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The Safety of Sodium Oxybate in Treating Narcolepsy

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Chapter 1

Dr. Kushida:
Welcome to Chapter 1. I’m Dr. Clete Kushida, and here with me today is Dr. Sally Ibrahim. We're discussing the approximate 20 years of cardiovascular safety associated with the use of sodium oxybate in narcolepsy. We’ll examine both the immediate-release, or IR, and extended-release, or ER, formulations.

Welcome, Dr. Ibrahim.

Dr. Ibrahim:
Thank you. Glad to be here.

Dr. Kushida:
Dr. Ibrahim, could you provide our listeners with some context for our discussion today? Essentially, why are we focusing on the cardiovascular safety of sodium oxybate in narcolepsy?

Dr. Ibrahim:
Absolutely. The medication benefits of oxybates are very clear: improving sleep continuity, improving daytime alertness, and controlling cataplexy. But these medications, like any medications, are not without risk. So today we are discussing risk, particularly as it relates to cardiovascular safety.

We'll focus on cardiovascular risk and safety because there are clinical studies showing that people with narcolepsy are at risk for cardiovascular disease in general. Specifically, for example, hypertension and hyperlipidemia. Part of the considerations of why people with narcolepsy have these cardiovascular risks may relate to hypocretin deficiency and sleep disruption from the core pathophysiology of narcolepsy, but sodium intake is always a consideration in such patients, leading to the concerns for the high sodium content in sodium oxybate products. But the question really is, is there really an issue?

We can start with looking at the sodium content in general for sodium oxybate products. They range in dosage from 3 to 9 g, so you'll have anywhere from 550 mg to 1,640 mg in 2 equally divided doses, and that’s not including our lower-sodium oxybate choice, which has about 92% less sodium.

Governmental agencies suggest daily sodium in adults to be limited to less than or equal to 2,300 mg a day. However, most Americans will consume anywhere between 3,000 to 6,000 mg, on average, per day, and so clinicians often consider sodium intake in patients with narcolepsy, especially who have cardiovascular disease and comorbidities, when making a medication choice.

I, as I'm sure you do, Dr. Kushida, counsel my patients on being mindful of having a healthy diet in patients who have cardiovascular disease and who have narcolepsy, as well as those that we're going to start on sodium oxybate products, and stress the importance of overall lowering of sodium in the diet when taking these medications.

Dr. Kushida, is the sodium content of standard sodium oxybate a potential concern for patients with narcolepsy? What is the evidence for or against?

Dr. Kushida:
Thank you, Dr. Ibrahim. We published an article in 2020 in the journal *Sleep Medicine* that was entitled The Sodium in Sodium Oxybate: Is There Cause for Concern? in which we reviewed the relevant literature for evidence on the cardiovascular risk in relation to daily sodium intake and narcolepsy, as well as a cardiovascular risk in the setting of sodium oxybate treatment in patients with narcolepsy. The findings suggested that increased cardiovascular risk is associated with extremes of daily sodium intake and that narcolepsy is associated with comorbidities that may increase cardiovascular risk in some patients

However, data from studies regarding sodium oxybate use in patients with narcolepsy has shown a very low frequency of cardiovascular side effects, such as hypertension, and no overall association with cardiovascular risk. So in the absence of data that specifically addresses cardiovascular risk with sodium oxybate based on its sodium content, the clinical evidence to date suggests that sodium oxybate treatment does not confer additional cardiovascular risk in patients with narcolepsy.

Now, there have been multiple studies in which the relationship between sodium content and sodium oxybate demonstrated no, or insignificant, impact on the development or worsening of cardiovascular morbidity in patients with narcolepsy.

So in 2002, the US Xyrem Multicenter Study Group published results of a multicenter, double-blind, randomized, placebo-controlled trial that compared the effects of 3 doses of sodium oxybate with placebo in participants with narcolepsy. This study involved 136 participants. No cardiovascular events were reported.

In 2003, the same group published the results of a 12-month, multicenter, open-label extension trial of their previous 2002 randomized control trial, which evaluated long-term safety and efficacy of sodium oxybate in patients with narcolepsy. This study involved 118 narcolepsy participants previously enrolled in a 4-week double-blind sodium oxybate trial. There was one cardiovascular event reported, but it was not considered to be related to sodium oxybate therapy.

