

The Clinical Development of γ -Hydroxybutyrate (GHB)

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Abstract: The discovery of gamma-hydroxybutyrate (GHB) over 40 years ago led to its immediate use as a general anesthetic agent. Subsequent research demonstrated that GHB is an endogenous compound in the mammalian brain and current research suggests that GHB is a probable neurotransmitter. In the United States, reports of anabolic effects lead to its misuse among body builders during the 1980's while the intoxicating properties of the drug lead to its popularization as a substance of abuse during the 1990's. GHB became associated with reports of drug-facilitated sexual assault and cases of physical dependence and withdrawal. Efforts to ban GHB caused increased use of GHB analogues and pro-drugs. Against this backdrop, GHB was being developed for the treatment of narcolepsy, leading to the approval of Xyrem® (sodium oxybate) oral solution in 2002 for the treatment of cataplexy in patients with narcolepsy. A risk management program permits the safe handling and distribution of the approved product, minimizes the risk for diversion, provides professional and patient education about the risks and benefits of sodium oxybate, and includes physician and patient registries. Post-marketing surveillance indicates sodium oxybate has an acceptable safety profile and presents minimal risk for the development of physical dependence.

Keywords: GHB, sodium oxybate, gamma-hydroxybutyrate, risk management, drug safety.

INTRODUCTION

Xyrem® (sodium oxybate) oral solution, a pharmaceutical preparation of gamma-hydroxybutyrate (GHB), was developed for the treatment of narcolepsy amid controversy surrounding the growing abuse of GHB and reports of its use to facilitate sexual assault. Narcolepsy is a life-long sleep disorder classically described as a tetrad of symptoms, consisting of excessive daytime sleepiness, cataplexy, sleep paralysis and hypnagogic hallucinations. Excessive daytime sleepiness results from the inability to achieve restorative sleep while the remaining symptoms are believed to represent the inappropriate expression of rapid eye movement (REM) sleep during wakefulness. In addition, patients with narcolepsy may suffer from fragmented nighttime sleep, automatic behaviors, problems with mental concentration and memory, and visual and other sensory disturbances [1, 2]. This paper discusses the clinical development of sodium oxybate and describes the steps taken to address safety concerns and how regulatory challenges were overcome. Details of the comprehensive risk management program that was established and the results of more than 2 years of post-marketing surveillance are also presented. Over 40 years since its discovery, gamma-hydroxybutyrate has been appropriately employed in clinical medicine for the treatment of a rare disorder and is poised for further research and clinical development, which may result in beneficial treatment of the unmet needs of other patient populations.

NEUROPHYSIOLOGY

GHB was discovered in 1960 by Henri Laborit while searching for therapeutically-useful analogues of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter

[3]. It was later discovered to be a naturally-occurring substance in the brain and many peripheral tissues [4]. The *in vivo* synthesis in the brain occurs primarily by the metabolism of GABA to succinic semialdehyde and reduction to GHB. Conversely, GHB metabolism involves oxidative conversion to succinic semialdehyde and then succinic acid, which enters the Krebs cycle. Thus, GHB is metabolized to carbon dioxide and water, without active metabolites. Minor routes of GHB metabolism include either conversion to GABA or by β -oxidation [5] (Fig. 1).

The need for better understanding of the role of GHB as an endogenous compound has been made even more evident by the description of an apparent inborn error of GHB metabolism due to a deficiency in succinic semialdehyde dehydrogenase (SSADH). This deficiency causes an accumulation of endogenous GHB, GABA and products of their β -oxidation, leading to motor problems including ataxia, hyporeflexia, seizures, mental retardation, hyperkinesia, psychosis and numerous other neurologic manifestations [6]. Although GHB is not normally detectable in healthy individuals [7], accumulated GHB in patients with this disorder has been shown to reach plasma concentrations as high as 100 $\mu\text{g/mL}$ in affected individuals [8].

