



The Xyrem® (Sodium Oxybate) Risk Evaluation and Mitigation Strategy (REMS) Program in the USA: Results From 2016 to 2017

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Abstract

Background Sodium oxybate, which is approved for the treatment of cataplexy or excessive daytime sleepiness in patients with narcolepsy, is available in the USA only through the restricted-distribution Xyrem® Risk Evaluation and Mitigation Strategy Program (Xyrem REMS Program, XRP). The XRP requires prescriber enrollment and certification, patient enrollment, and prescriber attestation of patient counseling. Sodium oxybate is dispensed only by the certified pharmacy. After pharmacist/patient counseling, sodium oxybate is shipped only to enrolled patients, with documentation of safe use. Documentation of enrollments, prescriptions, counseling, shipments, and adverse events in a central database, and risk management reporting of any suspicion of abuse, misuse, or diversion, ensure provider notification and facilitate monitoring.

Objective This analysis reports data from the XRP regarding assessment of the risks of serious adverse outcomes that may result from inappropriate prescribing, abuse, misuse, and diversion.

Methods Data collected from December 2016 to December 2017 were analyzed.

Results Prescriptions were from enrolled prescribers ($n = 4524$); 17,037 patients received one or more shipment of sodium oxybate. No patients were shipped sodium oxybate under more than one name/identifier or after being disenrolled; no individual patient had overlapping active prescriptions. Sodium oxybate was dispensed in 146,426 shipments containing 375,173 bottles; of those, 13 shipments (0.009%) and 26 bottles (0.007%) were lost in delivery and not recovered. Notifications regarding potential abuse ($n = 31$), misuse ($n = 343$), or diversion ($n = 22$) were discussed with prescribers. Most patients and prescribers were aware of the main safety risks of sodium oxybate.

Conclusions The XRP maintains controlled access to sodium oxybate; additional prescriber education on safety risks may be warranted.

Key Points

Sodium oxybate is an effective treatment for symptoms of narcolepsy (cataplexy and excessive daytime sleepiness).

Because of the risks of abuse, misuse, and diversion, the manufacturer of sodium oxybate has a Risk Evaluation and Mitigation Strategy program to limit availability of the medication and reduce risk.

This analysis of program records demonstrates that sodium oxybate treatment is provided in a controlled manner to patients, although additional education on mitigating the risks of abuse, misuse, and diversion would be beneficial.

Judi Profant: At the time the work was conducted.

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1 Background

1.1 Narcolepsy

Narcolepsy is a neurologic disorder characterized by excessive daytime sleepiness, cataplexy (a sudden loss of voluntary muscle control usually triggered by emotions), disrupted night-time sleep, hypnagogic and/or hypnopompic hallucinations (hallucinations upon going to sleep or waking up from sleep, respectively), and sleep paralysis [1]. Narcolepsy can have a devastating impact on patients' lives, contributing to loss of psychological, social, and job functionality and potentially endangering personal safety [2]. Patients with narcolepsy report impaired quality of life, withdrawal from social interactions, and emotional and social difficulties [3–5]. Job performance in patients with narcolepsy is often negatively affected by absenteeism, presenteeism, and disability [4]. Patients in school frequently have poor academic performance [6]. Furthermore, narcolepsy is associated with a higher prevalence of psychiatric and medical comorbidities, such as depression, anxiety, heart disease, and hypertension, as well as accidental injuries [7, 8]. Historically, because no medications were approved, cataplexy was treated off-label with antidepressants, often tricyclic antidepressants or monoamine oxidase inhibitors [9, 10]. However, antidepressant drugs had limited evidence of efficacy in patients with narcolepsy, were associated with safety concerns during treatment and upon discontinuation, and led to rebound cataplexy when withdrawn [9–12].

1.2 Sodium Oxybate

In the 1990s, gamma-hydroxybutyric acid (GHB) was a promising investigational treatment for narcolepsy [13]. However, concerns about potential illicit use and misuse of GHB led to its designation as a Schedule I controlled substance (i.e., a drug with no accepted medical use and a high potential for abuse [14]) and reservations about whether a pharmaceutical formulation could be safely marketed. In response, clinical trials were conducted to evaluate the efficacy and safety of sodium oxybate (SXB) [the sodium salt of GHB] in the treatment of patients with narcolepsy. Additionally, the sponsor of the clinical development program for SXB (Orphan Medical, now Jazz Pharmaceuticals) created a unique risk management program. Unlike GHB, SXB is a Schedule III controlled substance (i.e., a drug with moderate-to-low potential for physical and psychological dependence [14]). In developing the risk management program, the sponsor consulted with stakeholders, including patients with narcolepsy, the

US Congress, and the US Drug Enforcement Administration (DEA).

In 2002, the US Food and Drug Administration (FDA) approved SXB for the treatment of cataplexy in narcolepsy, with this risk mitigation and monitoring plan in place. In 2005, the FDA approved SXB for the treatment of excessive daytime sleepiness in narcolepsy. Legislation was enacted in 2007 to formalize Risk Evaluation and Mitigation Strategy (REMS) programs to ensure safe use of medications, and the risk mitigation and monitoring program for SXB was converted to a formal REMS program in 2015. In 2018, the FDA expanded the indication to the pediatric population aged 7–17 years based on results of a phase III clinical trial [15]. While this expansion occurred after the collection of data reported here, the present analysis includes data for children and adolescents who received SXB prescribed off-label.

