

A quarterly magazine published by the American Academy of Sleep Medicine

From research to relationships, how AASM members are improving sleep health in underserved communities. pg. 14-15



Practical advice for a career after sleep fellowship. pg. 18-19

Do your adult patients with **narcolepsy** feel boxed in?



Indications and Usage

 WAKIX is indicated for the treatment of excessive daytime sleepiness (EDS) or cataplexy in adult patients with narcolepsy.

Important Safety Information

Contraindications

 WAKIX is contraindicated in patients with known hypersensitivity to pitolisant or any component of the formulation. Anaphylaxis has been reported. WAKIX is also contraindicated in patients with severe hepatic impairment.

Warnings and Precautions

 WAKIX prolongs the QT interval; avoid use of WAKIX in patients with known QT prolongation or in combination with other drugs known to prolong the QT interval. Avoid use in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval. The risk of QT prolongation may be greater in patients with hepatic or renal impairment due to higher concentrations of pitolisant; monitor these patients for increased QTc. Dosage modification is recommended in patients with moderate hepatic impairment and moderate or severe renal impairment (see full prescribing information). WAKIX is not recommended in patients with end-stage renal disease (ESRD).

Adverse Reactions

 In the placebo-controlled clinical trials conducted in patients with narcolepsy with or without cataplexy, the most common adverse reactions (≥5% and twice placebo) for WAKIX were insomnia (6%), nausea (6%), and anxiety (5%). Other adverse reactions that occurred at ≥2% and more frequently than in patients treated with placebo included headache, upper respiratory infection, musculoskeletal pain, heart rate increased, hallucinations, irritability, abdominal pain, sleep disturbance, decreased appetite, cataplexy, dry mouth, and rash.

Drug Interactions

 Concomitant administration of WAKIX with strong CYP2D6 inhibitors increases pitolisant exposure by 2.2-fold. Reduce the dose of WAKIX by half.

BREAK THROUGH with



WAKIX Is a First-in-Class Molecule With a Novel Mechanism of Action

First and only histaminergic treatment for excessive daytime sleepiness (EDS) *or* cataplexy in narcolepsy

- First and only FDA-approved non-scheduled treatment for EDS or cataplexy in narcolepsy
- WAKIX is not a stimulant
- No clinically important pharmacokinetic interactions with modafinil or sodium oxybate
- Convenient once-daily morning dosing
- Concomitant use of WAKIX with strong CYP3A4 inducers decreases exposure of pitolisant by 50%. Dosage adjustments may be required (see full prescribing information).
- H₁ receptor antagonists that cross the blood-brain barrier may reduce the effectiveness of WAKIX. Patients should avoid centrally acting H₁ receptor antagonists.
- WAKIX is a borderline/weak inducer of CYP3A4 and may reduce the effectiveness of sensitive CYP3A4 substrates, including hormonal contraceptives. Patients using hormonal contraception should be advised to use an alternative non-hormonal contraceptive method during treatment with WAKIX and for at least 21 days after discontinuing treatment.

Use in Specific Populations

 There is a pregnancy exposure registry that monitors pregnancy outcomes in women who are exposed to WAKIX during pregnancy. Patients should be encouraged to enroll in the WAKIX pregnancy registry if they become pregnant. To enroll or obtain information from the registry, patients can call 1-800-833-7460.

- The safety and effectiveness of WAKIX have not been established in patients less than 18 years of age.
- WAKIX is extensively metabolized by the liver. WAKIX is contraindicated in patients with severe hepatic impairment. Dosage adjustment is required in patients with moderate hepatic impairment.
- WAKIX is not recommended in patients with end-stage renal disease. Dosage adjustment of WAKIX is recommended in patients with moderate or severe renal impairment.
- Dosage reduction is recommended in patients known to be poor CYP2D6 metabolizers; these patients have higher concentrations of WAKIX than normal CYP2D6 metabolizers.

To report suspected adverse reactions, contact Harmony Biosciences at 1-800-833-7460 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Brief Summary on the following pages.



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Learn more at WAKIXhcp.com/today

WAKIX® (pitolisant) tablets, for oral use

BRIEF SUMMARY - See Full Prescribing Information available at WAKIXhcp.com.

Initial U.S. Approval: 2019

1 INDICATIONS AND USAGE

WAKIX is indicated for the treatment of excessive daytime sleepiness (EDS) or cataplexy in adult patients with narcolepsy.

4 CONTRAINDICATIONS

WAKIX is contraindicated in patients with:

- known hypersensitivity to pitolisant or any component of the formulation. Anaphylaxis
 has been reported in patients treated with WAKIX [see Adverse Reactions (6.2)].
- severe hepatic impairment. WAKIX is extensively metabolized by the liver and there is a significant increase in WAKIX exposure in patients with moderate hepatic impairment [see Use in Specific Populations (8.6)].

5 WARNINGS AND PRECAUTIONS

5.1 QT Interval Prolongation

WAKIX prolongs the QT interval. The use of WAKIX should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong the QT interval *[see Drug Interactions (7.1)]*. WAKIX should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval *[see Clinical Pharmacology (12.2)]*. The risk of QT prolongation may be greater in patients with hepatic or renal impairment due to higher concentrations of pitolisant. Monitor patients with moderate hepatic impairment for increased QTc. Dosage modification is recommended in patients with moderate hepatic *(2.2, 2.3)*. WAKIX is contraindicated in patients with severe hepatic impairment *[see Contraindications (4]]*. WAKIX is not recommended in patients with end-stage renal disease (ESRD) *[see Dosage and Administration (2.3), Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

• QT Interval Prolongation [see Warnings and Precautions (5.1)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the clinical trials for narcolepsy, 172 patients were treated with WAKIX in placebocontrolled trials for up to 8 weeks and in open-label extension trials for up to 5 years. In trials in which WAKIX was directly compared to placebo, 6 of the 152 patients (3.9%) who received WAKIX and 4 of the 114 patients (3.5%) who received placebo discontinued because of an adverse event.

Most Common Adverse Reactions

In the placebo-controlled clinical trials conducted in patients with narcolepsy with or without cataplexy, the most common adverse reactions (occurring in \geq 5% of patients and at least twice the rate of placebo) with the use of WAKIX were insomnia (6%), nausea (6%), and anxiety (5%).

Table 1 presents the adverse reactions that occurred at a rate of $\geq 2\%$ in patients treated with WAKIX and more frequently than in patients treated with placebo in the placebo-controlled clinical trials in narcolepsy.

Table 1: Adverse Reactions that Occurred in ${\geq}2\%$ of WAKIX-Treated Patients and More Frequently than in Placebo-Treated Patients in Three Placebo-controlled Narcolepsy Studies

Adverse Reaction	WAKIX (n=152) %	Placebo (n=114) %
Headache*	18	15
Insomnia*	6	2
Nausea	6	3
Upper respiratory tract infection*	5	3
Musculoskeletal pain*	5	3
Anxiety*	5	1
Heart rate increased*	3	0
Hallucinations*	3	0
Irritability	3	2
Abdominal pain*	3	1
Sleep disturbance*	3	2
Decreased appetite	3	0
Cataplexy	2	1
Dry mouth	2	1
Rash*	2	1

* The following terms were combined:

Abdominal pain includes: abdominal discomfort; abdominal pain; abdominal pain upper

Anxiety includes: anxiety; nervousness; stress; stress at work

Hallucinations includes: hallucination; hallucination visual; hypnagogic hallucination Headache includes: cluster headache; headache; migraine; premenstrual headache; tension headache

Heart rate increased includes: heart rate increased; sinus tachycardia; tachycardia

Insomnia includes: initial insomnia; insomnia; middle insomnia; poor quality sleep

Musculoskeletal pain includes: arthralgia; back pain; carpal tunnel syndrome; limb discomfort; musculoskeletal pain; myalgia; neck pain; osteoarthritis; pain in extremity; sciatica

Rash includes: eczema; erythema migrans; rash; urticaria

Sleep disturbance includes: dyssomnia; sleep disorder; sleep paralysis; sleep talking

Upper respiratory infection includes: pharyngitis; rhinitis; sinusitis; upper respiratory tract infection; upper respiratory tract inflammation; viral upper respiratory tract infection

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of WAKIX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

General disorders and administration site conditions: fatigue

Immune system disorders: hypersensitivity (anaphylaxis)

Investigations: weight increased

Nervous system disorders: epilepsy

Psychiatric disorders: abnormal behavior, abnormal dreams, anhedonia, bipolar disorder, depression, depressed mood, nightmare, sleep disorder, suicide attempt, suicidal ideation *Skin and subcutaneous tissue disorders:* pruritus

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with WAKIX

Table 2: Clinically Significant Drug Interactions with WAKIX

Effect of Other Drugs on WAKIX			
Strong CYP2D6 Inhibitors			
Clinical Implication:	Concomitant administration of WAKIX with strong CYP2D6 inhibitors increases pitolisant exposure by 2.2-fold.		
Prevention or Management:	Reduce the dose of WAKIX by half [see Dosage and Administration (2.4), Clinical Pharmacology (12.3)].		
Examples:	paroxetine, fluoxetine, bupropion		
Strong CYP3A4 Inducers			
Clinical Implication:	Concomitant use of WAKIX with strong CYP3A4 inducers decreases exposure of pitolisant by 50%.		
Prevention or Management:	Assess for loss of efficacy after initiation of a strong CYP3A4 inducer.		
	For patients stable on WAKIX 8.9 mg or 17.8 mg once daily, increase the dose of WAKIX to reach double the original daily dose (i.e., 17.8 mg or 35.6 mg, respectively) over 7 days. If concomitant dosing of a strong CYP3A4 inducer is discontinued, decrease WAKIX dosage by half <i>[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)].</i>		
Examples:	rifampin, carbamazepine, phenytoin		
Histamine-1 (H1) Receptor Antagonists			
Clinical Implication:	WAKIX increases the levels of histamine in the brain; therefore, H1 receptor antagonists that cross the blood-brain barrier may reduce the effectiveness of WAKIX.		
Prevention or Management:	Avoid centrally acting H1 receptor antagonists.		
Examples:	pheniramine maleate, diphenhydramine, promethazine (anti-histamines) imipramine, clomipramine, mirtazapine (tri or tetracyclic antidepressants)		

QT Interval Prolongation			
Clinical Implication:	Concomitant use of drugs that prolong the QT interval may add to the QT effects of WAKIX and increase the risk of cardiac arrhythmia.		
Prevention or Management:	Avoid the use of WAKIX in combination with other drugs known to prolong the QT interval <i>[see Warnings and Precautions (5.1)]</i> .		
Examples:	Class 1A antiarrhythmics: quinidine, procainamide, disopyramide; Class 3 antiarrhythmics: amiodarone, sotalol; Antipsychotics: ziprasidone, chlorpromazine, thioridazine; Antibiotics: moxifloxacin		
Effect of WAKIX on Other Drugs			
Sensitive CYP3A4 Substrates			
Clinical Implication:	WAKIX is a borderline/weak inducer of CYP3A4. Therefore, reduced effectiveness of sensitive CYP3A4 substrates may occur when used concomitantly with WAKIX <i>[see Clinical Pharmacology (12.3)]</i> .		

	may be reduced when used with WAKIX and effectiveness may be reduced for 21 days after discontinuation of therapy.
Prevention or Management:	Patients using hormonal contraception should be advised to use an alternative non-hormonal contraceptive method during treatment with WAKIX and for at least 21 days after discontinuation of treatment [see Use in Specific Populations (8.3)].

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7.2 **Drugs Having No Clinically Important Interactions with WAKIX**

A clinical study was conducted to evaluate the concomitant use of WAKIX with modafinil or sodium oxybate. This study demonstrated no clinically relevant effect of modafinil or sodium oxybate on the pharmacokinetics of WAKIX and no effect of WAKIX on the pharmacokinetics of modafinil or sodium oxybate [see Clinical Pharmacology (12.3)].

A clinical study showed that strong CYP3A4 inhibitors (e.g., ketoconazole, grapefruit juice) have no effect on the pharmacokinetics of WAKIX [see Clinical Pharmacology (12.3)].

8 **USE IN SPECIFIC POPULATIONS**

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women who are exposed to WAKIX during pregnancy. Patients should be encouraged to enroll in the WAKIX pregnancy registry if they become pregnant. To enroll or obtain information from the registry, patients can call 1-800-833-7460.

Risk Summary

Available case reports from clinical trials and postmarketing reports with WAKIX use in pregnant women have not determined a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproductive studies, administration of pitolisant during organogenesis caused maternal and embryofetal toxicity in rats and rabbits at doses ≥13 and >4 times the maximum recommended human dose (MRHD) of 35.6 mg based on mg/m² body surface area, respectively. Oral administration of pitolisant to female rats during pregnancy and lactation adversely affected maternal and fetal health and produced developmental delay at doses \geq 13 times the MRHD, based on mg/m² body surface area and increased the incidence of major malformations at 22 times the MRHD (see Data in Full Prescribing Information).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of pitolisant in human milk, the effects on the breastfed infant, or the effect of this drug on milk production.