A substantial amount of evidence supports the role of GHB as a neurotransmitter in the central nervous system (CNS) [5, 9]. Specifically, following neuronal synthesis, GHB is located within discrete axonal storage vesicles where it is subsequently released in a calcium-dependent manner and reuptake occurs *via* a sodium-dependent, high-affinity membrane transport system. GHB binds to high- and low-affinity binding sites located in neural tissue which have high specificity for GHB [5].

Although the specific function of naturally-occurring GHB beyond possible neuromodulation is unknown at this time, the administration of exogenous GHB results in several actions within the central nervous system, including a dose-

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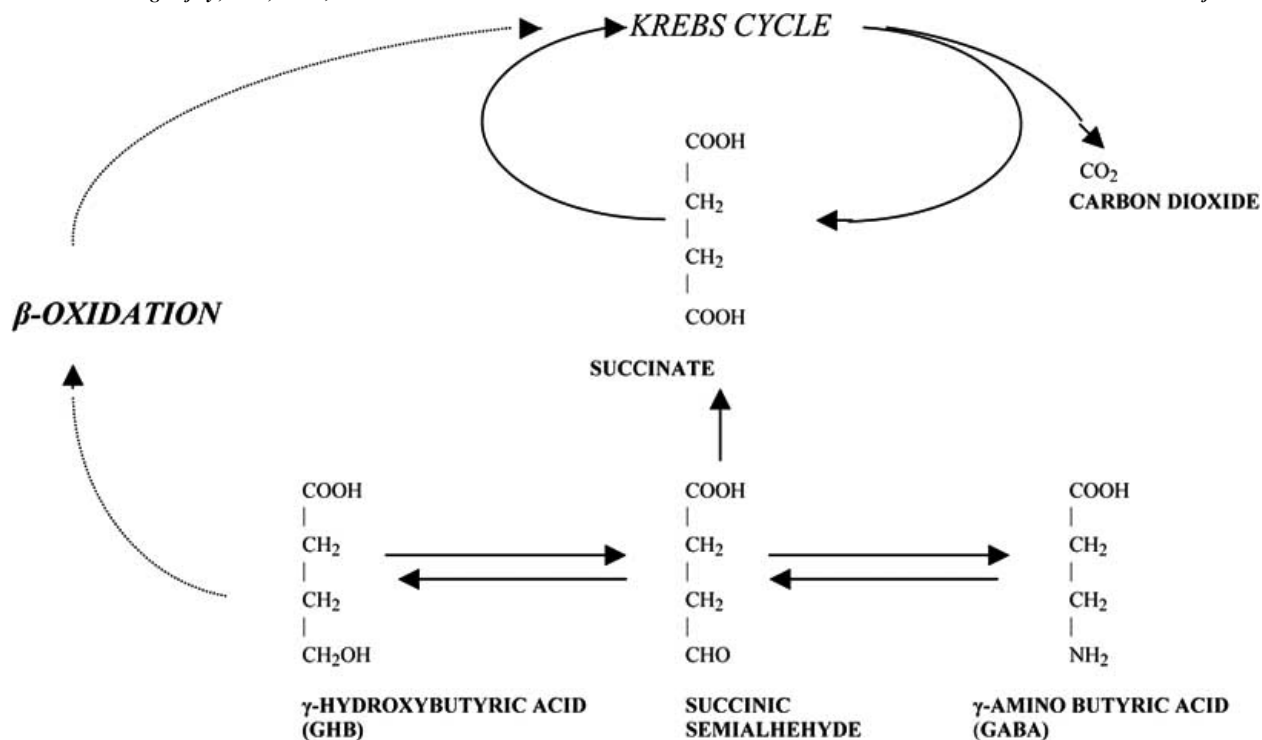


Fig. (1). Metabolism of gamma-hydroxybutyric acid.

dependent increase in dopamine concentration, increased serotonin turnover [5], and the release of growth hormone [10].

In addition to the CNS, many peripheral organs contain GHB. The concentrations of GHB in the heart, kidney, skeletal muscle, and brown fat are considerably higher than in the brain, suggesting it may participate in metabolic processes in these tissues [11]. For example, there is evidence that GHB can reduce energy substrate consumption in the brain and peripheral tissues and that it can protect these tissues from the damaging effects of anoxia or excessive metabolic demand [12]. In light of these findings, it is interesting to note that endogenous GHB concentrations have been found to be significantly elevated postmortem [7, 13]. The clinical implications of these findings remain to be elucidated.