1.3 Xyrem REMS

Traditional distribution and dispensing of prescription controlled substances presents many potential points for theft or diversion [16]. Diversion can occur via illegal or improper prescribing, prescription forgery, pharmacy theft, “doctor shopping,” and illegal sales of prescription drugs through the internet, pharmacies, or pain clinics [16]. Abuse and misuse are defined as agents being used in a manner other than as prescribed. By contrast, the risk management program for SXB (the Xyrem® US REMS Program [XRP]) prevents distribution through wholesalers, distributors, or other third parties. The name of the program was recently (as of 21 July, 2020) changed to include Xywav™ (calcium, magnesium, potassium, and sodium oxybate), a lower sodium oxybate formulation that was approved in the USA in July 2020 for the same indications as SXB. Lower sodium oxybate is available in the USA through the same REMS program as SXB.

The program comprises requirements for prescriber enrollment, education, and certification, patient enrollment and education, prescriber attestation of prescriber/patient counseling, and documentation of pharmacist/patient counseling through completion of a pharmacist counseling checklist. Sodium oxybate is dispensed by a single certified pharmacy. The certified pharmacy was required to ensure that all pharmacists complete the XRP Certified Pharmacy Training Program. This training program ensures that all pharmacists are informed of the risks and safe use of SXB. The certified pharmacy verifies prescriber enrollment and certification and documents prescriber attestation of prescriber/patient counseling. Each patient then receives additional counseling

from a pharmacist before the first shipment of SXB is dispensed. After pharmacist/patient counseling, a limited quantity (≤ 90 -day supply) of SXB is then shipped directly only to enrolled patients, with documentation of safe use. Delivery requires address confirmation and signature of the patient or adult designee. All prescriber, patient, and prescription data collected, including enrollments, prescriptions, counseling, shipments, and adverse events, are documented in the central database maintained by the sponsor. Risk management reporting of any suspicion of abuse, misuse, or diversion ensures provider notification and facilitates ongoing longitudinal monitoring. All reports of lost/stolen shipments are investigated and recorded in the central database (Fig. 1). Beyond required contacts between pharmacy, prescriber, and patient (during enrollment), the pharmacy call center is available to respond to questions from prescribers, patients, and family members. Details of the XRP are described in the following sections.

1.3.1 Prescriber Enrollment

To prescribe SXB, providers must be enrolled and certified. Completion of the prescriber enrollment form documents that all requirements for prescriber enrollment and certification have been met. Prescribers must confirm that they have reviewed educational materials, understand the approved indications and risks of SXB, and agree to the requirements of the XRP. This information is entered into the central database so that the certified pharmacy can verify that the prescriber is enrolled in the program as part of its validation process; the certified pharmacy fills prescriptions only from prescribers who have completed certification in the XRP or were certified under the previous risk management program

and continued to meet the requirements of the XRP. Upon receipt of an initial prescription, the certified pharmacy checks the central database to ensure that the prescriber is certified and to verify the prescriber’s name, DEA number, and state license number so that only prescriptions written by individuals who can legally prescribe a Schedule III controlled substance are filled.

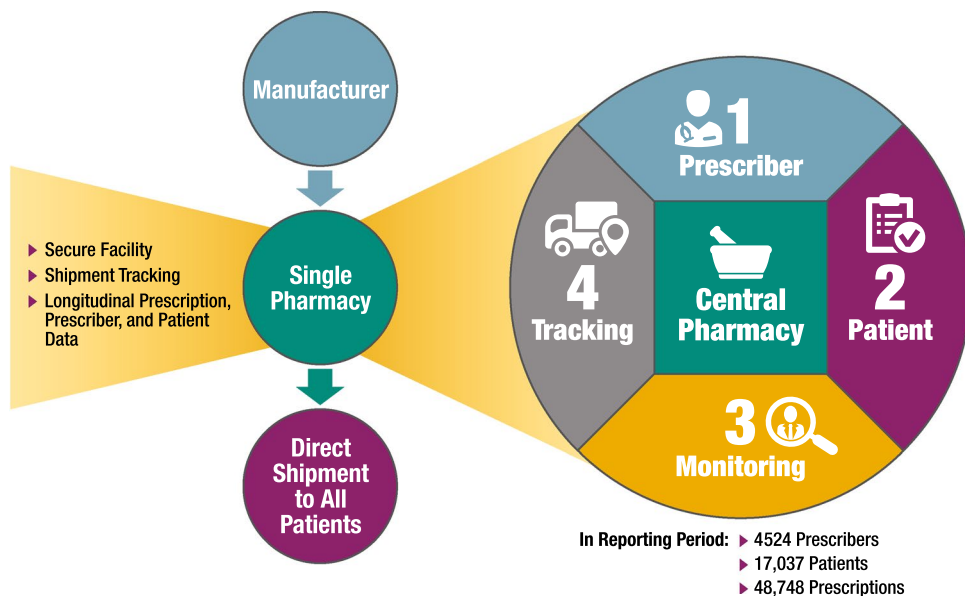
1.3.2 Prescriber Disenrollment

Prescribers can be disenrolled from the XRP for various reasons, as described subsequently (Sect. 3.1.3). The pharmacy disenrolls prescribers from the XRP after consultation with the sponsor.

1.3.3 Patient Enrollment

The XRP requires that all patients be enrolled before they begin treatment. A certified prescriber completes an enrollment form with each patient, which is submitted to the XRP for processing and completion of enrollment. The form is jointly reviewed and signed by the prescriber and patient. This form captures patient demographic and insurance information, links the certified prescriber to that enrolled patient, and documents that specified requirements have been met, including an attestation that the prescriber has counseled the patient on the serious risks and safe use of SXB. This information is entered into the central database, allowing the certified pharmacy to verify that the patient is enrolled as part of the pharmacy validation process prior to dispensing SXB. The prescriber is notified once a patient is successfully enrolled and can be prescribed SXB.