Pitolisant is present in the milk of lactating rats (see Data in Full Prescribing Information). When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for WAKIX and any potential adverse effects on the breastfed child from WAKIX or from the underlying maternal condition.

Females and Males of Reproductive Potential 8.3

Contraception

WAKIX may reduce the effectiveness of hormonal contraceptives. Patients using hormonal contraception should be advised to use an alternative non-hormonal contraceptive method during treatment with WAKIX and for at least 21 days after discontinuing treatment [see Drug Interactions (7.1), Clinical Pharmacology (12.3)].

Pediatric Use 8.4

The safety and effectiveness of WAKIX in pediatric patients have not been established.

Limited pharmacokinetic data from 24 pediatric patients with narcolepsy (ages 7 to <18 years) receiving a single dose of WAKIX suggest that pediatric patients have higher exposure to pitolisant than adults. The exposure (C_{max} and AUC) of pitolisant was 2-fold higher in pediatric patients 12 to <18 years and 3-fold higher in pediatric patients 7 to <12 years compared to adults.

8.5 **Geriatric Use**

Limited pharmacokinetic data are available in healthy elderly subjects. A pharmacokinetic study that compared 12 elderly subjects (age 68 to 82 years) to 12 healthy adults (age 18 to 45 years) did not reveal any significant differences in drug exposure [see Clinical Pharmacology (12.3)].

Of the total number of patients with narcolepsy in clinical studies of WAKIX. 14 patients (5%) were ≥65 years old. No overall differences in safety or effectiveness were observed between these patients and younger patients in these clinical trials, but greater sensitivity of some older individuals cannot be ruled out. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, and cardiac function, concomitant diseases, and other drug therapy.

Hepatic Impairment 8.6

WAKIX is contraindicated in patients with severe hepatic impairment (Child-Pugh C) as it has not been studied in this population. WAKIX is extensively metabolized by the liver and there is a significant increase in WAKIX exposure in patients with moderate hepatic impairment [see Contraindications (4), Clinical Pharmacology (12.3)].

Monitor patients with moderate hepatic impairment (Child-Pugh B) and adjust the dosage of WAKIX [see Dosage and Administration (2.2)].

Monitor patients with mild hepatic impairment (Child-Pugh A). No dosage adjustment of WAKIX is recommended in patients with mild hepatic impairment.

Renal Impairment 8.7

The pharmacokinetics of WAKIX in patients with end-stage renal disease (ESRD) (eGFR of <15 mL/minute/1.73 m²) is unknown [see Clinical Pharmacology (12.3)]. Therefore, WAKIX is not recommended in patients with ESRD (see Dosage and Administration (2.3), Warnings and Precautions (5.1)].

Dosage adjustment of WAKIX is recommended in patients with moderate (eGFR 30 to 59 mL/minute/1.73 m²) and severe (eGFR 15 to 29 mL/minute/1.73 m²) renal impairment [see Dosage and Administration (2.3)].

8.8 **CYP2D6 Poor Metabolizers**

Dosage reduction is recommended in patients known to be poor CYP2D6 metabolizers because these patients have higher pitolisant concentrations than normal CYP2D6 metabolizers [see Dosage and Administration (2.5), Clinical Pharmacology (12.3, 12.5)].

12 **CLINICAL PHARMACOLOGY**

12.1 Mechanism of Action

The mechanism of action of pitolisant in excessive daytime sleepiness (EDS) or cataplexy in adult patients with narcolepsy is unclear. However, its efficacy could be mediated through its activity as an antagonist/inverse agonist at histamine-3 (H3) receptors.

12.2 Pharmacodynamics

Pitolisant binds to H3 receptors with a high affinity ($K_i = 1 \text{ nM}$) and has no appreciable binding to other histamine receptors (H1, H2, or H4 receptors; $K_i \ge 10 \ \mu$ M).

Cardiac Electrophysiology

WAKIX at the highest recommended dosage (i.e., 35.6 mg daily) led to a QTc increase of 4.2 msec. Exposures 3.8-fold higher than achieved at the highest recommended dose increase QTc 16 msec (mean) [see Warnings and Precautions (5.1)].

See Full Prescribing Information available at WAKIXhcp.com.

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American Academy of SLEEP MEDICINE

Montage is a quarterly magazine published by the American Academy of Sleep Medicine. It offers a unique opportunity to recognize our membership and highlight changes in the field by featuring member profiles, exclusive interviews, research advances, and the latest developments impacting patient care.

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Advertising For more information, contact Annette Delagrange at adelagrange@aasm.org. elcome to the Winter issue of Montage. The COVID-19 pandemic exposed a great health divide. In this issue, we explore how AASM members are working to improve sleep health in minority and low-income communities. By understanding how systemic racism threatens public health, recognizing the social and environmental factors contributing to poor sleep, and improving access to care in marginalized populations, we can make progress toward ensuring that everyone has the opportunity for healthy sleep.

The AASM will be partnering with community organizations in areas disproportionately impacted by obstructive sleep apnea to raise awareness of the disease and increase screening and treatment. It's part of a chronic disease awareness program funded by the Centers for Disease Control and Prevention. The three-year project will target public health professionals, nonsleep health care providers and the public.

The AASM is also excited to be developing a certification program for artificial intelligence-based sleep scoring systems. In this issue, we describe how the Sleep ISR Record Rewards Program will benefit sleep centers and the AASM by building a dataset of diverse sleep studies against which AI systems can be evaluated.

Finally, we'll introduce you to a pediatric sleep specialist who offers medical school advice, hear from a group of sleep physicians who have advice for those entering the field, and review interim final rules related to Medicare surprise billing. In addition to all of this, we'll take a sneak peek at the return to inperson events with SLEEP 2022 in Charlotte, North Carolina.

The Montage Team

We want to hear from you! Share your experience in sleep medicine with your fellow members. Submit content to **montage@aasm.org** for it to be considered for publication in an upcoming issue of Montage!

Viewpoints



DEI Efforts Make Meaningful Impact

Andrew Spector, MD

Chair, AASM Diversity, Equity, and Inclusion Committee

Diversity and inclusion are core values of the AASM and vital to its mission of advancing sleep care and enhancing sleep health to improve lives. Among similar organizations, the AASM has an advantage with the inherent diversity of our members' careers: technologists, dentists, advanced practice providers, scientists, psychologists, physicians, and more. However, diversity is of no value without inclusion.

One of the primary aims of the Diversity, Equity, and Inclusion (DEI) Committee is to ensure that members from all of these backgrounds have the opportunity to actively engage in the AASM. To this end, the DEI Committee has been holding a series of discussions with members of groups that have been identified as being underrepresented in AASM leadership roles, such as solo practitioners, advanced practice providers, and sleep technologists. Additional discussion groups took place with members who identify as Black or Hispanic as these members are underrepresented in the AASM compared to the national population and the community of physicians. These discussions yielded valuable insights that will inform the ongoing work of the DEI Committee going forward as we work to remove barriers to membership and leadership at the AASM.

The DEI Committee actively tracks the diversity of our members, volunteers, and leaders. In order to achieve this, the committee relies on the demographic data in member profiles. We encourage all members to take a moment to complete four additional demographic questions located in your online member profile. This can also be accomplished when registering for AASM webinars or conferences.

It is also the DEI Committee's mission to provide AASM members with opportunities to learn more about topics related to diversity, equity, and inclusion. If you missed the recent webinar on implementation of institutional DEI with David J. Brown, MD, associate dean for health equity and inclusion at the University of Michigan Medical School, you can catch it on demand on the AASM learning page. Watch your emails and Twitter feeds for updates on our upcoming education series.

Last year, the DEI Committee assisted the AASM in implementation of two new programs to encourage diversity and inclusion efforts and conference attendance diversity, respectively. Charlene Gamaldo, MD, of the Johns Hopkins University School of Medicine, won the inaugural Diversity, Equity, and Inclusion Leadership Award for her years of work both improving diversity within sleep medicine and researching and promoting health equity. This joint award presented by the AASM and Sleep Research Society is open for nominations again this year, and we encourage members to apply or nominate a colleague.

The second new effort is a grant offering a travel stipend for members who identify with an underrepresented group to reduce the financial barrier of attending an AASM conference. The DEI Committee accepts a broad definition of "underrepresented," which includes but is not limited to race/ethnicity, practice type (e.g., solo practitioners), sexual orientation or gender identity, national origin, or economic background.

Since its inception in 2018, the DEI Committee has had an internal focus on improving the AASM. This year, however, the committee is turning its focus to sleep health equity. We are currently developing a survey for accredited facilities to gather data on how these facilities are currently caring for underserved populations and how the AASM can facilitate these efforts. We are also preparing a report on practices within sleep medicine that contribute to health care disparities with suggestions for strategies to reduce these inequities.

My three-year term as chair of the DEI Committee will be coming to an end in June. It has been a privilege working with and getting to know more than 30 committee members during this time. Kyra Clark, MD, has been a tremendous partner as vice chair of the DEI Committee, and Mariam Owodele, AASM membership manager, has been an invaluable force driving us forward. These personal connections are one of the main benefits of serving on an AASM committee.

My tenure on the DEI Committee has also taught me that the AASM is deeply committed to diversity and inclusion; these are not just buzzwords. We are fortunate to have a board of directors that is committed to these principles and functions as an active partner with our committee as we develop initiatives to make the AASM even stronger. The board has committed extensive time and resources to our endeavors, including participating in professional DEI training, and has endorsed the type of structural changes that will serve the organization well for years to come.

The DEI Committee is always interested to hear from the AASM community. Please visit our DEI page (aasm.org/about/diversity-and-inclusion/) to read more about these topics or to provide anonymous feedback to our committee.

Find Your Way Back to SLEEP in Charlotte, North Carolina, this June

This June, go "Back to SLEEP" with the Associated Professional **Sleep Societies at the** 36th annual meeting in Charlotte, North Carolina. Returning to an in-person gathering June 4-8, SLEEP 2022 will include leading speakers in sleep medicine, sleep and circadian science, and sleep health presenting the latest research and clinical applications. The meeting also will include favorites like the plenary session and presentation of awards. Meet the Professor sessions, the popular poster hall and exhibit hall.

This year's meeting organizers, representing the Sleep Research Society and the AASM, are excited to interact with their colleagues in real life.

SLEEP 2022 "Being in person is critical to the brainstorming and networking that is so important to what conferences do for my science," said APSS program Co-Chair Rebecca Spencer, PhD, who has a doctorate in neuroscience and is professor of psychological and brain sciences at the University of Massachusetts. "In a virtual meeting, I see a cool talk, or present my own work, and the Q&A is nice, but it is the continual digestion you do with colleagues over dinner or later on in the halls after you process it more that is inspirational. And while networking is important for me, it is really crucial to our trainees and junior colleagues. I love the opportunity to meet our trainees and hear the latest from the junior scientists."

SLEEP Co-Chair Shalini Paruthi, MD, co-director of the Sleep Medicine and Research Center at St. Luke's Hospital in St. Louis, agrees.

"People are more engaged, and it sparks more effective and efficient communication when we're in person," she said. "It allows for pop-up discussions that just can't happen in virtual meetings. You never know who you're going to bump into."

The SLEEP meeting attracts physicians, researchers, clinicians, technologists, students, and other sleep professionals eager to learn and share the latest research and best practices related to sleep medicine and sleep and circadian science.

While the SLEEP 2022 program is still being finalized, the keynote speaker and invited lecturers are confirmed. Susan Redline, MD, professor of sleep medicine and epidemiology at Harvard University, and director of the programs in sleep and cardiovascular medicine and sleep medicine epidemiology at Brigham and Women's Hospital, will deliver the keynote address on sleep apnea and cardiovascular disease during the plenary session on June 6.

"We have a lot of fantastic studies showing the links between sleep apnea and cardiovascular disease, but we have much less showing the impact of treatment on attenuating those cardiovascular disease risks," Dr. Redline said. "I plan to talk about why there may be some discrepancies between our observational data and our intervention data and review some of the newer ways to characterize sleep apnea that may be better for identifying people with sleep apnea who may most benefit from intervention."

One invited lecturer that Dr. Spencer is looking forward to hearing from is Mark Blumberg, PhD, who has a doctorate in biopsychology and is chair of the department of psychological and brain sciences at the University of Iowa.

"Mark Blumberg is doing some really fascinating work on twitches in sleep in early life, both in animals and humans, and it's really provocative to think that these could be a very early form of learning in sleep," she said.

