrand et al., 2008). In the U.S., GBL is a List I chemical (a chemical that is used in, and important to, the manufacture of a controlled substance) and is subject to regulatory controls; 1,4-BD is neither controlled nor listed at the Federal level (Controlled Substances Act, 2008), but is controlled in some U.S. states under State Law (e.g., Hawaii, Nevada; Hawaii Revised Statute, 2008; Nevada Administrative Code, 2008). Canada lists sodium oxybate/GHB and all salts as Schedule III.

Distinguishing between illicit GHB and licit GHB or sodium oxybate from clinical case reports of abuse and dependence is difficult. Many of the epidemiological studies or case reports that describe the effects of illicit GHB refer to the molecule simply as GHB (e.g., Kim et al., 2008). Without forensic analysis of the substance consumed or of a biological sample from the consumer, extrapolating effects reported after the administration of illicit GHB or a GHB precursor to the effects of chemical grade GHB or sodium oxybate requires several assumptions to be made, such as the illicit formulation contained GHB, the illicit formulation was not contaminated or adulterated by other chemicals, and the effects were not caused by a co-administered drug or chemical.

However, studies examining the effects of GHB are applicable to sodium oxybate. All pharmaceutical products have chemical names (e.g., sodium gamma-hydroxybutyrate), non-proprietary pharmaceutical names (e.g., sodium oxybate), and trade names (e.g., Xyrem). Clinical studies that were conducted with pharmaceutical grade GHB prior to the development of sodium oxybate as a commercial product (e.g., Broughton and Mamelak, 1979; Scharf et al., 1985) use the chemical name GHB and are applicable to the pharmaceutical product. The use of the chemical name in the scientific literature has likely persisted because of the availability and use of chemical grade GHB for non-human studies (e.g., Carter et al., 2003; Goodwin et al., 2005)

It is important, however, to recognize that illicit GHB and sodium oxybate have different risks or liabilities of abuse and using "GHB" to refer to both illicit GHB and sodium oxybate has blurred this distinction in the scientific literature and in the popular press. The purpose of this review is to summarize the differences between the relative abuse liability of sodium oxybate and that of illicit GHB, with a specific focus on the availability and prevalence of non-medical use, and the risks and consequences of misuse and abuse. Relative abuse liability includes both a drug's liability *for* abuse (likelihood that the drug will be abused) and its liability *of* abuse (consequences of abuse; Griffiths et al., 2003). Information on sodium oxybate, GHB, and illicit GHB from three types of sources are presented in this review: data from the peer-reviewed scientific literature; data from national surveys of drug use, abuse, and law enforcement activity; and data from Jazz Pharmaceuticals on the rates of abuse, diversion, drug-facilitated sexual assault, and deaths associated with sodium oxybate.

2. Characteristics of illicit GHB compared to those of sodium oxybate

2.1. Availability

2.1.1. Availability of illicit GHB. After GHB was scheduled in the U.S. in 2000 and became an illegal drug, it continued to be sold as a dietary supplement under a variety of different names, as a GHB alternative, or more covertly, as a solvent not recommended for human consumption (Maxwell and Spence, 2005). Chemistry kits, reagents, and recipes to convert GHB precursors into GHB also became available for purchase over the internet; however, the availability of these kits, reagents, and recipes is thought to have diminished in recent years (Nicholson and Balster, 2001; Mason and Kerns, 2002; European Monitoring Centre for Drugs and Drug Addiction Annual Report, 2007; National Drug Intelligence Center U.S. Department of Justice, 2008). Epidemiological data show that illicit GHB remains accessible to individuals in the U.S., Europe, and Australia (Degenhardt et al., 2005; Barker et al., 2007; Sumnall et al., 2008). International restrictions on the production and sale of GHB are thought to have shifted recreational use from GHB toward the GHB precursors GBL and 1,4-BD in the U.S., Europe, and Australia (Winickoff et al., 2000; Zvosec et al., 2001; Dupont and Thornton, 2001; Caldicott et al., 2004; Palmer, 2004; European Monitoring Centre for Drugs and Drug Addiction Annual Report, 2008; Hillebrand et al., 2008; Knudsen et al., 2008; Wood et al., 2008). GBL and 1,4-BD are ingested for recreational use presumably because they are converted to GHB in the body (Doherty and Roth, 1978; Lettieri and Fung, 1978), but they can