In 2004, the same study group published the results of a multicenter, randomized, treatment withdrawal trial that assessed the efficacy of sodium oxybate for the long-term treatment of cataplexy in participants with narcolepsy. It involved 55 participants with narcolepsy with cataplexy who had received sodium oxybate for 7 to 44 months and were then enrolled in a double-blind treatment withdrawal study. No cardiovascular events were reported in this study.

In 2005, the same group published the results of a multicenter, double-blind, randomized, placebo-controlled trial that further measured the effects of sodium oxybate on cataplexy in participants with narcolepsy. This study involved 220 participants, and no cardiovascular events were reported in this study.

In 2015, Mamelak and colleagues published the results of a multicenter, open-label trial that evaluated the safety and efficacy of sodium oxybate titrated to effect. This 12-week trial enrolled 202 participants with a history of narcolepsy with cataplexy who were sodium oxybate naïve or had participated in 1 of 3 randomized clinical trials of sodium oxybate and had not been titrated to adequate clinical effect. No cardiovascular events were reported.

In 2018, Plazzi and colleagues published the results of a multicenter, double-blind, placebo-controlled, randomized withdrawal trial with an open-label extension. This study evaluated safety and efficacy of sodium oxide in children and adolescents with narcolepsy type 1, or NT1. It enrolled 106 participants who were either sodium oxybate naïve or treated with sodium oxybate at entry. No cardiovascular events were reported.

Now, switching to different types of studies. An international post-marketing surveillance study covering the years 2002 to 2008 that was published by Wang and colleagues in 2009 reviewed the cumulative post-marketing and clinical safety experience with sodium oxybate. For product introduction in the US, the EU, European Union, and Canada through March 2008, increased blood pressure was reported in 0.4% out of 26,000.

Now, second international post-marketing surveillance study covering the years 2002 to 2011 was published by the same authors in 2011, and this study presented additional safety data to correct the previously reported number that was published in the prior international post-marketing surveillance study and to provide updated information and analysis of these cases through May 31st of 2011. There were 17 cardiac events and 6 cerebrovascular accidents.

In 2018, Mayer and colleagues published the results of a post-authorization noninterventional surveillance study that was conducted at the request of the European Medicines Agency, or EMA, to inform the risk management plan for sodium oxybate. A total of 749 patients were enrolled, with 730 included in the intent-to-treat population. Regarding treatment-emergent AEs for those with NT1, hypertension was observed in 0.4% or 3 out of 670 participants; angina pectoris in 0.3%, that's 2 out of 670; cerebrovascular disorder in 0.1%, 1 out of the 670; and circulatory collapse in 0.1, same thing, 1 out of 670.

So in summary, the collective cardiovascular findings of sodium oxybate use in patients with narcolepsy demonstrate, one, a very low frequency of cardiovascular side effects such as hypertension, and two, no overall association with cardiovascular risk.

Dr. Ibrahim, any final comments?

Dr. Ibrahim:
Thank you, Dr. Kushida. That was a wonderful overview of the current body of evidence, and it certainly doesn't show that there's any direct cardiovascular risk, so clinicians can safely continue to prescribe sodium oxybate for narcolepsy.

Dr. Kushida:
Thank you, Dr. Ibrahim, for joining in this discussion. In Chapter 2, we'll be discussing the cardiovascular safety data for once-nightly sodium oxybate in narcolepsy, so stay tuned.

Chapter 2
Dr. Ibrahim:
Welcome back. In Chapter 2, we're now focused on the safety of a once-nightly formulation of sodium oxybate in the management of narcolepsy.

Dr. Kushida, can you describe the unique features associated with the extended-release once-nightly formulation of sodium oxybate, and what are the presumptive benefits of this formulation as opposed to standard twice-nightly dosing?