Fig. 1 Xyrem® Risk Evaluation and Mitigation Strategy Program (XRP) supply chain controls. Reporting period, 27 December, 2016 to 26 December, 2017



1.3.4 Patient Discontinuation and Disenrollment

Discontinued patients are defined as patients whose treatment has been interrupted but who are eligible to restart treatment if appropriate (i.e., not disenrolled). If a patient has not been sent a shipment and has not had any contact with the pharmacy for ≥ 90 days, the patient is considered discontinued but remains eligible to restart treatment with a prescription from a certified prescriber, without needing to re-enroll in the XRP. If a patient has not been sent a shipment of SXB for > 180 days, the patient is considered discontinued and must complete pharmacist/patient counseling with certified pharmacy staff to be eligible to restart treatment. *Disenrolled* patients are defined as patients removed from the program for either death or noncompliance. The pharmacy disenrolls patients from the XRP.

1.3.5 Shipments

The certified pharmacy tracks each SXB shipment through the carrier's website to confirm delivery. Tracking reports are generated to confirm the receipt of orders shipped during the previous 48 h. If an order is not delivered on the initial attempt, the carrier makes two additional delivery attempts. If delivery attempts are not successful, the carrier returns the shipment to the certified pharmacy, per the agreement between the carrier and the certified pharmacy. Per the requirements of the XRP, a risk management report (RMR) is completed for any lost shipment. If loss of a shipment is reported by the carrier, approval by the pharmacist-in-charge is required before a replacement can be shipped.

1.3.6 Participant Risk Education

Prescribers attest to having read and understood the SXB prescribing information [17] and the XRP prescriber brochure to be certified. Before the first prescription of SXB is shipped to each patient, the prescriber must attest that prescriber/patient counseling has been provided regarding the serious risks and safe use of SXB. In addition, each patient must complete pharmacist/patient counseling with a pharmacist at the certified pharmacy. All certified pharmacy personnel are required to complete training annually and achieve scores of $> 80\%$ on all knowledge assessments.

1.3.7 Monitoring and Interventions for Abuse, Misuse, and Diversion

The XRP is centrally administered by the certified pharmacy with a dedicated team of pharmacists and staff. The central database contains longitudinal information on all

prescribers, patients, and prescriptions; this information is readily accessible to inform pharmacist decision making with respect to suspicion of abuse, misuse, or diversion, as well as the need for provider notification or consultation, RMR investigation, and/or disenrollment of a patient or prescriber. Investigations into potential abuse, misuse, and diversion are a requirement of the pharmacy "Elements to Assure Safe Use" component of the XRP. The principal tool used by the pharmacy to monitor for inappropriate prescribing, misuse, abuse, and diversion of SXB is the RMR. A pharmacist must complete an RMR for any event that gives rise to a reasonable suspicion of abuse, misuse, or diversion of SXB. This includes all requests for early refill and all reports of lost, stolen, destroyed, or spilled drug. The XRP requires that the pharmacy notify the prescriber of suspected abuse, misuse, or diversion of drug when a patient requests an early refill. The reports may be used as an opportunity for additional patient counseling. Finalized RMRs are submitted to the sponsor.

Each completed RMR includes patient identifier and profile information, the date of the event, a descriptive narrative, a record of the certified pharmacy contact(s) with the prescriber related to the event, the outcome(s) of the event, including any action taken by the certified pharmacy related to the event, and a list of any documents or reports related to the event (e.g., adverse event reports, police reports, DEA Form 106 for lost shipments, and/or fire reports). In many cases, RMR documentation of investigations includes multiple pharmacy-patient and/or pharmacy-prescriber interactions that transpired over several days. The completed RMR provides a concise compilation of relevant information associated with each potential risk event and, once documented in the XRP central database, provides longitudinal data the certified pharmacy can review to determine whether a pattern of behavior indicates likelihood of abuse, misuse, diversion, or inappropriate prescribing.

The RMR history for each enrolled patient who received SXB from the certified pharmacy is available for consultation and review by certified pharmacy staff; RMR history review by the pharmacist is required in response to any early refill request or any suspicion of abuse, misuse, or diversion of SXB. In addition, prescriber notification by the pharmacist is required in response to any early refill request or any suspicion of abuse, misuse, or diversion of SXB. Review of a patient's RMR history with the prescriber ensures that both the prescriber and pharmacist are fully informed of all relevant events and are able to identify patterns of potential abuse or misuse when deciding whether to approve or deny an early refill request, modify the dose, add an alert to the patient's profile, or ultimately disenroll the patient. Reports of suspected misuse also present additional opportunities for prescribers and pharmacists to consider providing additional patient counseling. The detailed monitoring of RMR history

for each patient provides opportunities to reinforce education regarding the risks associated with SXB and the conditions for its safe use. Documentation of patient RMR history, and ongoing review of that history, enables patient access to this important medication while ensuring appropriate monitoring for signs of abuse, misuse, or diversion.

An early refill request occurs when a patient or prescriber reports that the patient would not have sufficient SXB to last until the next scheduled shipment and would require SXB to be shipped sooner than scheduled. Early refill requests do not include changes to shipment scheduling that result from shipment logistics, such as the carrier not shipping on weekends and holidays. In these cases, SXB is delivered prior to a patient’s next shipment date, but the patient’s subsequent refill date does not shift, thus ensuring that the patient does not receive more SXB than was prescribed. The pharmacist is required to notify the prescriber of the request, complete an RMR for every early refill request, and monitor a patient’s history of early refill requests as part of the required monitoring of patients for abuse, misuse, and diversion of the medication (Fig. 2).

1.4 Objective of Current Analysis

The objective of this analysis was to report data from the XRP related to its goal of mitigating the risks of serious adverse outcomes that may result from inappropriate prescribing, abuse, misuse, and diversion of SXB.