Dr. Paruthi also expects Yo-El Ju, MD, professor of neurology at Washington University in St. Louis, to deliver a fascinating talk.

"She has been doing years of dedicated research in REM sleep behavior disorder, and I think she'll provide a lot more insight on the advancements that we're making in better understanding the disorder and how it relates to some of the neurodegenerative disorders that we see some associations and links with," she said.

For more information about SLEEP 2022, visit the meeting website at <u>sleepmeeting.org</u>. It will be updated frequently as the program is finalized.



Increasing awareness, screening for OSA goal of new CDC-funded program

The American Academy of Sleep Medicine has been awarded a three-year grant from the Centers for Disease Control and Prevention to develop an awareness program focused on improving recognition of obstructive sleep apnea. The project will target public health professionals, non-sleep health care providers, and the public, including communities disproportionately impacted by health disparities. The grant was awarded through the CDC's National Center for Chronic Disease Prevention and Health Promotion as part of the "Expanding the National Approach to Chronic Disease Education and Awareness" funding opportunity. The first year of funding awarded to the AASM is approximately \$327,000.

Nearly 30 million American adults have obstructive sleep apnea, and 80% are undiagnosed, costing the U.S. more than \$149 billion annually in increased health care and mental health care costs, lost work productivity, and increased accidents.

"Millions of Americans don't even know they have sleep apnea, which puts them at greater risk for other health problems such as high blood pressure, heart disease, stroke, diabetes and depression," said AASM President Raman Malhotra, MD. "This grant from the CDC will support education and outreach to improve sleep apnea awareness so that people can get the treatment they need to sleep better and enhance their quality of life."

The AASM is partnering with several other specialty medical societies that have members who are active in the delivery of clinical care for obstructive sleep apnea, the patient-focused Alliance of Sleep Apnea Partners, and the National Sleep Foundation, which has an established history of directly educating the public about sleep health. The program also will support the sleep health objectives of Healthy People 2030, the nation's 10year public health plan, which includes the objective, "Increase the proportion of adults with sleep apnea symptoms who get evaluated by a health care provider." Baseline data show that only 33.1 percent of adults aged 20 years and over with symptoms of obstructive sleep apnea sought medical evaluation in 2015 – 2016. Another focus of the program will be to address sleep health disparities by developing strategies to improve awareness in Black, Native American, and Hispanic communities, in which the prevalence of obstructive sleep apnea is higher.

"This grant will help us improve national awareness efforts, including initiatives supporting racial and ethnic minority populations that have a higher prevalence of sleep apnea," said Dr. Malhotra. "It is important for people to identify the warning signs of sleep apnea and discuss their symptoms with a health care provider."

The program will be led by the AASM and its key partner, the Sleep Research Society. Collaborating organizations include the Alliance of Sleep Apnea Partners, American Academy of Dental Sleep Medicine, American Academy of Otolaryngology – Head and Neck Surgery, American College of Chest Physicians, American Society for Metabolic and Bariatric Surgery, American Thoracic Society, public relations agency Hager Sharp, and the National Sleep Foundation. These organizations are committed to raising awareness of obstructive sleep apnea and providing expertise to educate the public and providers about this chronic disease affecting millions of Americans.

Sleep Fact Sloth: Walruses' Strange Sleep Habits



Walruses can sleep up to 19 hours a day on land and have been tracked swimming for as long as 84 hours straight! In the ocean, they experience "unihemispheric sleep," where one half of their brain sleeps while the other stays active. This means walruses can continue swimming while also resting!



Pediatric Sleep Specialist Offers Advice on Surviving Med School

Sujay Kansagra, MD, is a pediatric neurologist and pediatric sleep specialist at Duke Health. Among other books, he's written a medical school memoir and a guide for parents struggling to get their child to sleep. Dr. Kansagra is the voice behind Twitter's @medschooladvice, where he shares survival tips with his 100,000+ followers.

Tell us about your medical background.

My medical training history is a mix of the light and dark blues of North Carolina. I went to medical school at Duke followed by a pediatrics residency at UNC Chapel Hill. Subsequently, I did my child neurology training at Duke, followed by a sleep medicine fellowship back at UNC Chapel Hill. To finish out the pattern, I joined Duke as faculty in 2012. People often ask which team I cheer for given this history. For basketball, I cheer for UNC, my undergrad alma mater. For medicine, I cheer for Duke.

What led to your interest in pediatrics, and pediatric neurology and sleep in particular?

I've always hoped to make a positive impact on the lives of children and their families. I was drawn to pediatric neurology and sleep for this reason. Giving a child the gift of great sleep can impact just about every medical, emotional, and behavioral issue the child may face. You can literally change the trajectory of a child's life by changing their relationship with sleep at this early stage.

You wrote a book on getting kids to sleep, My Child Won't Sleep: A Quick Guide for the Sleep-Deprived Parent. Based on the reviews, it's been a lifesaver for some parents! What's the secret to a good night's sleep for the whole family?

It all starts with prioritizing sleep, both for the kids and for the parents. The keys to great sleep for kids change as they grow. For young infants, establishing healthy routines and encouraging consistency is important. For older infants and toddlers, teaching children how to self-soothe is truly a gift for the child that has a myriad of short- and long-term benefits. For adolescents, having parents model the right behaviors is critical.

Despite the rigors of med school, residencies, and fellowships, you've taken time to write about your experiences. Tell us about your med school memoir and advice books.

I was fortunate to have an older sister who went into medicine, so I always had a mentor and advisor. But I knew that many didn't have such guidance, and the world is full of misinformation about the process. The medical education advice books are my small way of helping students who need guidance.

The memoir of my years in medical school began as a journal that was intended for only me. It was a way to look back to the time when I first saw the world of medicine with fresh eyes. I wanted to remember the feeling of walking into my first patient room and the thrill of delivering my first baby. But as I continued to write, I realized it could be a way to share the wonder of medicine with others. To this day, I get messages from medical students and residents who say they read my book, and it encouraged them to pursue medicine. It makes my day.

You run the Twitter account @medschooladvice. How has it been an effective way to communicate with new or aspiring med students?

The goal is to use social media to not only spread humor and advice about medical education but to also educate about sleep. I've found that humor and positive messages are much needed in the social media space since there is often so much negativity. It's also a great platform to spread information and amplify the voice of physicians and other health care workers.

At the end of the day, I want @medschooladvice and my books to leave a positive message about the path to a career in medicine. I recently had a medical student working in my clinic, and to my surprise, he said he followed my Twitter account for many years and read my book while in undergrad. He said it helped convince him to go to medical school, and in particular, to apply to Duke. I asked if he had any regrets, and thankfully he did not. It's these stories that keep me tweeting.

What's the best advice you ever received about med school?

Don't delay living life. The work never ends, but your youth does.

What do you think is the most important advice you give today's med students?

- 1. Find things you are passionate about and pursue those things.
- 2. You belong here. Don't doubt your abilities.
- 3. Strongly consider a career in sleep medicine!

AASM Advocates for Sleep Health in D.C.

The AASM is strengthening its voice in Washington, D.C., through the formation of the Congressional Sleep Health Caucus and virtual visits with legislators. Formed in 2020, the Sleep Health Caucus held its first briefing last fall to discuss sleep health during the pandemic. Additional virtual visits with lawmakers in November provided further opportunities to encourage involvement in the caucus and discuss sleep health issues.

Congressional Sleep Health Caucus

The Sleep Health Caucus was established to emphasize the need for healthy sleep for optimal health and to promote high-quality, patient-centered care for the millions of Americans who have a sleep disorder. The caucus is chaired by Reps. Zoe Lofgren (D-Calif.) and Rodney Davis (R-III.). The first caucus briefing focused on issues related to the COVID-19 pandemic and allowed legislative staff to learn about the importance of sleep health from several sleep experts.

Patient concerns, including access to care and appropriate treatment during the pandemic, were shared from the patient advocate perspective, and the pandemic's effect on children's sleep also was highlighted during the briefing. The recorded briefing is available on the AASM's YouTube channel, and members are encouraged to share it with their representatives while asking them to join the Sleep Health Caucus to further amplify our voice in Washington. Future caucus briefings will address topics such as daylight saving time, school start times, and sleep health disparities.

Virtual Hill Day

A broad group of sleep health advocates met with 11 congressional offices during virtual Hill Days Nov. 9 and 10, 2021, to advocate for legislative policies and issues important to AASM members and the larger sleep community. The meetings built on the productive discussions that were held during the AASM's virtual Hill Day last April.

Participants included members of the AASM Advocacy Committee, Public Awareness Advisory Committee, Public Safety Committee, and Political Action Committee Advisory Panel, as well as patient advocates representing several patient advocacy organizations: Alliance of Sleep Apnea Partners, Circadian Sleep Disorders Network, Hypersomnia Foundation, RLS Foundation, and Wake Up Narcolepsy. Groups of AASM members and patient advocates discussed and shared their personal stories in relation to a variety of AASM legislative and policy priorities and other issues of importance related to specific sleep disorders.

Public Awareness Advisory Committee Chair Seema Khosla, MD, participated in Hill Day for the first time and said the experience was enlightening.

"It made me realize how important it is for us to get out of our silos and speak to people who can facilitate the change we hope for," she said. "Even though we live in a hyper-polarized political climate, Hill Day allowed us to talk about issues that face us all as Americans, regardless of political leanings. I wasn't sure what to expect, but it all came down to elevating what we felt were the most important issues amenable to policy."

Telemedicine

Advocates focused heavily on the importance of expanded telehealth provisions, including the need for telemedicine provisions from the COVID-19 pandemic to be made permanent. Dr. Khosla, who visited with staff from the offices of Sens. Diane Feinstein (D-Calif.) and John Hoeven (R-N.D.), and Rep. Kelly Armstrong (R-N.D.), said they were universally supportive of telemedicine legislation to improve access to care. The Telehealth Modernization Act would protect telehealth access for rural patients and remove Medicare's geographic and originating site restrictions. Several patient participants shared their personal experience and explained the need for expanded telehealth coverage, which underscored the impact of telemedicine on people's everyday lives.

Philips Recall

Some meetings focused on the Philips PAP device recall as advocates described the situation and its impact on patients with sleep apnea. Discussion also focused on how the federal government may address issues that have resulted from the recall, as well as how similar situations may be prevented in the future.

Daylight Saving Time

With these visits occurring directly after the Nov. 7 change back to standard time, many offices were interested in discussing daylight saving time. Advocates described the negative effects of the time change on the American people and the need for permanent standard time, as detailed in the AASM's daylight saving time position statement.

Dr. Khosla encouraged members to visit the advocacy page on the AASM website to get more information on the AASM's legislative and policy priorities and to participate in current campaigns.

"As sleep clinicians, it's important that we advocate for what we believe," she said. "Sleep is essential to health. We all know that, but we need to be better at sharing that message with people who can implement structural, large-scale change and health policy."

AASM members can submit questions about these issues to policy@aasm.org.

Sleep ISR Record Rewards Program Sets Stage for Future of Sleep Medicine

Matthew Anastasi, AASM Sleep Scoring Project Manager

"There is a Chinese curse which says, 'May he live in interesting times.' Like it or not, we live in interesting times. They are times of danger and uncertainty; but they are also the most creative of any time in the history of mankind." — Robert F. Kennedy, "Day of Affirmation Address," Capetown, South Africa, 1966.

Every era has its own "interesting time." The increasing complexity of health care delivery and the proliferation of new technologies in sleep medicine have led some down a path of uncertainty. But change presents an opportunity to contribute to how this transformation takes place, and the AASM is here to help.

While the sleep field is evolving, polysomnography (PSG) endures as the most consequential source of physiologic data in sleep medicine. The AASM recognizes the importance of using a diverse set of records that are more closely representative of our patient populations in the Sleep ISR program.

The AASM also serves as an independent leader in setting standards in sleep medicine and is a key stakeholder in ensuring that the influence of emerging technology like artificial intelligence (AI) moves forward in a way that benefits the profession. The AASM has therefore introduced the <u>Sleep ISR Record Rewards Program</u> to address two needs: a) diversifying the catalog of records available through Sleep ISR to improve competency among sleep scorers, and b) providing an assorted source for the comparison of manual to automated scoring as part of a pilot program to certify AI scoring software packages.



The Importance of Diversity



Precision medicine, sometimes called "personalized medicine," is an approach that considers individual differences to allow for tailored treatments that target the unique needs of each patient. Although the approach is not new, awareness of precision medicine — and scientific interest in it — has grown dramatically in the past few years.