EARLY CLINICAL USE

Soon after its discovery, Laborit outlined the merits of GHB as an anesthetic agent and also suggested potential beneficial effects in obstetrics, psychiatry, alcohol and opiate withdrawal syndromes and even on lipid metabolism [3]. Although GHB has been employed clinically in Europe in the field of anesthesia, it has no analgesic properties and must be used in combination with an opiate analgesic or other anesthetic agent. During induction and emergence from GHB anesthesia, random clonic movements (myoclonus) can occur. Thus, GHB never gained widespread acceptance as a general anesthetic agent [14].

Interestingly, it was found that the bedtime administration of GHB did not significantly change the normal sleep cycle as measured by EEG [15] and for this

reason, early investigators hypothesized that GHB may be beneficial for the treatment of disorders of disturbed nocturnal sleep. The marked disturbance of night-time sleep in patients with narcolepsy lead Broughton and Mamelak to use GHB in an attempt normalize the sleep in these patients in the hope that this would help control daytime symptoms [16, 17]. This treatment resulted in prompt improvements in the subjective quality of night-time sleep and produced gradual improvement in daytime symptoms of narcolepsy. In fact, the patients in these early studies found it easier to stay awake during the day and attacks of cataplexy virtually disappeared.

These and subsequent trials demonstrated that the nightly administration of GHB increased total nocturnal sleep time, decreased nighttime awakenings and increased the total duration of Stage 3 and 4 sleep [18-20]. These improvements in nocturnal sleep were also associated with improvements in daytime sleep attacks, cataplexy, sleep paralysis and hypnagogic hallucinations. The promising results of these trials lead to the formal clinical development of sodium oxybate, discussed below.

GHB ABUSE

During the 1980's, GHB had been marketed in the U.S. as an unregulated dietary supplement in health food stores, training gyms and fitness centers. Anabolic benefits were allegedly produced by stimulating growth hormone release and it was used by body builders and for strength training. In addition, it was promoted as a "natural" treatment for insomnia and to induce weight loss. Following reports of fatal overdoses among several body-builders in California and Florida, all GHB sales were banned by the FDA in 1990 [21].

Unfortunately, these steps did little to curb the abuse of GHB. Restrictions placed on the sale of GHB by the FDA and tighter state regulations led to an increase in illegally synthesized GHB and the use of so-called GHB analogues, such as gamma-butyrolactone (GBL), 1,4-butandiol (1,4-BD), which serve as pro-drugs in that they are metabolized to GHB *in vivo*. Products containing these industrial compounds quickly became available through various sources including the Internet. GBL was also sold over-the-counter in kit form with sodium hydroxide and instructions for the home synthesis of GHB [22]. As these analogs are converted to GHB following ingestion [23], GBL and 1,4-BD produce clinical manifestations similar to GHB although they may vary in potency and toxicokinetic properties.

By the mid-1990's, homemade and other illicit versions of GHB had developed notoriety as "club drugs" and were being widely used at "raves", or all-night dance parties [24]. Recreational users of the drug claimed to experience an alcohol-like euphoria, disinhibition and sexual arousal without unpleasant hang-over effects. Also at this time, a number of GHB users were experiencing acute overdose, often as a consequence of combining GHB with other drugs of abuse and ethanol [25, 26].

GHB was also implicated in a number of sexual assault cases, and like flunitrazepam (Rohypnol®, Hoffman-LaRoche, Inc.), was being labeled as a "date rape" drug in the U.S.[27]. Like many CNS depressants, GHB causes anterograde amnesia, especially when combined with ethanol, often leaving the victim unable to recall any details of the event [22].

By the end of the decade, the serious consequences of chronic abuse including dependence and withdrawal were being recognized [28]. Abuse over extended periods of time, ranging from months to years, has been reported. Some abusers allegedly escalated their daily GHB intake to approximately 150 gm per day [29, 30]. Interestingly, animal studies suggest that GHB has a low abuse potential [31].