2 Methods

2.1 REMS Assessment

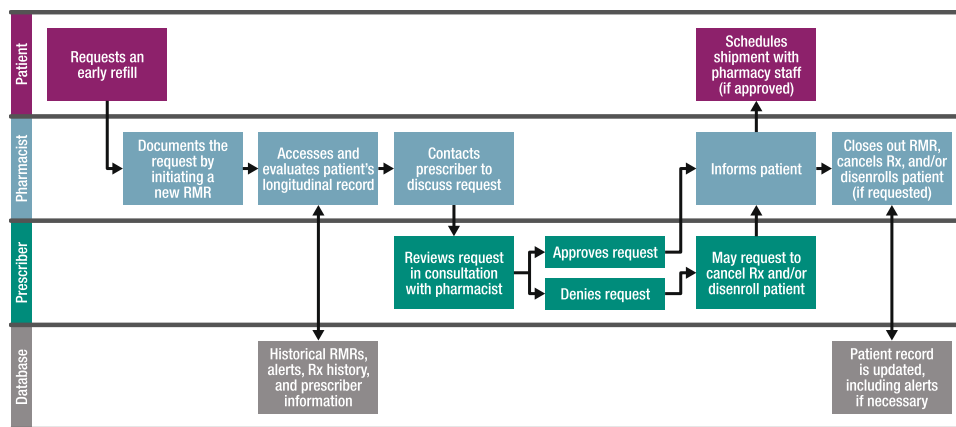
Periodic assessments of the XRP are performed at regular intervals, 6 months after approval and annually thereafter. This report is based on the fourth assessment and includes

data collected in the XRP central database over the 12-month reporting period from 27 December, 2016 to 26 December, 2017 and cumulative data for the 28 months from the beginning of REMS program implementation (24 August, 2015) through the end of this reporting period. Descriptive data include prescriber certification and patient enrollment, prescription dispensing, shipments of medication, participant risk education surveys, RMRs, police reports and DEA notifications for lost shipment replacement requests, and notification to prescribers of suspicion of potential abuse, misuse, or diversion. A subset of patients and prescribers was surveyed annually regarding their knowledge of the risks and safe use of SXB, including potential risks of concomitant use with alcohol and/or sedative hypnotic agents.

2.2 Patient Knowledge Assessment

A survey was administered to assess the effectiveness of the communication of the key XRP information in approximately 2% of enrolled patients. At least 20% of the sample were patients who had been enrolled for greater than 1 year. Recruiting occurred via phone, fax, or e-mail. Randomized stratified sampling was employed to minimize sampling bias and ensure patients with varying levels of experience with SXB were represented. To further minimize bias, the survey was conducted by an experienced, independent, third-party market research provider and administered via a website. The sponsor of the study was not disclosed. The recommended sample size was selected to establish a confidence interval of 8 percentage points at the 98% confidence level if 80% of the questions were answered correctly. At conclusion of the survey, a reinforcement of the REMS information was provided to participants who answered the questions correctly and redirection for those answered incorrectly. Therefore, the survey also reinforced education on key REMS information.

Fig. 2 Risk management report (RMR) process flow for early refill requests. Rx prescription



2.3 Prescriber Knowledge Assessment

A knowledge assessment was administered to assess the effectiveness of communication of key safety and use information to approximately 3% of prescribers enrolled in the XRP. Respondents were recruited from active prescribers (defined as having written a prescription during the past 12 months). At least 20% were prescribers who had ten or more patients enrolled in the XRP. To minimize bias, randomized stratified sampling was employed to ensure that prescribers with various levels of experience were recruited. Surveys were conducted by a third-party market research vendor via a website. The sponsor of the study was not disclosed. The recommended sample size was selected to establish a confidence interval of 8 percentage points at the 98% confidence level if 80% of the questions were answered properly.

3 Results

3.1 Enrollment

3.1.1 Prescriber Enrollment

During the reporting period, a total of 685 prescribers enrolled in the XRP, resulting in a cumulative total of 1766 prescribers enrolled since implementation of the current

REMS program (Table 1). During the reporting period, a total of 4524 prescribers (both those who enrolled under the current REMS and those previously enrolled in the prior risk management program) wrote at least one valid prescription that was shipped, resulting in a cumulative total number of 5528 prescribers who wrote at least one valid prescription that was shipped since implementation of the REMS program. The most common primary specialties represented among enrolled prescribers were pulmonology ($n = 35\%$) and neurology ($n = 27\%$). Approximately 70% of prescribers (3179/4524) were treating between one and three patients each.

3.1.2 Patient Enrollment

During the reporting period, a total of 4149 patients completed enrollment in the XRP, with a cumulative total of 9803 patients who completed enrollment during the 28 months from implementation of the REMS program (24 August, 2015) to the end of this reporting period (Table 1). Patients who enrolled were included in these totals regardless of whether they received a shipment of SXB. A total of 2293 of 17,037 (13%) unique patients, including both new and existing patients (i.e., patients enrolled during this reporting period and those enrolled prior to this reporting period) who received at least one shipment of SXB during the reporting period were associated with more than one prescriber during the reporting period. None of the patients associated with more than one prescriber received more

Table 1 Summary of prescribers and patients enrolled

| | Previous period ^a (24 August, 2015 to 26 December, 2016) | Current period (27 December, 2016 to 26 December, 2017) |
|---|---|---|
| Prescribers | | |
| Number of prescribers who enrolled ^b | 1081 | 685 |
| Number of prescribers (new and existing) who have written at least 1 prescription ^c | 1004 | 4524 |
| Disenrolled prescribers | 134 | 339 |
| Patients | | |
| Number of enrolled patients ^d | 5654 | 4149 |
| Number of enrolled patients (new and existing prior to formal XRP) who received at least 1 shipment during the reporting period | 4971 | 17,037 |
| Number of patients with more than 1 prescriber during therapy | 2515 | 2293 |
| Disenrolled patients ^e | 1432 | 1248 |