For example, as the population ages, the rate of complex patient cases will only increase due to an escalation of comorbid conditions. This is something we have already seen in our patient areas. This tendency toward more variability in patient disease makes imperative an approach that takes these disease states into account. What this means for Sleep ISR and AI scoring is the requirement for a more robust, heterogeneous presentation of patient physiological states through a PSG catalog that more accurately reflects the diversity of our patient population.

Growing the Sleep ISR Catalog

Until recently, the AASM has relied upon trusted but finite sources for compiling records that our Gold Standard Panels use in their scoring analysis. Although the Gold Standard Panels comprise members with wide-ranging backgrounds, each with extensive experience in sleep record scoring and review, their records represent a limited patient population. The Record Rewards Program will infuse a more diversified archive of records to draw from, enhancing the efforts of

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the panelists to demonstrate scoring examples and educate Sleep ISR scoring users to improve their familiarity and meet competencies defined by The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. It is important for the Sleep ISR records to represent the broad spectrum of patients seen in the sleep lab.



Al Stage Scoring Pilot Certification

Record Rewards is the next step in an effort to grow Sleep ISR while also addressing the needs of a changing sleep medicine field. The modern sleep disorders center is seeing a shift to a mixture of manual and automated tasks, and PSG is no exception. According to a recent AASM position statement on artificial intelligence in sleep medicine, AI has the potential to deepen our understanding of sleep disorders, improve patient-centered sleep care, augment day-to-day clinical operations, and increase our knowledge of the role of sleep in health at a population level. But the benefit of AI will ultimately hinge upon whether it is appropriately and responsibly used.

On the one hand, we have Sleep ISR to ensure scoring is performed accurately. On the other, our AI Stage Scoring Certification is the first effort to apply oversight to machine learning scoring packages, which will require a variety of sleep studies that are representative of our patient populations. By uploading sleep studies, you are adding to that mix and helping the field move forward in an innovative way that promotes population health parity and oversight of emerging technologies. Starting soon, the AASM will be using these records to evaluate the performance of AI sleep scoring packages by comparing them to records scored by humans.

The AASM has launched a two-year pilot certification program to evaluate the accuracy of sleep stage scoring from AI/auto-scoring software packages. Autoscored records will be compared to the same records scored by humans to validate the software's accuracy. These are important steps for the AASM to provide oversight of these systems.

One of the things we hope to learn through the pilot program is how best to manage a certification program that causes the least amount of disruption within a sleep lab as possible. The reality is that auto-scoring software has already been developed and is innovating rapidly thanks to advances in AI and machine learning.

How to Get Involved in the Rewards Program

If you are a user of Sleep ISR, you may have noticed a new section header called "Rewards Program" on your dashboard. Take a look and you'll see a series of

dropdown sections including an overview, which includes a background and instructions on how to get started, and information about how you can receive



points for uploading de-identified PSG records from your sleep lab. Points can be traded in for gifts like Amazon gift cards.

Sleep ISR administrators have the ability to grant their staff access to a submission tool within the ISR platform to submit PSG studies.

In order to participate in the Sleep ISR Record Submissions Program, the administrator will need to complete the "opt-in" process.

For admins to get started, simply log in to your Sleep ISR account and go to the Submit Sleep Study dropdown under the Rewards Program header. Click "enroll" in the prompted message below, review the AASM Participation Agreement, and check the box if you agree to these terms.

In exchange for your records that are submitted and accepted, you will be awarded points that can be redeemed for items such as Amazon gift cards. As the program develops, we plan to find more ways to recognize participation with additional reward offerings. To make it fun, we even have bonus opportunities to earn points faster.

We look forward to your participation! For more information about Sleep ISR or the Record Rewards Program, email isr@aasm.org.

AASM Members Address Inequities in Sleep Health

Jennifer Gibson, AASM Communications Manager

The COVID-19 pandemic brought a new level of attention to health disparities. People in communities of color are at greater risk of getting sick and dying from COVID, and studies show that racial and ethnic minorities are disproportionately impacted by poor sleep quality, sleep disorders, and comorbidities. While it's taken a crisis the magnitude of a pandemic to bring these health inequities to the forefront, advocates in the sleep medicine community are taking action to address the systems that perpetuate these inequities and impress upon minority and marginalized communities the importance of healthy sleep.

Understanding Social Determinants of Health

Studies have found that Black and Hispanic people regularly get less sleep than white people. Blacks are five times more likely to have short sleep duration compared with whites, and they are twice as likely to have sleep disorders. The lack of sufficient, healthy sleep makes communities of color more vulnerable to other chronic diseases. Dayna Johnson, PhD, an epidemiologist at Emory University, is among those leading efforts to increase awareness of disparities, understand their causes, and implement solutions.

"Sleep is a privilege," said Dr. Johnson, who has a doctorate in epidemiologic science and whose research focuses on understanding the social and environmental factors that cause sleep health disparities. She points to structural racism and discrimination as the fundamental causes of sleep disparities and overall health disparities. According to Dr. Johnson, it is a history of marginalizing Black Americans that has led to a lack of financial resources, fewer educational opportunities, inadequate access to food and housing, and limited access to care, all of which contribute to poor health.

Other barriers commonly found in low socio-economic neighborhoods are environmental factors such as noise, light, and air pollution that further increase the risk for sleep disorders, including sleep apnea, along with stressors like violence and inadequate safety, explained Dr. Johnson.

"It's really important for people to understand that the environment matters," she said. "We can look at a neighborhood and identify the factors that contribute to poor sleep."

Her research points to community-level interventions that can help at-risk populations. From ensuring local factories follow environmental regulations to updating neighborhoods with sidewalks and greenspace, efforts that improve and stabilize communities can lead to improved sleep and overall health. The sleep community can help by improving access to care, promoting healthy sleep strategies, and developing culturally appropriate education and intervention materials. Dr. Johnson said it's time to go beyond traditional sleep hygiene recommendations to understand barriers at the grassroots level.

"What we have to do as researchers and clinicians is expand our thoughts around what are the parameters for this person being able to sleep in a dark, quiet room, and think about how we can adjust our recommendations in order to improve sleep in these populations," she said. "We have to chip away at each of these individual things, and then we can address the broader issue."

Improving Awareness, Building Trust

Girardin Jean-Louis, PhD, has spent years cultivating relationships with people in at-risk communities to help them understand the importance of healthy sleep and the link between poor sleep and overall health. Like Dr. Johnson, Dr. Jean-Louis, who has a doctorate in psychology and recently launched the translational sleep and circadian sciences program at the University of Miami, also focuses his research on social and environmental determinants of health in low-income and Black communities. He said one of the most important things sleep clinicians and researchers can do to understand and address sleep health disparities is go into the neighborhoods and talk to residents.

"Most of us are trained to do everything in our offices and our labs," he said. "But going to a medical office or institution is not something that minority communities really think about very seriously because of this issue of a lack of trust. So, if they're not going to come to us, we have to go to them."

However, it isn't as easy as showing up and knocking on doors. Dr. Jean-Louis almost got kicked out when he showed up at a barber shop with a clipboard in hand. He said it took about 18 months to build trust and rapport in targeted communities. While at New York University, his team developed a tailored approach to sleep health education that utilized community stakeholders such as barbers and church leaders.

"If you have folks who know those communities well, access is no longer an issue, and this is what has led to the level of success that we have had," said Dr. Jean-Louis. Improved technology and home-based screening also have made a significant difference in diagnosing and treating sleep apnea in underserved communities by allowing direct access to patients in their homes, which also provides an opportunity for education about other factors, such as obesity, that contribute to sleep apnea.

"You can't have a conversation about poor sleep and not have conversations about high blood pressure, diabetes, cardiovascular disease, even cancer," he said.

Another key is to allow patients to oversee their own medical decisions. The sleep team can talk about sleep issues, risk factors, and symptoms of sleep disorders, but the individuals need to be able to go home, talk to their families and neighbors, and make the best choice for their treatment.

Dr. Jean-Louis encourages other providers and researchers to follow the framework his team has established to reach underserved communities with custom information that will resonate.

Collaborating With the Community

Dr. Johnson said Black people tend to under-report insomnia. If you look at the depictions of Blacks during slavery, she said, sleeping was interpreted as laziness, which perpetuates a stereotype that getting sufficient sleep implies being lazy. Given the data showing longer sleep onset and shorter sleep duration in communities of color, it's likely Black people experience a higher prevalence of insomnia than white people.

The first line of treatment for chronic insomnia is cognitive behavioral therapy, which isn't always available in minority communities. Suzanne Bertisch, MD, associate physician and clinical director of behavioral sleep medicine at Brigham and Women's Hospital and assistant professor of sleep medicine at Harvard Medical School, is part of a research team that will investigate the effectiveness of brief behavioral treatment for insomnia (BBTI) in underserved communities.

"We want to do this research based largely on our clinical experience in seeing patients who aren't able to access CBTI or BBTI because they lack insurance coverage or have high outof-pocket costs or language barriers," said Dr. Bertisch. "We're motivated to get people who would benefit from BBTI more treatment."

She added, "BBTI has never been tested in a racially diverse, underserved population."

Dr. Bertisch said BBTI is a more realistic treatment than CBTI because it is more scalable and can be delivered by more providers like social workers and nurse practitioners. Those enrolled in the study rarely are able to see a specialist, so Dr. Bertisch will work with primary care physicians to adapt BBTI treatment for patients with insomnia disorder. Again, it's building on trust.

"To do the work in the communities takes a really long time because you have to establish the relationships and trust," Dr. Bertisch said. "They know their primary care doctor, so we're leveraging the relationships. The ultimate goal is to figure out a way to get patients this treatment within the primary care framework. Most people don't know this is an option."

Dr. Bertisch's team was awarded funding from the AASM Foundation for the research, which will lay the groundwork for a larger and longer-term study that tests the effectiveness of BBTI in the real-world setting, which could fundamentally advance the treatment of insomnia for health disparate groups, who commonly lack access to behavioral sleep medicine.

Each of these researchers emphasizes the importance of building trust and relationships to make a meaningful impact on minority communities. The systemic racism and discrimination that led to their health disparities also creates skepticism. But for those willing to make a commitment to advance health equity in their communities, there are strategies to follow. Improving health equity will make all communities healthier, stronger, and safer.

"As sleep researchers and clinicians, this is our time that we can really make a difference in reducing health inequities overall if we can figure out how to improve sleep," said Dr. Johnson.

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AASM Analysis of the Requirements Related to Part I and II of the Surprise Billing Interim Final Rule

Steve McEllin, AASM Health Policy Project Manager

On Dec. 27, 2020, the Consolidated Appropriations Act, which includes the "No Surprises Act," was signed into law. This legislation, which took effect Jan. 1, 2022, bars surprise billing in most health care settings and establishes new transparency requirements. Surprise medical billing occurs when an insured patient unknowingly receives care from an out-of-network provider and then is presented with a bill for services and payment obligation beyond what the patient's insurer will cover. Surprise medical bills arise out of emergencies when patients have no or limited ability to select the facility or provider rendering services. Surprise billing can also occur when patients receive planned care. On July 1, 2021, the U.S. Departments of Health and Human Services (HHS) and Treasury and Labor, along with the Office of Personnel Management, released a first Interim Final Rule with comment (IFR), related to Surprise Billing. On Sept. 30, 2021, the groups released a second IFR related to Surprise Billing.

The July 1 regulation details the following: 1) Methodology for calculating the qualifying payment amount (QPA)

When an insured patient receives emergency care and certain nonemergency services from an out-of-network provider, the patient's cost-sharing obligation will be capped at amounts that would apply if the services had been furnished by an in-network provider. That amount will be either determined by an applicable All-Payer Model Agreement; defined under state law, where applicable; or the QPA. The QPA is the annual median contracted rate recognized by the issuer for the same or similar item or service by a similar provider in the same insurance market, which will be increased annually based on the Consumer Price Index for All Urban Consumers (CPI-U).

- Similar items and services, providers and facilities, and geographic regions that will be used to calculate a median rate, and the methodology for arranging contracted rates to determine a median rate are further defined.
- The QPA methodology will be based on contracted rates and will not consider actual amounts of paid claims.
- States are given wide-ranging discretion in implementing All-Payer Claims Databases, which will be considered unconditionally eligible to serve as a resource for calculating the QPA.
- The QPA influences consumers' cost sharing and payments to providers, and it will be considered in determining payment during arbitrable disputes.
- HHS and the other departments seek to limit financial burden of payer-provider disputes on consumers' cost sharing by tying cost sharing to a recognized amount.

2) Definitions of emergency services and emergency medical conditions

The act defines "emergency medical condition" to mean a medical condition revealing itself by acute symptoms or pain of enough severity that a prudent layperson could rationally assume the absence of urgent medical attention would result in placing an individual's health in serious risk. This definition extends to mental health conditions and substance use disorders. Emergency services can also include items and services provided to patients after they are stabilized and as part of outpatient observation, or as part of an inpatient stay or outpatient visit.