Dose escalation associated with increased frequency of dosing, with reported dosing as often as every 30 minutes to three hours around-the-clock [32], forms the basis for the withdrawal syndrome. A distinct syndrome has been reported following abrupt cessation of illicit forms of GHB, which may persist for 5 – 15 days. Symptoms have included nausea, vomiting, anxiety, confusion, tremor, insomnia, agitation, psychosis, auditory and visual hallucinations, tachycardia and hypertension. For some of these individuals, withdrawal symptoms may be severe and require extremely high doses of benzodiazepines [32]. Pentobarbital has been used successfully and propofol has also been suggested as an alternative when benzodiazepines are insufficient [33, 34].

LEGAL HURDLES TO THE DEVELOPMENT OF SODIUM OXYBATE ORAL SOLUTION

The formal clinical development of sodium oxybate for the treatment of narcolepsy began in 1994. Orphan Medical was approached by the National Organization of Rare Disorders (NORD) and the Food and Drug Administration (FDA) Orphan Products Development Division, each suggesting the development of GHB (now called by its official generic name sodium oxybate) for the treatment of

narcolepsy. This suggestion was based on the promising results obtained by several independent investigators, as previously discussed, who reported on the efficacy of sodium oxybate (GHB) as a treatment for narcolepsy. In these early clinical trials, the nocturnal administration of sodium oxybate greatly improved the quality of nighttime sleep in patients with narcolepsy with an associated reduction in daytime sleep attacks, cataplexy and other symptoms of narcolepsy [17-20, 35].

By the late 1990s, however, there was a well-established awareness of the scale and consequences of the abuse epidemic of GHB and related analogues. The increasing number of cases of abuse, fatal overdose and drug-facilitated sexual assault prompted the Drug Enforcement Agency (DEA) to begin the formal rulemaking process to control GHB. This action threatened to greatly hinder the future development of GHB for legitimate medicinal purposes.

A primary issue was the application of a drug Schedule that would apply the harshest criminal penalties possible for the illicit use and unlawful distribution of GHB and related chemicals, yet allow access to sodium oxybate by patients who need it. Therefore, members of Congress were challenged to devise an acceptable legislative solution that addressed the urgent needs of law enforcement and patients with rare diseases. The resulting legislation was the Hillary J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000 (Public Law [PL] 106-172). This law stipulated a novel bifurcated scheduling and directed the U.S. Attorney General to amend the Controlled Substances Act by listing GHB as a Schedule I agent and creating an exception to place FDA-approved formulations of GHB in Schedule III. In addition, GBL was designated a List I chemical [36]. An additional provision to this act promoted continued evaluation of sodium oxybate as an Orphan Drug by permitting Schedule III storage conditions for investigational drug products containing GHB. The new law also made it clear that the use of any form of GHB to facilitate sexual assault was a federal crime and that illicit possession or distribution of any form of GHB would be subject to the criminal penalties of Schedule I.

Although each state has the option of imposing more restrictive scheduling than the Federal guidelines, the groundbreaking Schedule I/III status promoted by Congress has been adopted by 44 states in the U.S. and state-specific scheduling is in place in 5 other states. As of June 2005, legalization for prescription use is still pending in Oklahoma.

THE CLINICAL DEVELOPMENT OF SODIUM OXYBATE ORAL SOLUTION

Orphan Medical established the safety and efficacy of sodium oxybate for the treatment of cataplexy associated with narcolepsy in two multicenter, randomized, double-blind, placebo-controlled, parallel-group studies (Trials A, B)[37, 38]. Additional safety data was provided by a long-term, open-label trial, Trial C, a 12-month, open-label extension of Trial A, in which sodium oxybate doses were titrated to optimal clinical response for each patient [39]. Details of these Orphan Medical-sponsored trials are provided in Table 1. The results of these trials, in addition to the results of two small trials conducted by independent