REMS Risk Evaluation and Mitigation Strategy, SXB sodium oxybate, XRP Xyrem[®] REMS Program

^aPeriod prior to conversion of the risk and mitigation and monitoring program for SXB to a formal REMS program in 2015

^bIncludes only newly enrolled prescribers and not continuing prescribers who were previously enrolled

^cNumber of unique prescribers who wrote at least 1 valid (shipped) prescription

^dThis number includes only newly enrolled patients and not continuing patients previously enrolled prior to the formal XRP, regardless of whether they received an SXB shipment

^eDisenrolled patients are defined as those who have been removed from the program for death or noncompliance

than one SXB prescription at a time. No medication was shipped to a patient after disenrollment from the XRP. During the reporting period, no patient with duplicate profiles was shipped SXB under more than one name or identifier.

3.1.3 Prescriber Removal and Disenrollment

A total of 134 prescribers were removed from the XRP during the reporting period (Table 2). The most common reasons (> 50 prescribers, accounting for 124 prescribers in all) were change in prescriber location, prescriber retirement, prescriber request, or prescriber death. Two prescribers were disenrolled because of disciplinary action (neither involving SXB) and four because of DEA/state license issues.

3.1.4 Patient Discontinuation and Disenrollment

A total of 5573 unique patients discontinued and 1248 disenrolled from the XRP during the reporting period (Table 3). The most common reasons (> 100 patients) for patient discontinuation were unreachable patient (26%), inactivity (no refill for > 90 days; 23%), prescriber disenrolled (21%), prescriber request (10%), patient request (6%), voluntary/personal reasons (5%), side effects (4%), and unknown reason (3%). The most common reason (> 100 patients) for patient disenrollment was prescriber disenrollment. Patients

disenrolled because of prescriber disenrollment are eligible to re-enroll following transfer of care to a certified prescriber.

3.1.5 Pharmacy Certification

All pharmacists and pharmacy staff at the single certified pharmacy maintained compliance with the requirements of the XRP Pharmacy Training Program. The pharmacy remained certified throughout the reporting period. There were no significant critical observations from an audit conducted by the sponsor.

3.2 Prescriptions

During the reporting period, a total of 48,748 unique SXB prescriptions were verified, dispensed, and shipped from the certified pharmacy to enrolled patients; there were 3335 shipments of an initial SXB prescription and 143,091 refills, for a total of 146,426 shipments. The recommended dose range for SXB in adults is 6–9 g/night, which was the effective range in the adult clinical trial program [17]. Of the 17,037 patients who received at least one shipment of SXB, 447 (3%) were prescribed a total nightly dose of more than 9 g; of these, 374 (84%) were between 9 and 12 g, and 73 (16%) were more than 12 g.

Table 2 Number of prescribers disenrolled by reason

| | Current period (27 December, 2016 to 26 December, 2017) | Cumulative period (24 August, 2015 to 26 December, 2017) |
|--|---|--|
| Location change/address no longer valid | 64 | 175 |
| Prescriber retired | 33 | 71 |
| Prescriber requested | 21 | 46 |
| Prescriber expired | 6 | 13 |
| DEA/state license number issue | 4 ^a | 7 |
| Disciplinary issue | 2 ^b | 12 |
| Unable to process/missing required information | 2 | 6 |
| Prescriber no longer practicing | 1 | 5 |
| Unknown | 1 ^c | 2 |
| Unable to verify credentials | 0 | 1 |
| Unable to re-enroll | 0 | 1 ^d |
| Total | 134 | 339 |

DEA Drug Enforcement Agency, REMS Risk Evaluation and Mitigation Strategy

^aOne prescriber had his state license suspended for insurance fraud and allowing an unlicensed psychiatrist (with a revoked license) to treat patients, 1 prescriber has his state license suspended for criminal sexual contact with a minor, 1 prescriber had his state license suspended and his DEA license was lapsed, and 1 prescriber had a lapsed DEA license but chose not to renew it because she was moving to a new location

^bDisciplinary issues include 1 instance of a prescriber’s medical license being revoked for practicing as an oncologist without oncology experience, education, and/or training and 1 instance of a prescriber facing charges of Medicare and Medicaid fraud

^cCould not contact prescriber

^dIncluded in a previous assessment report under location change/address no longer valid; reason was updated to unable to re-enroll when prescriber could not re-enroll in the REMS because of a DEA license issue

Table 3 Number of patients disenrolled or discontinued by reason, after receiving at least one shipment

| | Current period (27 December, 2016 to 26 December, 2017) | Cumulative period (24 August, 2015 to 26 December, 2017) |
|--|---|--|
| Number of patients disenrolled after receiving at least 1 shipment for the following reasons ^a | 1248 | 2680 |
| Prescriber disenrolled ^b | 1198 | 2559 |
| Death (included under patients discontinued in this table) | 41 | 91 |
| Prescriber requested | 3 | 10 |
| Unable to process/missing required information | 3 | 4 |
| Patient request | 1 | 8 |
| Prescriber never enrolled | 1 ^c | 2 |
| Unable to re-enroll | 1 | 1 |
| Patient noncompliance | 0 | 5 |
| Number of patients discontinued after receiving at least 1 shipment for the following reasons ^d | 5573 | 11,548 |
| Unreachable patient ^e | 1435 | 2543 |
| Inactivity (no refill > 90 days) | 1263 | 2835 |
| Prescriber disenrolled | 1198 | 2557 |
| Prescriber request | 572 | 1252 |
| Patient request ^f | 325 | 520 |
| Voluntary/personal reasons ^f | 272 | 735 |
| Side effects | 240 | 503 |
| Unknown reason ^g | 143 | 310 |
| Death (also included under disenrollment) | 41 | 91 |
| Financial issues | 31 | 46 |
| Insurance denied | 22 | 43 |
| Drug not effective | 18 | 68 |
| Refused shipment | 4 | 19 |
| Unable to process/missing required information | 4 | 5 |
| Prescriber never enrolled | 3 ^c | 4 |
| Prescriber noncompliance | 1 | 11 |
| Unable to re-enroll | 1 | 1 |
| Patient noncompliance (also included under disenrollment) | 0 | 5 |