- It prevents payers from limiting coverage based on the final diagnosis code alone or general policy exclusions.
- By expanding the definition of emergency services, HHS seeks to prevent activities that may circumvent coverage in emergency situations.

3) Payer Disclosures

The No Surprises Act requires that payers make publicly available, post on their public website, and include in their explanation of benefits a description of the prohibitions related to surprise billing and the circumstances in which they apply.

- Payers are also required to disclose to non-participating providers the QPA for each item or service involved, along with a statement that the QPA applies for purposes of the recognized amount.
- Payer disclosures serve as early notice that will give providers greater clarity on how the payment amount was reached and whether they should pursue Independent Dispute Resolution.

4) Processes for receiving consumer complaints

The No Surprises Act requires plans, health care providers and facilities to make and post notices about the new requirements related to surprise billing. The act requires HHS and the other departments to establish a process to receive consumer complaints regarding violations of payers' application of the QPA and directs HHS to establish a parallel complaints process for consumer complaints to provider violations of the balance billing requirements. The act also requires HHS and other departments to respond to consumers' payer and provider complaints within 60 days of receipt.

• The complaints processes for reporting payer and provider violations are still a work in progress, and while an outline has been developed, these processes may be expanded.

5) Notice and Consent Requirements

This regulation establishes the content, language and timing standards related to notice and consent forms and how these forms must be delivered. Notice and consent provisions are to ensure that patients can maintain provider choice and that they are not pressured into waiving balance billing protections.

- Excluding certain ancillary services, the No Surprises Act provides exceptions to the balance billing protections for non-emergency services if the patient is given notice and consents to be financially liable for out-of-network financial obligations.
- The act also requires consents where patients acknowledge they were given written notice about payment information and its impact on cost sharing.
- The provider must retain consents for seven years and must provide timely notification to the payer as to whether balance billing and in-network cost sharing protections apply to the item or service.

The September 30 regulation details the following: 1) Establishes an independent dispute resolution (IDR) process and timeline to determine out-of-network payment amounts between providers (including air ambulance providers) or facilities and health plans

The No Surprises Act establishes a process and timeline for initiating the IDR process that may be used to determine rates when an all-payer model agreement or specified state law does not apply. The act seeks to minimize reliance on IDR by first requiring a 30-day negotiation period. This negotiation phase begins when the party seeking to negotiate payment disagreements opens a negotiation notice, in writing (which may be in an electronic format) detailing the items or services in dispute, the initial payment or notice of denial, and an offer for the out-of-network rate. Parties may reach an agreement before 30 business days, but they may not proceed to the next phase before the 30 business days have expired. If negotiations fail, the provider or payer have four days after the end of the 30-day period to initiate the IDR process.

2) Requires good faith estimates of medical items or services for uninsured (or self-paying) individuals

The No Surprises Act requires providers to give good faith estimates of items and services to uninsured or self-pay individuals before services are rendered. All providers and facilities must inquire about an individual's health coverage status and provide a notification that the individual may receive a good faith estimate of the expected charges for furnishing the item or service. Good faith estimates must reflect the anticipated billed charges, including any discounts or other relevant adjustments that the provider or facility expects to apply, and be provided orally and in writing (HHS foresees a model notification) for advising the availability of good faith estimates. When a state provides similar good faith requirements, providers and facilities must still comply with the federal good faith estimate requirements.

3) Establishes a patient-provider dispute resolution process for uninsured or self-paying individuals to determine payment amounts due to a provider or facility under certain circumstances

The act establishes a patient-provider dispute resolution process under which an uninsured or self-pay individual who received a good faith estimate of expected charges may seek a determination of the amount to be paid if the billed charges substantially exceed the expected charges. The regulation provides eligibility details for this dispute resolution process, a definition of "substantially in excess," which is defined as at least \$400 over the good faith estimate, and further information on the select dispute resolution (SDR) procedure, which must be initiated within 120 calendar days of the patient receiving the bill. When a state law provides a similar process for resolving disputes between an uninsured individual and a provider or facility, the state process should continue to apply if it meets or exceeds the act's consumer protections. HHS will establish a procedure for determining whether a state patientprovider dispute resolution process provides at least the same level of consumer protections as the federal process.

4) Provides for external review of certain health plan decisions

The act expands the scope of adverse benefit determinations eligible for external review to include determinations that involve whether a plan or issuer is complying with the surprise billing and cost-sharing protections and its implementing regulations. Grandfathered plans will be subject to external review requirements for coverage decisions that involve whether a plan or issuer follows the surprise billing and cost-sharing protections under the act.

AASM staff will review part 3 of the Surprise Billing Interim Final Rules and share analyses with AASM members when it is released. Questions regarding the Surprise Billing Interim Final Rules can be sent to <u>coding@aasm.org</u>.

Advice for Early Career Physicians in Academic Sleep Medicine

The Early Career Physician Assembly is an online community for members who are early in their sleep medicine careers, giving them an opportunity to network and learn from colleagues with a similar professional background. AASM member students, fellows, trainees, and physician members under 40 years old are automatically included in the assembly.

Leaders of the assembly asked AASM members in academic sleep medicine what they wish they had known when transitioning from a fellowship to their new career. We heard from recent fellowship graduates, David Earl, MD, PharmD, and Sullafa Kadura, MD; a new program director in mid-career, Joyce Lee-lannotti, MD; and AASM President Raman Malhotra, MD. They described their challenges and successes and provided advice to new sleep practitioners.



David C. Earl II, MD, PharmD

Dr. Earl specializes in psychiatry and sleep medicine. He received his doctorate in pharmacy in 2008 followed by his doctorate in medicine in 2016. He completed his residency in psychiatry at the University of New Mexico in 2020. He was a sleep fellow at the University of New Mexico Sleep Disorders Center in 2020-2021 and now practices sleep medicine and psychiatry at the UNM.

What did you find challenging about the transition into your new career after fellowship?

Dr. Earl: I felt uncertain about the contract process as the details were not particularly clear to me, and the contract was not made available until just before the start date. I had to negotiate my position with my primary specialty as I am working at an academic center, and while that process was not particularly uncomfortable, it did add time to the hiring process as two departments are funding fractions of my salary. Uncertainties related to the financial effects of the pandemic, as well as the recent use of a consulting firm to help my employer improve revenue, led to the inability of some of my superiors to fully inform me as to what to expect.

What helped with this transition?

Dr. Earl: The transition to attending life was made easier by my program director guiding me through the process. The fellowship did a really good job of preparing me for what to expect.



Sullafa Kadura, MD, MBA

Dr. Kadura is an assistant professor of clinical medicine in the department of medicine and pulmonary/critical care at the University of Rochester Medical Center, where she completed her sleep medicine fellowship in June 2021. She is also a director of clinical informatics.

What advice would you give those who are transitioning into a new career after fellowship?

Dr. Kadura: Early preparation is essential before transitioning from fellowship to attending, especially since the sleep medicine fellowship is only one year. During our training, we had to settle for just any position with an already established template. This transition is very different.

I think the most critical step is knowing what you are looking for in a career. Sit back, reflect, and take the time to identify your values, needs, and wants - both professionally and personally. Be as specific as possible and prioritize from most to least important. Your values ideally will align with your new employer. Being clear about your wants and needs also increases your chances of successful negotiation.

The other thing is that potential employers may pressure you to make a decision too quickly. Give yourself several months to negotiate your needs and wants, compare other employment opportunities, and review your contract in detail.



Joyce K. Lee-lannotti, MD

Dr. Lee-Iannotti is the director of the sleep disorders center and program director of the sleep medicine fellowship at the University of Arizona College of Medicine. She completed medical school at the University of South Carolina School of Medicine, residencies in internal medicine and neurology at the Cleveland Clinic Foundation,

and fellowships in sleep medicine at the Cleveland Clinic and vascular neurology at the Mayo Graduate School of Medicine in Phoenix.

What do you think is most challenging for those transitioning into a new career after fellowship?

Dr. Lee-lannotti: I feel the transition is tough, regardless of whether the fellow plans to pursue an academic or a private practice career. Many fellows are PGY-4 to PGY-7's and advanced in training, but I'm not sure anything truly prepares you for taking the dive into becoming a full-fledged faculty. Once you graduate, you are no longer "supervised" and expected to practice independently – this can be overwhelming!

What advice would you give those to ease this transition? Dr. Lee-lannotti: First, realize that sleep medicine is a oneyear fellowship, but the learning continues well beyond fellowship. I am 10+ years out and still learning new things every day! Sleep is multi-disciplinary and complex – this is what makes it so fascinating! For example, just today I realized in discussions with an ortho resident rotating with me that OSA is associated with osteoporosis and decreased bone-healing post-fractures! This led us to explore OSA as a risk factor for fractures/osteoporosis and decreased success after orthopedic surgeries. So, do not get frustrated if you feel like you don't know everything – no one does. Continue to read journals, be involved in AASM, attend local sleep grand rounds, do CMEs, and commit yourself to being a lifelong learner.

Second, find good mentors and colleagues, people who can become invested in your learning and your success. They are the people you call for advice on a difficult patient, help with a book chapter, advice on leadership and political obstacles within your department or hospital. I have three mentors that I am grateful for every day, and I continue to benefit from their mentorship after a decade. I am also surrounded by extremely supportive colleagues.

Attend meetings, join the AASM, network! This keeps you "in the loop," helps you find a sense of community with people who share your passion, and updates you on the latest and greatest advances in sleep medicine.

Find a niche. Be able to treat and manage every sleep disorder but find your true passion and area of interest. If you are an academician, this will build on your ability to be innovative and create pilot studies.

Be a great doctor; be a good person but also learn to be financially savvy, whether you're in an academic position or private practice. Be conscientious of insurance coverage policies, financial flows and your overall financial security. Learn also to be a good manager – a well-supported clinic and knowledgeable staff will only benefit your patient.

Lastly, practice what you preach. Practice good sleep hygiene, work-life balance, wellness, stress relief, resilience, exercise, good health. In our realm of sleep medicine, all of these are so important. Patients will look to us to lead the way to sleep health.



Raman K. Malhotra, MD

Dr. Malhotra is president of the AASM and professor of neurology and program director of the sleep medicine fellowship at Washington University School of Medicine in St. Louis. He completed medical school at

the University of Missouri – Kansas City School of Medicine, and a residency in neurology and a fellowship in sleep medicine at the University of Michigan Medical Center.

What do you wish you knew going into attending life? Dr. Malhotra: It would have been helpful to have more

knowledge about typical clinical expectations (RVUs, encounters) for a clinician educator at an academic institution. I am sure this would have also been helpful to have if I was going into private practice. We usually only know about the practice environment that we trained at, and it can be helpful to learn about other practice environments.

What helped with your transition into your new career after fellowship?

Dr. Malhotra: Past trainees who had already started their careers were very helpful to me. There were also resources available at the AASM and other medical societies that could be used for reference. I also felt meeting more sleep medicine providers in my stage in my career either at the APSS meeting or other events was very helpful.

What advice did you seek?

Dr. Malhotra: I needed assistance with contract negotiation and making sure I was asking for the appropriate support as I started my career. It was also helpful to get advice about time management, and setting goals for the next three, five, and 10 years. It was helpful to try and identify specific goals and objectives that I could work toward, for example requirements for promotion to the next academic level at my institution. I also sought advice on how to become more active in the AASM.

> For more resources about the transition from fellowship to an early career sleep medicine physician, check out these AASM resources:

- <u>Early Career Physician Assembly</u> to connect with other early career physicians.
 Eligible members can access the assembly under "My Communities" on AASM Engage
- <u>Choose Sleep</u> for educational resources and webinars, including contract negotiation and billing
- AASM Mentorship Program to become a mentee or mentor

In the next issue of Montage, we will share advice from early career sleep medicine physicians in private practice.

ASIM FOUNDATION

AASM FOUNDATION RAISES FUNDS IN HONOR OF SLEEP MEDICINE FELLOWS AND FACULTY

Honor Graduates & Faculty

In 2020, the faculty at the University of Miami Miller School of Medicine and Miami VA Healthcare System joined together to make a special \$1,600 donation to honor three fellows when they completed their year-long sleep medicine fellowship training program.

Their generosity inspired the AASM Foundation to encourage all faculty in sleep medicine and research programs to recognize the 2021 graduating sleep medicine fellows, trainees and others by contributing to our special Honor Graduates and Faculty Campaign.

Thanks to the following participants, the Foundation raised more than \$4,000 in honor of sleep medicine fellows and faculty. Donations to the Honor Graduates and Faculty Campaign support expansion of the Foundation's programs including a new Diversity Supplement Award and the Sleep Medicine Fellow Funding Award.