Table 1. Summary of Sodium Oxybate Clinical Trials

| Trial | Description | Nightly Sodium Oxybate Dose (g) |
|---------|--|---------------------------------|
| Trial A | A 4-week trial that assessed 136 narcolepsy patients with moderate to severe cataplexy at baseline. The primary efficacy measure was the number of cataplexy attacks. | 3 - 9 |
| Trial B | A 4-week withdrawal trial that enrolled 55 narcolepsy patients who had been taking open-label sodium oxybate for 7 to 44 months and was designed to evaluate the efficacy of sodium oxybate after long-term use by demonstrating a return of cataplexy after discontinuation of sodium oxybate treatment. | 3 - 9 |
| Trial C | 12-month, open-label extension of Trial A, in which Xyrem doses were titrated to optimal clinical response for each patient. | 3 - 9 |
| Trial D | An 8-week trial that assessed 228 narcolepsy patients with moderate to severe symptoms. Primary efficacy measures were subjective changes in excessive daytime sleepiness, using the Epworth Sleepiness Scale, and Clinical Global Impression of Change. | 4.5 - 9 |
| Trial E | An 8-week, double-dummy trial that assessed 222 narcolepsy patients with moderate to severe symptoms. During the active treatment phase, patients received placebo, sodium oxybate, modafinil, or sodium oxybate plus modafinil. The primary efficacy measure was the change in excessive daytime sleepiness as measured by the Maintenance of Wakefulness Test. | 6 - 9 |

investigators [19, 20], formed the basis for the approval of sodium oxybate for the treatment of cataplexy in patients with narcolepsy in the U.S.

Encouraging results in these trials on symptoms of daytime sleepiness, and the results of a pilot study on the effect of sodium oxybate on sleep architecture and daytime alertness [40] lead to two multicenter trials (Trials D & E) evaluating the effects of sodium oxybate on sleep architecture and daytime functioning (Table 1) [41, 42]. The results of these trials on the treatment of excessive daytime sleepiness showed promising results and have been included in a supplemental new drug application submitted to the FDA in January 2005 seeking broader indications for the treatment of narcolepsy [42].

The data from these clinical trials indicate that the nightly administration of sodium oxybate for the treatment of narcolepsy is associated with significant improvements in nighttime sleep, including dose-related increases in slow wave sleep [18-20, 40, 42] and decreases in nocturnal awakenings [17-20, 40, 42]. These improvements coincided with improvements in cataplexy [17, 19, 41] and subjective and objective measures of daytime sleepiness [17, 18, 20, 40, 42].

SAFETY DATA

The following safety summary is based on combined data from the three large parallel-group studies: Trial A, Trial D, and Trial E. Note that data from patients in Trial B have not been included in this summary. All patients in that trial had been recruited from other studies in which they were treated with sodium oxybate for six months or more, and they were then randomized in double-blind fashion to continued treatment with sodium oxybate or placebo. The return of cataplexy in placebo-treated patients was used as evidence of long-term efficacy of the drug; however, the treatment-emergent events in this withdrawal paradigm were considered unlikely to be the same as those in patients newly introduced to sodium oxybate treatment.

Table 2 lists the incidence of treatment emergent adverse events for which there was an incidence of $\geq 2\%$ in any dosage group with greater than 100 patients, and the

incidence in at least one dosage group on drug was greater than placebo. The number of patients in each dosage group represents the total number of patients treated at each dose.

The most common adverse events were nausea, dizziness, vomiting, somnolence and enuresis. Certain adverse events were significantly more common during sodium oxybate than placebo treatment: diarrhea, nausea, vomiting, disturbance in attention, dizziness, paresthesia, tremor, enuresis, and hyperhidrosis. Discontinuations of treatment due to adverse events were most common at the highest dose of sodium oxybate. A dose-response relationship was observed for nausea, vomiting, paresthesia, disorientation, irritability, disturbance in attention, feeling drunk, sleepwalking and enuresis with the incidence of these events being notably higher at 9 g/d. Dizziness was most common at 3 and 9 g/d.