^aNote that patients were discontinued before being disenrolled

^bIncludes patients who were disenrolled when their prescriber was disenrolled; the prescribers may have subsequently re-enrolled

^cIncludes discontinued ($n = 3$) or disenrolled ($n = 1$) patients who received shipments from enrolled prescribers and were subsequently discontinued or disenrolled when their new prescribers did not complete enrollment

^dIncludes patients who may have been disenrolled after the cut-off for this reporting period

^ePharmacy practice is to attempt to contact the patient multiple times. If the patient is not reachable, the pharmacy contacts the prescriber for an alternate telephone number for the patient or to see if there is an update on patient status. If the patient does not respond to a call at the alternate number and is still unreachable after 60 days, the pharmacy will move the patient to an on-hold status and, after another 30 days with no contact, to a discontinued status

^fThe terms “patient request” and “voluntary/personal reason” are used when the discontinuation was for a stated reason or not, respectively (and a reason was not otherwise available through a different source; e.g., issues relating to side effects or cost)

^gPatient or prescriber states that he or she does not want to pursue enrollment or to receive drug any longer but does not give a reason

Although prescriptions for up to 90 days are permissible (supplies for longer periods are permissible only under special circumstances, such as foreign travel, and require approval from the certified pharmacy), only 130 (0.1%) prescriptions were written for a supply of ≥ 30 days during the reporting period. All prescriptions were written by

certified prescribers (i.e., no prescriptions were written by a prescriber who was not enrolled, educated, and certified), there were no overlapping or duplicate active prescriptions for any individual patient, and no prescriptions were filled for a patient not enrolled in the XRP.

3.3 Shipments

During the reporting period, SXB was dispensed in 146,426 shipments containing 375,173 bottles. Of those, 13 shipments containing 26 bottles (0.009% of shipments and 0.007% of bottles) were lost and not recovered. Five shipments were lost in transit; the carrier investigated each delivery and made multiple unsuccessful tracking and retrieval efforts. Patients reported that four shipments were missing one of the three bottles in the package; in all instances, the shipping weight when the package left the pharmacy was a full shipment and losses were investigated. Three shipments were either delivered to the correct address and signed for or delivered to an alternate address when the patient was not there and signed for by an unknown person. One shipment was stolen when the carrier’s office was burglarized. None of the bottles were lost during delivery to the certified pharmacy.

3.4 Participant Risk Education

Of 5919 patients invited to participate in the knowledge survey, 201 (3.4%) completed the questionnaire (Table 4). Approximately three-quarters (74.6%) of patients indicated that someone reviewed the Medication Guide and Patient

Start Guide with them when they were first prescribed SXB. Most patients acknowledged the risk of confusion (82.0%) and trouble breathing while asleep (90.5%), whereas fewer patients knew of the risk of abuse and misuse, depression, and loss of consciousness (69.7%, 70.1%, and 62.7%, respectively). Smaller proportions of patients incorrectly identified risks of anaphylaxis (12.4%) and Stevens–Johnson Syndrome (4.5%; neither is associated with SXB; hence, these are incorrect responses). Nearly all patients knew that it was against the law to sell or give their SXB to someone (99.5%), that use of alcohol and SXB may result in serious side effects (99.5%), and that SXB should not be taken with other sleep medicines or sedatives (98.0%). Some patients incorrectly believed that SXB should not be used with stimulants (41.8%) but very few incorrectly thought that both doses of SXB should be taken together (1.5%).

Of 5985 prescribers invited to participate in the survey, 121 (2.0%) completed the questionnaire (Table 5). Most prescribers knew that SXB was indicated to treat cataplexy (90.9%) and excessive daytime sleepiness (80.2%); however, 24.0% incorrectly believed that SXB is indicated for insomnia. Responses affirming acknowledgment of risks associated with SXB were as follows: respiratory depression (77.7%), abuse and misuse (86.8%), confusion (80.2%), profound decreases in level of consciousness, coma and death

Table 4 Patient knowledge assessment (*n* = 201)

| Question | Correct response | Number responding yes (%) |
|--|------------------|---------------------------|
| When you were first prescribed SXB, did someone review the Medication Guide and Patient Start Guide with you? | NA | 150 (74.6) ^a |
| Which of the following risks are associated with SXB? | | |
| Confusion | Yes | 165 (82.0) |
| Trouble breathing while asleep | Yes | 182 (90.5) |
| Abuse and misuse | Yes | 140 (69.7) |
| Depression | Yes | 141 (70.1) |
| Loss of consciousness | Yes | 126 (62.7) |
| Anaphylaxis | No | 25 (12.4) |
| Stevens–Johnson syndrome | No | 9 (4.5) |
| Is it against the law to sell or give your SXB to anyone else? | Yes | 200 (99.5) |
| Use of alcohol and SXB may result in serious side effects | Yes | 200 (99.5) |
| You should not take SXB if you use other sleep medicines or sedatives (medications that cause sleepiness) | Yes | 197 (98.0) |
| SXB should not be used with stimulants | No | 84 (41.8) |
| You should take both doses of SXB at the same time | No | 3 (1.5) |
| What information do the Medication Guide and Patient Quick Start Guide say you should tell your doctor about right away? | | |
| If you have or had depression or tried to harm yourself | Yes | 189 (94.0) |
| If you are on a salt-restricted diet or have high blood pressure, heart failure, or kidney problems | Yes | 188 (93.5) |
| If you are pregnant or plan to become pregnant or are breastfeeding a child | Yes | 188 (93.5) |
| If you have liver problems | Yes | 153 (76.1) |