Have you made a donation to the AASM Foundation? Visit foundation.aasm.org/donate and learn about the many ways to you can support our grants and training programs.

Case Western Reserve University/University Hospitals Cleveland Medical Center Carol Rosen, MD In recognition of fellow:



Moshe Prero, MD

Duke University School of Medicine Andrew Spector, MD In recognition of fellows:





Marjorie Kilgore, MD

Ashley Miller, MD

Emory University School of Medicine

Joanne Shirine Allam, MD Lynn Marie Trotti, MD, MSc Barry Fields, MD In recognition of fellows:







Syed Gilani, MD

Meredith Greer, MD Nittu Singh, MD

Andrew Upchurch, MD (no image)

Indiana University School of Medicine

Stephanie Stahl, MD In recognition of fellow:

Mayo Clinic College of Medicine and Science

In recognition of Sleep Medicine Fellowship



Eric Olson, MD

Program Director:

Mohammed Jomha, MD

Kannan Ramar, MD

Meghna Mansukhani, MD

Diane Lim, MD

Naresh Punjabi, MD

Alberto Ramos, MD, MSPH

Shirin Shafazand, MD, MS

University of Michigan Medicine

Anita Shelqikar, MD, MHPE In recognition of fellows:



Abdullah Arjomand, MD





Lulu Guo, MD



Syed Kamal Nasser, MD

Marri Horvat, MD, MS

Not pictured:

MBBS

Subhendu Rath, Stephanie Meyer Tarnacki, MD

Wayne State University School of Medicine Safwan Badr, MD James Rowley, MD

In recognition of fellows:

Rahul Dasgupta, MD



Noman Ahmed, MD







Tanureet Kochar, MD

Not pictured: Emad Alkhankan, MD

Michael Hill, MD

University of Washington Medicine Vishesh Kapur, MD, MPH

In recognition of fellows: Ankit Amin, MD Jeremy Chan, MD Vidhi Kapoor, MD In recognition of faculty:



From left to right, Lourdes DelRosso, Vidhi Kapoor, Ankit Amin, Jeremy Chan and Vishesh Kapur

Not pictured: Brian Palen, MD

Madiha Khan, MD

Douglas Wallace, MD

Lourdes DelRosso, MD



University of Miami Miller School of Medicine and

Andres Martinez Chacon, MD

Miami VA Healthcare System

Alexandre Abreu, MD

Alejandro Chediak, MD

In recognition of fellows:

Kori Ascher, DO

Hao Cheng, MD

Salim Dib, MD



Moe Zaw, MD

Help your patients living with narcolepsy

SEIZE THE DAY

With XYWAV—the first and only lower-sodium oxybate FDA approved for treating cataplexy or EDS* in patients ages 7 years and older with narcolepsy.¹⁻³

*Excessive daytime sleepiness.



(calcium, magnesium, potassium, and sodium oxybates) oral solution @

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Consider XYWAV

Whether a patient is taking XYREM[®] (sodium oxybate) oral solution now or is new to oxybate treatment.



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92% less sodium than sodium oxybate³

XYWAV contains the same active moiety at the same concentration as XYREM[®] (sodium oxybate) oral solution.^{1,4,5} Both contain 0.413 g/mL of oxybate in solution.^{1,4,5}

Visit **XywavHCP.com** to sign up for information and learn more about how to start or transition appropriate patients.

INDICATIONS AND USAGE

XYWAV[™] (calcium, magnesium, potassium, and sodium oxybates) oral solution, 0.5 g/mL total salts (equivalent to 0.413 g/mL of oxybate) is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

Important Safety Information

WARNING: CENTRAL NERVOUS SYSTEM DEPRESSION and ABUSE AND MISUSE.

<u>Central Nervous System Depression</u>

XYWAV is a CNS depressant. Clinically significant respiratory depression and obtundation may occur in patients treated with XYWAV at recommended doses. Many patients who received XYWAV during clinical trials in narcolepsy were receiving CNS stimulants.

• Abuse and Misuse

The active moiety of XYWAV is oxybate or gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death.

Because of the risks of CNS depression and abuse and misuse, XYWAV is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Xywav and Xyrem REMS.

Please see additional Important Safety Information on the following pages and Brief Summary of full Prescribing Information, including BOXED Warning.



(calcium, magnesium, potassium, and sodium oxybates) oral solution @

Important Safety Information (continued)

Contraindications

XYWAV is contraindicated in combination with sedative hypnotics or alcohol and in patients with succinic semialdehyde dehydrogenase deficiency.

Warnings and Precautions

- CNS Depression: Use caution when considering the concurrent use with other CNS depressants. If concurrent use is required, consider dose reduction or discontinuation of one or more CNS depressants (including XYWAV). Consider interrupting XYWAV treatment if short-term opioid use is required. After first initiating treatment and until certain that XYWAV does not affect them adversely, caution patients against hazardous activities requiring complete mental alertness or motor coordination such as operating hazardous machinery, including automobiles or airplanes. Also caution patients against these hazardous activities for at least 6 hours after taking XYWAV. Patients should be queried about CNS depression-related events upon initiation of XYWAV therapy and periodically thereafter.
- Abuse and Misuse: XYWAV is a Schedule III controlled substance. The rapid onset of sedation, coupled with the amnestic features of GHB particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (eg, assault victim).
- Respiratory Depression and Sleep-Disordered Breathing: XYWAV may impair respiratory drive, especially in patients
 with compromised respiratory function. In overdoses of oxybate and with illicit use of GHB, life-threatening respiratory
 depression has been reported. Increased apnea and reduced oxygenation may occur with XYWAV administration in
 adult and pediatric patients. A significant increase in the number of central apneas and clinically significant oxygen
 desaturation may occur in patients with obstructive sleep apnea treated with XYWAV. Prescribers should be aware that
 sleep-related breathing disorders tend to be more prevalent in obese patients, in men, in postmenopausal women not
 on hormone replacement therapy, and among patients with narcolepsy.
- Depression and Suicidality: In a randomized-withdrawal clinical trial in adult patients with narcolepsy (n=201), depression and depressed mood were reported in patients treated with XYWAV. In most cases, no change in XYWAV treatment was required. In clinical trials of Xyrem (same active moiety as XYWAV) in adult patients with narcolepsy (n=781), depression was reported by 7% of Xyrem-treated patients, with four patients (<1%) discontinuing because of depression. In the pediatric clinical trial with Xyrem in patients with narcolepsy (n=104), one patient experienced suicidal ideation, and two patients reported depression while taking XYREM. Monitor patients for the emergence of increased depressive symptoms and/or suicidality while taking XYWAV, which require careful and immediate evaluation.
- Other Behavioral or Psychiatric Adverse Reactions: Monitor patients for impaired motor/cognitive function or the emergence of or increase in anxiety and/or confusion. The emergence or increase in the occurrence of behavioral or psychiatric events in patients taking XYWAV should be carefully monitored.
- Parasomnias: In a randomized-withdrawal clinical trial, parasomnias, including sleepwalking were reported in adult
 patients treated with XYWAV. Parasomnias, including sleepwalking, also have been reported in a pediatric clinical trial
 with sodium oxybate (same active moiety as XYWAV) and in postmarketing experience with sodium oxybate. Episodes of
 sleepwalking should be fully evaluated and appropriate interventions considered.

Most Common Adverse Reactions

In the adult clinical trial, in patients with narcolepsy, the most common adverse reactions (incidence \geq 5% of XYWAV-treated patients) were headache, nausea, dizziness, decreased appetite, parasomnia, diarrhea, hyperhidrosis, anxiety, and vomiting. In the pediatric clinical trial with Xyrem (same active moiety as XYWAV) in patients 7 years of age and older with narcolepsy, the most common adverse reactions (\geq 5%) were nausea (20%), enuresis (19%), vomiting (18%), headache (17%), weight decreased (13%), decreased appetite (9%), dizziness (8%), and sleepwalking (6%). The safety profile in pediatric patients with XYWAV is expected to be similar to that of adult patients treated with XYWAV and to that of pediatric patients treated with Xyrem.

Please see additional Important Safety Information on previous page and Brief Summary of full Prescribing Information, including BOXED Warning, on following pages.

References: 1. XYWAV[™] (calcium, magnesium, potassium, and sodium oxybates). Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc. 2. Thorpy MJ. Recently approved and upcoming treatments for narcolepsy. *CNS Drugs*. 2020;34(1):9-27. 3. Bogan RK, Thorpy MJ, Dauvilliers Y, et al. Efficacy and safety of calcium, magnesium, potassium, and sodium oxybates (lower-sodium oxybate [LXB]; JZP-258) in a placebo-controlled, double-blind, randomized withdrawal study in adults with narcolepsy with cataplexy. *Sleep*. Published online October 14, 2020. doi.org/10.1093/ sleep/zsaa206. 4. Data on File (JZP258-2020-013). Jazz Pharmaceuticals, Inc. 5. XYREM[®] (sodium oxybate). Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc.



(calcium, magnesium, potassium, and sodium oxybates) oral solution @



XYWAV[™] (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII **BRIEF SUMMARY OF PRESCRIBING INFORMATION: Consult the full Prescribing** Information for complete product information.

Initial U.S. Approval: 2002

WARNING: CENTRAL NERVOUS SYSTEM DEPRESSION and ABUSE AND MISUSE.

- **Central Nervous System Depression** XYWAV is a CNS depressant, and respiratory depression can occur with XYWAV use [see Warnings and Precautions (5.1)(5.4)]. Many patients who received XYWAV during clinical trials in narcolepsy were receiving central nervous system stimulants [see Clinical Trials (14)1.
- Abuse and Misuse The active moiety of XYWAV is oxybate or gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB is associated with CNS adverse reactions, including seizure, respiratory depression, decreased consciousness, coma, and death [see Warnings and Precautions (5.2)].

XYWAV is available only through a restricted program called the XYWAV and XYREM REMS [see Warnings and Precautions (5.3)].

INDICATIONS AND USAGE 1

XYWAV is indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy.

CONTRAINDICATIONS

XYWAV is contraindicated for use in:

• combination with sedative hypnotics [see Warnings and Precautions (5.1)].

• combination with alcohol [see Warnings and Precautions (5.1)]. • patients with succinic semialdehyde dehydrogenase deficiency [see Clinical Pharmacology

(12.3)7

5 WARNINGS AND PRECAUTIONS

5.1 **Central Nervous System Depression**

XYWAV is a central nervous system (CNS) depressant. Clinically significant respiratory depression and obtundation has occurred in adult patients taking sodium oxybate (same active moiety as XYWAV) at recommended doses in clinical trials and may occur in patients treated with XYWAV at recommended doses. XYWAV is contraindicated in combination with alcohol and sedative hypnotics. The concurrent use of XYWAV with other CNS depressants, including but not limited to opioid analgesics, benzodiazepines, sedating antidepressants or antipsychotics, sedating anti-epileptic drugs, general anesthetics, muscle relaxants, and/or illicit CNS depressants, may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death.

If use of these CNS depressants in combination with XYWAV is required, dose reduction or discontinuation of one or more CNS depressants (including XYWAV) should be considered. In addition, if short-term use of an opioid (e.g., post- or perioperative) is required, interruption of treatment with XYWAV should be considered.

Healthcare providers should caution patients about operating hazardous machinery, including automobiles or airplanes, until they are reasonably certain that XYWAV does not affect them adversely (e.g., impair judgment, thinking, or motor skills). Patients should not engage in hazardous occupations or activities requiring complete mental alertness or motor coordination, such as operating machinery or a motor vehicle or flying an airplane, for at least 6 hours after taking XYWAV. Patients should be queried about CNS depression-related events upon initiation of XYWAV therapy and periodically thereafter. XYWAV is available only through a restricted program under a REMS [see Warnings and Precautions (5.3)]

5.2 Abuse and Misuse

XYWAV is a Schedule III controlled substance. The active moiety of XYWAV is oxybate, also known as gamma-hydroxybutyrate (GHB), a Schedule I controlled substance. Abuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. The rapid onset of sedation, coupled with the amnestic features of GHB, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim). Because illicit use and abuse of GHB have been reported, healthcare providers should carefully evaluate patients for a history of drug abuse and follow them closely, particularly for signs of misuse or abuse of GHB (including but not limited to increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy) [see Drug Abuse and Dependence (9.2)]. If abuse is suspected, treatment with XYWAV should be discontinued. XYWAV is available only through a restricted program under a REMS [see Warnings and Precautions (5.3)].

5.3 XYWAV and XYREM REMS

XYWAV is available only through a restricted distribution program called the XYWAV and XYREM REMS because of the risks of central nervous system depression and abuse and misuse [see Warnings and Precautions (5.1, 5.2)].