Potential pharmacokinetic drug interactions were analyzed in Phase I studies with other medications commonly prescribed in patients with narcolepsy, specifically, zolpidem, protriptyline and modafinil. These were single dose studies in which volunteers received sodium oxybate alone and together with one of the drugs noted above as single doses following a one-week washout period. No pharmacokinetic interactions were demonstrated [43, 44]. The potential for drug interactions by inhibition of human hepatic microsomal cytochrome P450 (CYP) isozymes was also assessed. Sodium oxybate did not affect the activity of human CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A isozymes [42]. Metabolic interactions with the large number of drugs metabolized through these pathways are, therefore, not anticipated. The antiepileptic drugs valproic acid, ethosuximide and the barbiturates inhibit the conversion of GHB to succinic semialdehyde by blocking the NADP-dependent GHB dehydrogenase, which may lead to potentiation of the effects of GHB (Maitre 1997).

RISK MANAGEMENT PROGRAM

Coincident with the clinical development of sodium oxybate was the creation and implementation of the risk management concept in the U.S. [45]. Ultimately, the goal of

Table 2. Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled Clinical Trials

| System Organ Class | Placebo (n=213) | Sodium Oxybate Oral Solution Dosage (g/d) at Onset | | | |
|---|-----------------|--|-----------|-----------|----------|
| MedDRA Preferred Term | | 4.5 (n=185) | 6 (n=258) | 9 (n=178) | p-value* |
| Gastrointestinal Disorders | | | | | |
| Abdominal Pain Upper | 4 (2%) | 5 (3%) | 3 (1%) | 4 (2%) | 0.3209 |
| Diarrhea | 3 (1%) | 6 (3%) | 6 (2%) | 7 (4%) | 0.0255 |
| Dry Mouth | 4 (2%) | 1 (1%) | 6 (2%) | 1 (1%) | >0.9999 |
| Nausea | 7 (3%) | 14 (8%) | 34 (13%) | 35 (20%) | <0.0001 |
| Vomiting | 3 (1%) | 3 (2%) | 11 (4%) | 20 (11%) | 0.0002 |
| General Disorders and Administration Site Conditions | | | | | |
| Feeling Drunk | 1 (1%) | 0 | 1 (0%) | 6 (3%) | 0.2725 |
| Edema Peripheral | 2 (1%) | 6 (3%) | 0 | 0 | 0.5067 |
| Pain | 3 (1%) | 2 (1%) | 1 (0%) | 5 (3%) | 0.5561 |
| Musculoskeletal and Connective Tissue Disorders | | | | | |
| Cataplexy | 3 (1%) | 2 (1%) | 2 (1%) | 4 (2%) | 0.7552 |
| Muscle Cramp | 2 (1%) | 3 (2%) | 1 (0%) | 4 (2%) | 0.5067 |
| Pain in Extremity | 1 (1%) | 5 (3%) | 3 (1%) | 2 (1%) | 0.1076 |
| Nervous System Disorders | | | | | |
| Disturbance in Attention | 0 | 2 (1%) | 0 | 7 (4%) | 0.0103 |
| Dizziness | 8 (4%) | 17 (9%) | 29 (11%) | 26 (15%) | <0.0001 |
| Paraesthesia | 1 (1%) | 4 (2%) | 3 (1%) | 5 (3%) | 0.0424 |
| Sleep Paralysis | 1 (1%) | 0 | 2 (1%) | 5 (3%) | 0.1723 |
| Somnolence | 9 (4%) | 2 (1%) | 8 (3%) | 15 (8%) | 0.2127 |
| Tremor | 0 | 0 | 4 (2%) | 9 (5%) | 0.0032 |
| Psychiatric Disorders | | | | | |
| Anxiety | 3 (1%) | 2 (1%) | 3 (1%) | 4 (2%) | 0.5580 |
| Disorientation | 2 (1%) | 1 (1%) | 4 (2%) | 6 (3%) | 0.1545 |
| Irritability | 2 (1%) | 0 | 1 (0%) | 5 (3%) | 0.5067 |
| Sleepwalking | 0 | 0 | 0 | 5 (3%) | 0.1688 |
| Renal and Urinary Disorders | | | | | |
| Enuresis | 2 (1%) | 6 (3%) | 7 (3%) | 13 (7%) | 0.0009 |
| Skin and Subcutaneous Tissue Disorders | | | | | |
| Hyperhidrosis | 0 | 1 (1%) | 3 (1%) | 6 (3%) | 0.0105 |