NA not applicable, SXB sodium oxybate

^aOther responses included No (*n* = 18 [9%]), Someone offered, but I declined (*n* = 3 [2%]), I don’t recall (*n* = 27 [13%]), and Don’t know/Not sure (*n* = 3 [2%])

(77.7%), and depression (54.5%), whereas risks not associated with SXB were less frequently affirmed (anaphylaxis, 35.5%; Stevens–Johnson Syndrome, 20.7%). All (100%) prescribers acknowledged the combined use of alcohol and SXB may result in the potentiation of central nervous system depressant effects. Most (90.9%) prescribers acknowledged that they could not prescribe SXB unless they had enrolled in the XRP, and 88.4% knew that SXB was contraindicated in patients treated with a sedative hypnotic. Approximately half (57.0%) acknowledged that patient follow-up was recommended every 3 months, while 24.0% thought that there was no specific recommendation for patient follow-up, and 13.2% thought follow-up was to be done periodically.

3.5 Monitoring and Interventions

3.5.1 RMRs for Potential Abuse, Misuse, and Diversion

A total of 3945 RMRs were finalized and submitted to the sponsor during the 12-month reporting period: 1155 for early refill requests and 2790 for other reasons (Table 6).

3.5.2 RMRs for Potential Abuse, Misuse, and Diversion

Of the 2790 RMRs submitted for other reasons, 757 were for patient's loss/misuse of the product (Table 6). Of the 17,037 patients who received at least one shipment of SXB, 3366 (20%) had at least one RMR, and 463 (3%) received more than one RMR.

The certified pharmacy provided notifications to prescribers regarding suspected abuse (31 cases), misuse (343 cases), and diversion (22 cases) during this reporting period (Table 7). Twelve RMRs completed during the reporting period were associated with suspicious or noncompliant prescriber behavior. In two cases, the pharmacy was concerned about whether there was a legitimate patient/physician relationship. Six of the cases were when the pharmacy became aware of disciplinary actions. In three cases, the prescriber's office accepted unused SXB from a patient and disposed of it on the patient's behalf. One case involved a physician attempting to practice telemedicine without an established practice location.

Table 5 Prescriber knowledge assessment ($n = 121$)

| Question | Correct response | Number responding yes (%) |
|--|------------------|---------------------------|
| For what symptoms is SXB indicated? | | |
| Cataplexy | Yes | 110 (90.9) |
| Excessive daytime sleepiness | Yes | 97 (80.2) |
| Insomnia | No | 29 (24.0) |
| Other | No | 6 (5.0) |
| Don't know/not sure | No | 1 (0.8) |
| According to the PI, which of the following risks are associated with SXB? | | |
| Respiratory depression | Yes | 94 (77.7) |
| Abuse and misuse | Yes | 105 (86.8) |
| Confusion | Yes | 97 (80.2) |
| Profound decreases in level of consciousness, coma, and death | Yes | 94 (77.7) |
| Depression | Yes | 66 (54.5) |
| Anaphylaxis | No | 43 (35.5) |
| Stevens–Johnson syndrome | No | 25 (20.7) |
| The combined use of alcohol and SXB may result in potentiation of the central nervous system depressant effects of alcohol and SXB | Yes | 121 (100) |
| Prescribers cannot prescribe SXB unless they have enrolled in the XRP | Yes | 110 (90.9) |
| SXB is contraindicated in patients treated with a sedative hypnotic agent | Yes | 107 (88.4) |
| SXB should not be used in combination with stimulants | No | 17 (14.0) |
| How often does the XRP recommend patient follow-up? | | |
| Every 3 months | Yes | 69 (57.0) |
| There is no specific recommendation for frequency of patient follow-up | No | 29 (24.0) |
| Periodically | No | 16 (13.2) |
| Annually | No | 7 (5.8) |

PI prescribing information, SXB sodium oxybate, XRP Xyrem® Risk Evaluation and Mitigation Strategy Program

Table 6 Number of risk management reports (RMRs) generated

| Reason for RMR generation | Current period (27 December, 2016 to 26 December, 2017) | Cumulative period (24 August, 2015 to 26 December, 2017) |
|---|---|--|
| Early refill request | 1155 | 2474 |
| Other reasons | 2790 | 5453 |
| Patient's loss/misuse of the product ^a | 757 | 2184 |
| Patient did not receive and carrier shows receipt | 7 | 14 |
| Lost/stolen package or bottle | 24 | 38 |
| Delivered to incorrect address and not returned | 3 | 7 |
| Tampering by an individual in contact with product | 2 | 6 |
| Counterfeiting the product ^b | 1 | 1 |
| Contaminating the product | 1 | 2 |
| Unexplained irreconcilable inventory | 0 | 3 |
| Inquiry and/or arrest by law because of misuse of product | 0 | 2 |
| Patient requests for early refills ^c | 2 | 7 |
| Prescribers whose DEA and/or state license is invalid | 6 | 19 |
| History of drug/alcohol abuse | 370 | 370 |
| Suicide attempt and/or ideation | 724 | 724 |
| Multiple prescribers | 2 | 2 |
| Potential or actual dose increase | 9 | 9 |
| Excess medication on hand | 451 | 451 |
| Suicide-death | 1 | 1 |
| Other | 430 | 1613 |
| Total | 3945 | 7927 |