Notable requirements of the XYWAV and XYREM REMS include the following:

- Healthcare Providers who prescribe XYWAV are specially certified
- XYWAV will be dispensed only by the central pharmacy that is specially certified XYWAV will be dispensed and shipped only to patients who are enrolled in the XYWAV and XYREM REMS with documentation of safe use.
- Further information is available at www.XYWAVXYREMREMS.com or 1-866-997-3688.

5.4 Respiratory Depression and Sleep-Disordered Breathing

XYWAV may impair respiratory drive, especially in patients with compromised respiratory function. In overdoses of oxybate and with illicit use of GHB, life-threatening respiratory depression has been reported [see Overdosage (10)].

Increased apnea and reduced oxygenation may occur with XYWAV administration in adult and pediatric patients. A significant increase in the number of central apneas and clinically significant oxygen desaturation may occur in patients with obstructive sleep apnea treated with XYWAV.

In a study assessing the respiratory-depressant effects of Xyrem (same active moiety as XYWAV) at doses up to 9 g per night in 21 adult patients with narcolepsy, no dose-related changes in oxygen saturation were demonstrated in the group as a whole. One of the four patients with preexisting moderate-to-severe sleep apnea had significant worsening of the apnea/hypopnea index during treatment.

In a study assessing the effects of Xyrem 9 g per night in 50 adult patients with obstructive sleep apnea, Xyrem did not increase the severity of sleep-disordered breathing and did not adversely affect the average duration and severity of oxygen desaturation overall. However, there was a significant increase in the number of central apneas in patients taking Xyrem, and clinically significant oxygen desaturation (<55%) was measured in three patients (6%) after Xyrem administration, with one patient withdrawing from the study and two continuing after single brief instances of desaturation.

During polysomnographic evaluation (PSG), central sleep apnea and oxygen desaturation were observed in pediatric patients with narcolepsy treated with Xyrem.

Prescribers should be aware that increased central apneas and clinically relevant desaturation events have been observed with sodium oxybate administration in adult and pediatric patients.

In clinical trials of Xyrem in 128 adult patients with narcolepsy, two patients had profound CNS depression, which resolved after supportive respiratory intervention. Two other patients discontinued sodium oxybate because of severe difficulty breathing and an increase in obstructive sleep apnea. In two controlled trials assessing PSG measures in adult patients with narcolepsy, 40 of 477 patients were included with a baseline apnea/ hypopnea index of 16 to 67 events per hour, indicative of mild to severe sleep-disordered breathing. None of the 40 patients had a clinically significant worsening of respiratory function, as measured by apnea/hypopnea index and pulse oximetry at doses of 4.5 g to 9 g per night

Prescribers should be aware that sleep-related breathing disorders tend to be more prevalent in obese patients, in men, in postmenopausal women not on hormone replacement therapy, and among patients with narcolepsy.

Depression and Suicidality 5.5

Depression, and suicidal ideation and behavior can occur in patients treated with XYWAV. In Study 1, depression and depressed mood were reported in 3% and 4%, respectively. of patients treated with XYWAV. Two patients (1%) discontinued XYWAV because of depression, but in most cases, no change in XYWAV treatment was required.

In clinical trials of Xyrem (same active moiety as XYWAV) in adult patients with narcolepsy (n=781), there were two suicides and two attempted suicides in patients treated with Xyrem, including three patients with a previous history of depressive psychiatric disorder. Of the two suicides, one patient used Xyrem in conjunction with other drugs. Xyrem was not involved in the second suicide. Adverse reactions of depression were reported by 7% of 781 patients treated with Xyrem, with four patients (<1%) discontinuing because of depression. In most cases, no change in Xyrem treatment was required. In a clinical trial with Xyrem in pediatric patients with narcolepsy (n=104), one patient experienced suicidal ideation and two patients reported depression while taking Xyrem

The emergence of depression in patients treated with XYWAV requires careful and immediate evaluation. Patients with a previous history of a depressive illness and/ or suicide attempt should be monitored carefully for the emergence of depressive symptoms while taking XYWAV.

5.6 Other Behavioral or Psychiatric Adverse Reactions

Other behavioral and psychiatric adverse reactions can occur in patients taking XYWAV. In Study 1, confusion occurred in 1% of patients treated with XYWAV and anxiety occurred in 5% of patients treated with XYWAV. One patient experienced visual hallucinations and confusion after ingesting approximately 9 grams of XYWAV. Other neuropsychiatric reactions reported in clinical trials of Xyrem (same active moiety as XYWAV) in adult patients with narcolepsy and in the postmarketing setting included hallucinations, paranoia, psychosis, aggression, and agitation.

In a pediatric clinical trial with Xyrem in patients with narcolepsy, neuropsychiatric reactions, including acute psychosis, confusion, and anxiety, were reported while taking Xyrem.

The emergence or increase in the occurrence of behavioral or psychiatric events in patients taking XYWAV should be carefully monitored.

5.7 Parasomnias

Parasomnias can occur in patients taking XYWAV.

In Study 1, parasomnias, including sleepwalking, were reported in 6% of patients treated with XYWAV. In a clinical trial of Xyrem (same active moiety as XYWAV) in adult patients with narcolepsy, five instances of sleepwalking with potential injury or significant injury were reported. Parasomnias, including sleepwalking, also have been reported in a pediatric clinical trial with sodium oxybate and in postmarketing experience with sodium oxvbate.

Episodes of sleepwalking should be fully evaluated and appropriate interventions considered

ADVERSE REACTIONS 6

The following clinically significant adverse reactions appear in other sections of the labeling:

- CNS depression [see Warnings and Precautions (5.1)]
- Abuse and Misuse [see Warnings and Precautions (5.2)]
 Respiratory Depression and Sleep-Disordered Breathing [see Warnings and Precautions (5.4)]
- Depression and Suicidality [see Warnings and Precautions (5.5)]
- Other Behavioral or Psychiatric Adverse Reactions [see Warnings and Precautions (5.6)] • Parasomnias [see Warnings and Precautions (5.7)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. Adult Patients

The safety of XYWAV was evaluated in a 16-week double-blind placebo-controlled randomized-withdrawal study in patients with narcolepsy with cataplexy (Study 1), which was followed by an open-label extension phase lasting 24 weeks [see Clinical Studies (14.1)]. Study 1 included an open-label titration period (OL OTTP), a stable-dose period (SDP), and a double-blind, placebo-controlled, randomized-withdrawal period (DB RWP). A total of 201 patients, ages 18 to 70 years, received XYWAV at individually titrated doses for 14 weeks, followed by randomization to XYWAV or matching placebo for 2 weeks of treatment. The mean exposure to XYWAV during this study, including titration, the randomized withdrawal period, and the open-label extension, was 151 days. In patients who remained on treatment, adverse reactions tended to occur early and diminish over time. Adverse Reactions Leading to Treatment Discontinuation

In Study 1, 9 of 201 patients (4%) reported adverse reactions that led to withdrawal from the study (anxiety, decreased appetite, depressed mood, depression, fatigue, headache, irritability, nausea, pain in extremity, parasomnia, somnolence, and vomiting). The most common adverse reaction leading to discontinuation was nausea (1.5%). The majority of adverse reactions leading to discontinuation began during the first few weeks of treatment.

Commonly Observed Adverse Reactions

The most common adverse reactions in Study 1 (incidence ≥ 5% of XYWAV-treated patients) were headache, nausea, dizziness, decreased appetite, parasomnia, diarrhea, hyperhidrosis, anxiety, and vomiting.

Adverse Reactions Occurring at an Incidence of 2% or Greater:

Table 1 lists adverse reactions observed in the open-label titration and stable dose periods of Study 1 that occurred at a frequency of 2% or greater in adult patients treated with XYWAV.

Table 1: Adverse Reactions Occurring in ≥2% of Adult Patients Treated with XYWAV in the Open-Label Titration and Stable Dose Periods in Study 1*

Adverse Reaction	Open-Label Titration Period + Stable Dose Period (14 weeks) (N=201) %
Headache	20
Nausea	13
Dizziness	10
Decreased appetite	8
Parasomnia ⁺	6
Diarrhea	6
Hyperhidrosis [‡]	6
Anxiety ^s	5
Vomiting	5
Fatigue [•]	4
Dry mouth	4
Depressed mood	4
Enuresis	4
Irritability	3
Paresthesia	3
Depression	3
Tremor	3
Somnolence	2
Muscle spasms	2

*Adverse reactions related to XYWAV were reported less frequently, as an overall incidence, in patients on Xyrem at study entry than in Xyrem-naïve patients.

[†]Includes abnormal dreams, abnormal sleep-related event, rapid eye movements sleep abnormal, sleep paralysis, sleep talking, sleep terror, sleep-related eating disorder, somnambulism

¹Includes hyperhidrosis and night sweats

^sIncludes anxiety, agitation, panic attack, tension

Includes fatigue and asthenia

Adverse Reactions Observed in Clinical Studies with Xyrem (≥2%), but not in Study 1, and Which May Be Relevant for XYWAV

Pain, feeling drunk, pain in extremity, cataplexy, disturbance in attention, sleep paralysis, and disorientation.

Pediatric Patients (7 Years of Age and Older)

In the pediatric clinical trial with Xyrem (same active moiety as XYWAV), 104 patients aged 7 to 17 years (37 patients aged 7 to 11 years; 67 patients aged 12 to 17 years) with narcolepsy received Xyrem for up to one year [see Clinical Studies (14.2)]. This study included an open-label safety continuation period in which eligible patients received Xyrem for up to an additional 2 years. The median and maximum exposure across the entire study were 371 and 987 days, respectively.

Adverse Reactions Leading to Treatment Discontinuation

In the pediatric clinical trial with Xyrem, 7 of 104 patients reported adverse reactions that led to withdrawal from the study (hallucination, tactile; suicidal ideation; weight decreased; sleep apnea syndrome; affect lability; anger, anxiety, depression; and headache)

Adverse Reactions in the Xyrem Pediatric Clinical Trial

The most common adverse reactions (>5%) were nausea (20%), enuresis (19%), vomiting (18%), headache (17%), weight decreased (13%), decreased appetite (9%), dizziness (8%), and sleepwalking (6%)

Additional information regarding safety in pediatric patients appears in the following sections

• Respiratory Depression and Sleep-Disordered Breathing [see Warnings and Precautions (5.4)]

• Depression and Suicidality [see Warnings and Precautions (5.5)] • Other Behavioral or Psychiatric Adverse Reactions [see Warnings and Precautions (5.6)] • Parasomnias [see Warnings and Precautions (5.7)]

The overall adverse reaction profile of Xyrem in the pediatric clinical trial was similar to that seen in the adult clinical trial program. The safety profile in pediatric patients with XYWAV is expected to be similar to that of adult patients treated with XYWAV and to that of pediatric patients treated with Xyrem.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of sodium oxybate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Arthralgia, fall*, fluid retention, hangover, hypersensitivity, hypertension, memory impairment, nocturia, and vision blurred.

*The sudden onset of sleep in patients taking sodium oxybate, including in a standing position or while rising from bed, has led to falls complicated by injuries, in some cases requiring hospitalization

DRUG INTERACTIONS 7

7.1 Alcohol, Sedative Hypnotics, and CNS Depressants

XYWAV is contraindicated for use in combination with alcohol or sedative hypnotics. Use of other CNS depressants may potentiate the CNS-depressant effects of XYWAV [see Warnings and Precautions (5.1)1.

7.2 Divalproex Sodium

Concomitant use of sodium oxybate with divalproex sodium results in an increase in systemic exposure to GHB, which was shown to cause a greater impairment on some tests of attention and working memory in a clinical study [see Clinical Pharmacology (12.3)]. A similar increase in exposure is expected with concomitant use of XYWAV and divalproex sodium; therefore, an initial dose reduction of XYWAV is recommended when used concomitantly with divalproex sodium [see Dosage and Administration (2.6)] Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of XYWAV and divalproex sodium is warranted.

USE IN SPECIFIC POPULATIONS 8

8.1 Pregnancy

Risk Summary

There are no adequate data on the developmental risk associated with the use of XYWAV or sodium oxybate in pregnant women. Oral administration of sodium oxybate to pregnant rats (0, 150, 350, or 1,000 mg/kg/day) or rabbits (0, 300, 600, or 1,200 mg/kg/ day) throughout organogenesis produced no clear evidence of developmental toxicity; however, oral administration to rats throughout pregnancy and lactation resulted in increased stillbirths and decreased offspring postnatal viability and growth, at a clinically relevant dose [see Data].