*p-value from the Fishers Exact test comparing the incidence of AEs in the sodium oxybate (Total) and Placebo groups.

risk management is to make certain that pharmaceutical products are developed, tested, manufactured, labeled, prescribed, dispensed, and used in a way that maximizes benefit to patients and minimizes risk of diversion and misuse. Risk management extends beyond the usual regulations on labeling, promotion and advertising to involve activities such as mandated education to healthcare providers and patients; restricted product distribution; post-marketing study requirements; a streamlined process for withdrawing the drug from the market in the event of a product recall; prescribing restrictions to specific patient populations; use of physician and patient registries, and/or establishment of a comprehensive method for overseeing the prescribing, dispensing, and use of the medication [46].

Because of the growing apprehension regarding the risk of possible drug diversion following the approval of sodium oxybate and concerns about safe use, Orphan Medical collaborated with the FDA, experts in drug diversion, drug abuse prevention and clinicians to create a risk management program [47]. The goals of this program are to ensure the responsible distribution of sodium oxybate to patients with narcolepsy and to educate physicians and patients about the safe and responsible use of sodium oxybate. Elements of the risk management program include:

- A single, centralized pharmacy housed in a secure facility,
- Physician and patient registries,

- Xyrem Success Program® educational materials for patients and physicians, and
- A post-marketing evaluation program (PMEP) for surveillance of adverse events.

Unlike traditional pharmacies, the central pharmacy maintains comprehensive patient and physician registries and verifies the eligibility of every prescribing physician before their sodium oxybate prescription is honored. Pharmacists are trained to be alert for compliance issues, such as rapidly escalating drug doses, short refill intervals, and suspicious questions or behaviors on the part of physicians or patients. They also provide ongoing counseling to monitor patient safety, compliance and provide educational and clinical support for patients and prescribers.

Each physician who wishes to prescribe sodium oxybate is sent the Xyrem Success Program® for physician education materials. These materials provide treatment guidelines for physicians to consider when prescribing sodium oxybate. Physicians are also encouraged to counsel their patients on the proper dosing and administration of sodium oxybate and to evaluate patients every three months and to re-write prescriptions for sodium oxybate at three month intervals.

After the pharmacy receives a new prescription, the patient is sent the Xyrem Success Program educational materials for patients, if it was not already provided to them by their physician. The program contains information that teaches them important aspects about the efficacy and safety of the product, cautions them about the dangers of combining sodium oxybate with alcohol or other sedating medications, and encourages them to not drive a car or perform hazardous tasks until 6 hours after the last dose of sodium oxybate. Before shipping the medication, a pharmacist contacts the patient to confirm that they understand the information in the Xyrem Success Program for patients and to address any additional questions or concerns.

Sodium oxybate is shipped to the patient using an overnight shipping service. The patient or their designee must be available to sign for the prescription or it will be returned to the pharmacy. The pharmacy staff also contacts the patient to ensure that their prescription has been received.

The central pharmacy records all reports of theft, losses or potential diversion of sodium oxybate on a Diversion Risk Report which are summarized and reported to the FDA on a quarterly basis. Since the commercial launch of sodium oxybate in September 2002 through March 31, 2005, sodium oxybate has been received by 8,391 registered patients. A total of 20 Diversion Risk Reports were completed by the central pharmacy during this period, consisting of reports of loss, theft, courier delivery issues and patient non-compliance.

POST-MARKETING SURVEILLANCE

As a condition of FDA approval, in consideration of the relatively small safety database generated in early clinical trials, a post marketing evaluation program (PMEP) was implemented to provide the FDA with information regarding the initial 6 months of sodium oxybate therapy in 1,000 patients. Each prescribing physician is requested to solicit

the occurrence of adverse events of special interest with their patients at 3- and 6-month clinic visits. Of special interest are reports of potentially serious events, such as vomiting, urinary incontinence (enuresis), sleepwalking, confusion or convulsions. In addition, physicians may use these forms to record information about suspected patient abuse or misuse of sodium oxybate. All obtained information is recorded on evaluation forms, included with the Xyrem Success Program for physicians materials, which are then faxed or mailed to an independent drug safety agency for data management.