DEA Drug Enforcement Agency, *SXB* sodium oxybate

^aLoss includes any instances where the patient runs out of medication earlier than scheduled, including spills. Misuse includes intentional and unintentional misuse as well as use with alcohol

^bA patient report to the pharmacy of a website offering counterfeit *SXB*; not a report of a patient counterfeiting *SXB*

^cThese RMRs include reports where a patient initially reports product loss and requests an early refill, but retracts the request prior to approval and shipment of the early refill

3.5.3 Early Refill Requests

During the reporting period, 987 patients requested 1155 early refills; of the 17,037 patients who received at least one shipment of medication, 5% requested a single early refill and 0.8% requested two or more early refills. In this reporting period, 193 early refill requests were based on a report of lost or discarded medication (188 were lost/discarded by patient, 3 were lost in transit by carrier, and 2 were reported as "health care facility lost/discarded product"); 499 on reports of spilled or leaked product; 14 on reports of stolen medication; and 5 on reports of damaged medication. Of the 1155 requests for early refill, 873 were prescriber approved, 100 were pharmacist approved, 48 were denied by the prescriber, 1 was denied by the pharmacist, and 133 were shipped as scheduled (cases in which the request was neither approved nor denied prior to the patient's next scheduled ship date).

4 Discussion

REMS programs are intended to implement surveillance of and mitigate risks associated with controlled medications that provide important medical benefits but also present serious safety concerns. The opioid crisis in the USA has brought the importance of these programs into sharp focus for regulatory authorities [18]. The FDA may mandate a REMS program for a controlled medication to ensure appropriate prescribing for the treatment of appropriate patients, and to reduce the risk of abuse and misuse as a public health concern [19]. Sodium oxybate is one such medication [19]. The XRP combines patient and prescriber education, supply chain and distribution control through a single certified pharmacy, collection and analysis of longitudinal data, and notification of prescribers regarding suspected abuse, misuse, and diversion with the aim of mitigating the risks of prescription *SXB*. The certified pharmacy plays a key role in overall risk mitigation through patient education, regular

Table 7 Outcomes of risk management report notifications to sodium oxybate prescribers regarding suspected abuse, misuse, or diversion

| Outcomes | 27 December, 2016, to 26 December, 2017 | | |
|--|---|--------------------------|---|
| | Abuse (<i>n</i> = 31) | Misuse (<i>n</i> = 343) | Diversion ^a (<i>n</i> = 22) |
| Prescriber approved shipment | 12 | 264 | 15 |
| Prescriber requested shipment hold | 1 | 1 | 0 |
| Prescriber requested shipment hold and patient follow-up | 0 | 0 | 0 |
| Prescriber denied shipment | 13 | 17 | 2 |
| Discussed event and received clarification | 1 | 5 | 1 |
| Discussed event and/or certified pharmacy decision | 0 | 6 | 1 |
| Certified pharmacy left voicemail message | 0 | 23 | 1 |
| Left message with office staff | 1 | 13 | 2 |
| Certified pharmacy spoke with office staff | 2 | 9 | 0 |
| Other ^b | 1 | 5 | 0 |

^aIncludes cases in which a patient reports that the medication has been stolen

^bIncludes further notifications to the prescriber, medication discontinued, patient disenrolled, new prescription received from the prescriber, additional counseling of the patient, and other responses requiring no further action

interactions with each patient to collect and update patient, prescriber, and prescription information in a central database, and notification to prescribers to support prescriber decision making regarding early refills, dose modifications, patient alerts, and patient disenrollments if warranted.

The data collected from the XRP since REMS program implementation demonstrate that the restricted distribution system effectively minimizes or prevents prescriptions filled from uncertified or disenrolled prescribers or shipment of medication to unenrolled or disenrolled patients. In addition, no patient has received multiple shipments from duplicate or overlapping active prescriptions during the 28-month period since implementation. The inventory controls and shipment tracking procedures have maintained minimal loss of product, with no product lost within the certified pharmacy, and 13 of the 146,426 total shipments (0.009%) lost in transit during this 12-month reporting period.

These data show that the XRP makes most patients and prescribers aware of the risks of SXB. Prescriber certification and patient enrollment verification ensure that both prescribers and patients are informed of the risks prior to patient enrollment. In addition, pharmacist/patient counseling has been completed prior to every initial shipment of SXB to ensure that each patient also has been counseled by the certified pharmacy before the first shipment of SXB. The knowledge assessment data showed that most patients were aware of serious risks associated with SXB (confusion and respiratory depression) and serious reactions if taken with alcohol or other sleep medicines, but a substantial fraction were confused about concomitant treatment with stimulants. While all prescribers acknowledged that the combination of alcohol and SXB could potentiate central nervous system depression, not all knew that respiratory depression and

profound decreases in level of consciousness, coma, and death were risks of SXB alone. More prescriber training might be beneficial.

These data also demonstrate that the XRP RMR process is successfully capturing and documenting cases of suspected abuse, misuse, and diversion, including all requests for early refills, within the central database. Importantly, the capture of these events is communicated, in real time, to the prescriber to ensure that the prescriber is aware of the event(s) and any history of previous events or patient alerts and can make fully informed decisions about the clinical management of the patient.

Unregulated distribution and dispensing of any prescription controlled substance presents many potential points for theft and diversion. The successful implementation of the XRP highlights the opportunity for risk management programs for other prescription controlled substances with complicated benefit/risk profiles to minimize supply chain security risks, limit at-risk patients to a single pharmacy [20], and implement certified pharmacy monitoring and prescriber notification to support prescriber decision making [18]. Moreover, these analyses indicate that prescribers of SXB view enrollment forms and mandated patient education as useful clinical tools in patient management.

5 Conclusions

These data suggest that the XRP is providing SXB in a controlled manner to patients who have medical needs; additional prescriber education on safety risks may be warranted.

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