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Clinical Considerations

Labor or Delivery

XYWAV has not been studied in labor or delivery. In obstetric anesthesia using an injectable formulation of sodium oxybate, newborns had stable cardiovascular and respiratory measures but were very sleepy, causing a slight decrease in Apgar scores. There was a fall in the rate of uterine contractions 20 minutes after injection. Placental transfer is rapid, and gamma-hydroxybutyrate (GHB) has been detected in newborns at delivery after intravenous administration of GHB to mothers. Subsequent effects of sodium oxybate on later growth, development, and maturation in humans are unknown. Data

Animal Data

Oral administration of sodium oxybate to pregnant rats (0, 150, 350, or 1,000 mg/kg/ day) or rabbits (0, 300, 600, or 1,200 mg/kg/day) throughout organogenesis produced no clear evidence of developmental toxicity. The highest doses of sodium oxybate tested in rats and rabbits were approximately 1 and 3 times, respectively, the maximum recommended human dose (MRHD) of 9 g per night on a body surface area (mg/m²) basis

Additionally, oral administration of sodium oxybate (0, 150, 350, or 1,000 mg/kg/day) to rats throughout pregnancy and lactation resulted in increased stillbirths and decreased offspring postnatal viability and body weight gain at the highest dose tested. The noeffect dose for pre- and post-natal developmental toxicity in rats is less than the MRHD on a mg/m² basis.

8.2 Lactation

Risk Summary

GHB is excreted in human milk after oral administration of sodium oxybate. There is insufficient information on the risk to a breastfed infant, and there is insufficient information on milk production in nursing mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XYWAV and any potential adverse effects on the breastfed infant from XYWAV or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of XYWAV for the treatment of cataplexy or excessive daytime sleepiness in pediatric patients 7 years of age and older with narcolepsy have been established. XYWAV has not been studied in a pediatric clinical trial. Use of XYWAV in pediatric patients 7 years of age and older with narcolepsy is supported by evidence from an adequate and well-controlled study of sodium oxybate in pediatric patients 7 to 17 years of age, a study in adults showing a treatment effect of XYWAV similar to that observed with sodium oxybate, pharmacokinetic data of sodium oxybate from adult and pediatric patients, and pharmacokinetic data of XYWAV from healthy adult volunteers [see Adverse Reactions (6.1) and Clinical Studies (14.1, 14.2)].

In the pediatric clinical trial with sodium oxybate administration in patients with narcolepsy, serious adverse reactions of central sleep apnea and oxygen desaturation documented by polysomnography evaluation; depression; suicidal ideation; neuropsychiatric reactions including acute psychosis, confusion, and anxiety; and parasomnias, including sleepwalking, have been reported [see Warnings and Precautions (5.4, 5.5, 5.6, 5.7) and Adverse Reactions (6.1)].

Safety and effectiveness of XYWAV in pediatric patients below the age of 7 years have not been established.

Juvenile Animal Toxicity Data

In a study in which sodium oxybate (0, 100, 300, or 900 mg/kg/day) was orally administered to rats during the juvenile period of development (postnatal days 21 through 90), mortality was observed at the two highest doses tested. Deaths occurred during the first week of dosing and were associated with clinical signs (including decreased activity and respiratory rate) consistent with the pharmacological effects of the drug. Reduced body weight gain in males and females and delayed sexual maturation in males were observed at the highest dose tested. The no-effect dose for adverse effects in juvenile rats is associated with plasma exposures (AUC) less than that at the maximum recommended human dose (9 g/night).

8.5 Geriatric Use

Clinical studies of XYWAV or Xyrem in patients with narcolepsy did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects.

In clinical studies of sodium oxybate in another population, 39 (5%) of 874 patients were 65 years or older. Discontinuations of treatment due to adverse reactions were increased in the elderly compared to younger adults (21% vs. 19%). Frequency of headaches was markedly increased in the elderly (39% vs. 19%). The most common adverse reactions were similar in both age categories. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

Because of an increase in exposure to XYWAV, the starting dose should be reduced by half in patients with hepatic impairment [see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]

DRUG ABUSE AND DEPENDENCE

9.1 **Controlled Substance**

XYWAV is a Schedule III controlled substance under the Federal Controlled Substances Act. Non-medical use of XYWAV could lead to penalties assessed under the higher Schedule I controls.

9.2 Abuse

The active mojety of XYWAV, oxybate, produces dose-dependent central nervous system effects, including hypnotic and positive subjective reinforcing effects. The onset of effect is rapid, enhancing its potential for abuse or misuse

Drug abuse is the intentional non-therapeutic use of a drug product or substance, even once, for its desirable psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes of a drug by an individual in a way other than prescribed by a health care provider or for whom it was not prescribed. Drug misuse and abuse may occur with or without progression to addiction. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

The rapid onset of sedation, coupled with the amnestic features of GHB, particularly when combined with alcohol, has proven to be dangerous for the voluntary and involuntary user (e.g., assault victim).

Illicit GHB is abused in social settings primarily by young adults. Some of the doses estimated to be abused are in a similar dosage range to that used for treatment of patients with cataplexy. GHB has some commonalities with ethanol over a limited dose range, and some cross tolerance with ethanol has been reported as well. Cases of severe dependence and craving for GHB have been reported when the drug is taken around the clock. Patterns of abuse indicative of dependence include: 1) the use of increasingly large doses, 2) increased frequency of use, and 3) continued use despite adverse consequences.

Because illicit use and abuse of GHB have been reported, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of GHB (e.g., increase in size or frequency of dosing, drug-seeking behavior, feigned cataplexy). Dispose of XYWAV according to state and federal regulations. It is safe to dispose of XYWAV down the sanitary sewer.

9.3 Dependence

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. There have been case reports of withdrawal, ranging from mild to severe, following discontinuation of illicit use of GHB at frequent repeated doses (18 g to 250 g per day) in excess of the recommended dosage range. Signs and symptoms of GHB withdrawal following abrupt discontinuation included insomnia, restlessness, anxiety, psychosis, lethargy, nausea, tremor, sweating, muscle cramps, tachycardia, headache, dizziness, rebound fatigue and sleepiness, confusion, and, particularly in the case of severe withdrawal, visual hallucinations, agitation, and delirium. These symptoms generally abated in 3 to 14 days. In cases of severe withdrawal, hospitalization may be required. The discontinuation effects of XYWAV have not been systematically evaluated in controlled clinical trials. In the clinical trial experience with Xyrem in narcolepsy/cataplexy patients at recommended doses, two patients reported anxiety and one reported insomnia following abrupt discontinuation at the termination of the clinical trial; in the two patients with anxiety, the frequency of cataplexy had increased markedly at the same time. In the XYWAV clinical trial in adult narcolepsy/cataplexy patients at recommended doses, one patient reported insomnia following abrupt discontinuation of XYWAV.

Tolerance

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose). Tolerance to XYWAV has not been systematically studied in controlled clinical trials. There have been some case reports of symptoms of tolerance developing after illicit use at dosages far in excess of the recommended XYWAV dosage regimen. Clinical studies of sodium oxybate in the treatment of alcohol withdrawal suggest a potential cross-tolerance with alcohol. The safety and effectiveness of XYWAV in the treatment of alcohol withdrawal have not been established.

OVERDOSAGE 10

10.1 Human Experience

Information regarding overdose with XYWAV is derived largely from reports in the medical literature that describe symptoms and signs in individuals who have ingested GHB illicitly. In these circumstances the co-ingestion of other drugs and alcohol was common, and may have influenced the presentation and severity of clinical manifestations of overdose.

In adult clinical trials with Xyrem (same active moiety as XYWAV), two cases of overdose were reported. In the first case, an estimated dose of 150 g, more than 15 times the maximum recommended dose, caused a patient to be unresponsive with brief periods of apnea and to be incontinent of urine and feces. This individual recovered without sequelae. In the second case, death was reported following a multiple drug overdose consisting of Xyrem and numerous other drugs. No cases of overdose (greater than 9 g) with XYWAV were reported in the XYWAV clinical trial.

10.2 Signs and Symptoms

Information about signs and symptoms associated with overdosage with XYWAV derives from reports of illicit use of GHB. Patient presentation following overdose is influenced by the dose ingested, the time since ingestion, the co-ingestion of other drugs and alcohol, and the fed or fasted state. Patients have exhibited varying degrees of depressed

consciousness that may fluctuate rapidly between a confusional, agitated combative state with ataxia and coma. Emesis (even when obtunded), diaphoresis, headache, and impaired psychomotor skills have been observed. No typical pupillary changes have been described to assist in diagnosis; pupillary reactivity to light is maintained. Blurred vision has been reported. An increasing depth of coma has been observed at higher doses. Myoclonus and tonic-clonic seizures have been reported. Respiration may be unaffected or compromised in rate and depth. Cheyne-Stokes respiration and apnea have been observed. Bradycardia and hypothermia may accompany unconsciousness, as well as muscular hypotonia, but tendon reflexes remain intact.

10.3 Recommended Treatment of Overdose

General symptomatic and supportive care should be instituted immediately, and gastric decontamination may be considered if co-ingestants are suspected. Because emesis may occur in the presence of obtundation, appropriate posture (left lateral recumbent position) and protection of the airway by intubation may be warranted. Although the gag reflex may be absent in deeply comatose patients, even unconscious patients may become combative to intubation, and rapid-sequence induction (without the use of sedative) should be considered. Vital signs and consciousness should be closely monitored. The bradycardia reported with GHB overdose has been responsive to atropine intravenous administration. No reversal of the central depressant effects of XYWAV can be expected from naloxone or flumazenil administration. The use of hemodialysis and other forms of extracorporeal drug removal have not been studied in GHB overdose. However, due to the rapid metabolism of oxybate, these measures are not warranted.

10.4 Poison Control Center

As with the management of all cases of drug overdosage, the possibility of multiple drug ingestion should be considered. The healthcare provider is encouraged to collect urine and blood samples for routine toxicologic screening, and to consult with a regional poison control center (1-800-222-1222) for current treatment recommendations.

PATIENT COUNSELING INFORMATION 17

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Central Nervous System Depression

Inform patients and/or caregivers that XYWAV can cause central nervous system depression, including respiratory depression, hypotension, profound sedation, syncope, and death. Instruct patients not to engage in activities requiring mental alertness or motor coordination, including operating hazardous machinery, for at least 6 hours after taking XYWAV. Instruct patients and/or their caregivers to inform their healthcare providers of all the medications they take [see Warnings and Precautions (5.1)]. Abuse and Misuse

Inform patients and/or caregivers that the active ingredient of XYWAV is gamma hydroxybutyrate (GHB), which is associated with serious adverse reactions with illicit use and abuse [see Warnings and Precautions (5.2)].

XYWAV and XYREM REMS

XYWAV is available only through a restricted program called the XYWAV and XYREM REMS [see Warnings and Precautions (5.3)]. Inform the patient and/or caregiver of the following notable requirements:

XYWAV is dispensed only by the central pharmacy
XYWAV will be dispensed and shipped only to patients enrolled in the XYWAV and XYREM REMS

XYWAV is available only from the central pharmacy participating in the program Therefore, provide patients and/or caregivers with the telephone number and website for information on how to obtain the product.

Alcohol or Sedative Hypnotics

Advise patients and/or caregivers that alcohol and other sedative hypnotics should not be taken with XYWAV [see Contraindications (4)].

Sedation

Inform patients and/or caregivers that the patient is likely to fall asleep quickly after taking XYWAV (often within 5 and usually within 15 minutes), but the time it takes to fall asleep can vary from night to night. The sudden onset of sleep, including in a standing position or while rising from bed, has led to falls complicated by injuries, in some cases requiring hospitalization [see Adverse Reactions (6.2)]. Instruct patients and/or caregivers that the patient should remain in bed following ingestion of each dose. Instruct patients and/or caregivers that the patient should not take a subsequent nightly dose until at least 2.5 to 4 hours after the previous dose [see Dosage and Administration (2.3)]. Administration Instructions

Inform patients and/or caregivers that the total nightly dosage of XYWAV is divided into two doses and that the first nightly dose of XYWAV should be taken at least 2 hours after eating

Respiratory Depression and Sleep-Disordered Breathing

Inform patients that XYWAV may impair respiratory drive, especially in patients with compromised respiratory function, and may cause apnea [see Warnings and Precautions (5.4)7.

Depression and Suicidality

Instruct patients and/or caregivers to contact a healthcare provider immediately if the patient develops depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or suicidal ideation [see Warnings and Precautions (5.5)]. Other Behavioral or Psychiatric Adverse Reactions

Inform patients and/or caregivers that XYWAV can cause behavioral or psychiatric adverse reactions, including confusion, anxiety, and psychosis. Instruct them to notify their healthcare provider if any of these types of symptoms occur [see Warnings and Precautions (5.6)].

Sleepwalking

Instruct patients and/or caregivers that XYWAV has been associated with sleepwalking and other behaviors during sleep, and to contact their healthcare provider if this occurs [see Warnings and Precautions (5.7)].

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