A total of 695 PMEP reports had been received as of 30 September 2004, representing 460 unique patients. No adverse events were reported in 467 of these reports (67% of all reports received). The number of "no adverse event" reports after less than 3 months, 3-6 months, 6-9 months and more than 9 months of sodium oxybate therapy were 184, 136, 79 and 54, respectively. The incidence of many adverse events occurred at a much lower frequency than currently cited in the product label. For example, the incidence of sleepwalking and convulsions were much less than previously reported.

Table 3 summarizes the most commonly reported adverse events (20 or more) from both spontaneous reports and reports arising from the PMEP. These commonly reported adverse events are consistent with those identified in clinical studies. Despite fairly extensive exposure to the product, no new safety concerns have been identified when analyzing the sodium oxybate post-marketing safety database.

The impact of the bifurcated scheduling of GHB can be indirectly measured by trends in emergency department visits related to drug abuse involving GHB. The Drug Abuse Warning Network (DAWN) is a public health surveillance system that monitors drug-related hospital emergency department visits and drug-related deaths for the purpose of identifying drug abuse trends in the US. Currently, these data are limited to reports obtained from 260 hospitals in 21 metropolitan areas; however, these data suggest that GHB-related emergency department visits peaked in 2000, the year in which the Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000 was enacted. Emergency department visits dropped by one-third in 2001 and showed a slight decline the following year [48]. Beginning in 2003, major new features of DAWN were initiated, including a change in the method by which data is collected and broadening the scope to include ED visits related to the use of drugs for legitimate therapeutic purposes. As a result, direct comparison of 2003 data with that from previous years is no longer possible; however, a total of 990 visits for GHB were recorded in the 3rd and 4th quarters of 2003 compared to approximately 47,000 visits for heroin and 120,000 visits for cocaine [49].

Reports to poison centers of exposures to GHB or its analogues have shown a similar decline since the enactment of the Hillory J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000. The number of exposures to GHB or its analogues has declined from 1,916 in 2001 (the first year data on GHB was collected) to 800 exposures in 2003, a 58% decline [50, 51]. Based on these findings, the commercial launch of sodium oxybate in 2002 does not

Table 3. Summary of Common Adverse Event Reports by System Organ Class

| | Spontaneous Reports | PMEP Reports | Total |
|---|---------------------|--------------|-------|
| Gastrointestinal Disorders | | | |
| Nausea | 43 | 33 | 76 |
| Vomiting | 23 | 17 | 40 |
| General Disorders and Administration Site Conditions | | | |
| Feeling abnormal | 26 | 1 | 27 |
| Nervous System Disorders | | | |
| Headache | 24 | 16 | 40 |
| Dizziness | 9 | 19 | 28 |
| Somnolence | 17 | 16 | 33 |
| Tremor | 14 | 8 | 22 |
| Psychiatric Disorders | | | |
| Confusion/confusional state | 19 | 28 | 47 |
| Insomnia | 28 | 15 | 43 |
| Depression | 16 | 6 | 22 |
| Anxiety | 12 | 9 | 21 |
| Renal and Urinary Disorders | | | |
| Enuresis/incontinence | 6 | 24 | 30 |

appear to have contributed in any substantive way to the abuse of GHB.

CONCLUSION

Coincident with the clinical development of sodium oxybate for the treatment of narcolepsy were growing concerns of potential misuse and abuse of GHB, fears of diversion and misuse of sodium oxybate following commercial availability and concerns of physical dependence. Following federal legislation, which created a unique bifurcated Schedule I/III for illicit GHB/sodium oxybate, reports of apparent abuse of illicit GHB appears to be steadily declining. The implementation of a risk management program has made sodium oxybate available to thousands of patients while few reports of suspected diversion have occurred. No cases of physical dependence have been reported and the overall safety profile of sodium oxybate in clinical use appears to be superior than was originally observed during clinical trials.

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