Dr. Kushida:
Thank you, Dr. Ibrahim, for this interesting question. So there is some drug delivery technology that's associated with the once-nightly formulation, and it basically employs the proprietary drug technology and contains a mixture of immediate-release, or IR, sodium oxybate and controlled-release, or CR, sodium oxybate microparticles. Now, the total sodium oxybate dose equivalent of once-nightly formulation is equivalent to two 3-g doses of sodium oxybate in twice-nightly formulation. Now, what this formulation does is it provides a single early peak of standard sodium oxybate, followed by a gradual decline with negligible levels at about 8 hours post dose.

Now, the pharmacokinetic profile of this formulation allows more normal sleep pattern in the first half of the night compared with twice-nightly dosing formulations.

So the once-nightly sodium oxybate demonstrated improvement of symptoms in a phase 3 randomized clinical trial in patients with narcolepsy. This trial was called REST-ON, and the goal of this REST-ON trial was to assess the efficacy and safety of a once-nightly formulation of sodium oxybate in patients with narcolepsy. In this study, narcolepsy patients aged 16 years or older were randomized 1:1 to up-titration of once-nightly sodium oxybate in 4.5-, 6-, 7.5-, and 9-g doses or placebo. Three coprimary endpoints were changed from baseline in mean sleep latency on the maintenance of wakefulness test, clinical global impression improvement rating, and weekly

cataplexy attacks at 9, 7.5, and 6 g. Secondary endpoints included change from baseline on the Epworth Sleepiness Scale. Safety included adverse drug reactions and clinical laboratory assessments.

There was a total of 222 patients who were randomized. Now, for the 3 coprimary endpoints on Epworth Sleepiness Scale, all 3 doses of once-nightly sodium oxybate demonstrated clinically meaningful, statistically significant improvement versus placebo, all at the *P* level of 0.001. For once-nightly sodium oxybate, 9 g versus placebo, increase in mean sleep latency was 10.8 versus 4.7 minutes. 72% versus 31.6% were rated much or very much improved on the clinical global impression improvement scale. And change in mean weekly number of cataplexy attacks was -11.5 versus -4.9. And finally, change in Epworth Sleepiness Scale was -6.5 and 2.7.

Now, in terms of safety, there were no clinically meaningful changes from baseline in clinical laboratory values, blood pressure, or heart rate for once-nightly sodium oxybate or clinically meaningful differences compared to placebo.

So in summary, once-nightly sodium oxybate achieved efficacy and safety compared to placebo at all doses that were evaluated, thus obviating the need for patients to disrupt their sleep by awakening in the middle of the night for a second dose that is required with conventional immediate release formulations of sodium oxybate.

Adverse reactions were consistent with the known side effect profile of sodium oxybate and were generally mild or moderate. And importantly, there were no cardiovascular events reported with no clinically significant changes in blood pressure nor heart rate from baseline.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Clete Kushida, and here with me today is Dr. Sally Ibrahim. Our focus is on assessing the cardiovascular safety of sodium oxybate formulations, as well as identifying strategies for reducing sodium oxybate dosing errors for our patients with narcolepsy.

Now, Dr. Ibrahim, can you introduce us to the phase 3 RESTORE study for the once-nightly sodium oxybate formulation? Also, how does the once-nightly sodium oxybate formulation, described in the Orange Book as its formulation, differ from the twice-nightly formulations?

Dr. Ibrahim:
In the phase 3 RESTORE extension switch study, which was a multicenter open-label study in which participants with narcolepsy type 1 or 2 who switched from twice-nightly to once-nightly oxybate took a nocturnal adverse events questionnaire at baseline, a patient preference questionnaire after 3 months on drug, and an end-of-study questionnaire. We'll discuss the RESTORE study in greater detail in Chapter 3, but aspects are also relevant in our current discussion in that they reflect on adherence and caregiver issues with twice-nightly sodium oxybate formulation.

In brief, they are as follows. With the switch from twice-nightly to single-night dosing of sodium oxybate, we found in the questionnaire data that those who are on twice-nightly had difficulty or inconvenience associated with chronically waking in the middle of the night to re-dose their second dose, or they had an increased burden on parents or caregivers or even bed partners to help wake them up for the second dose. I know in my own pediatric practice some parents are unable to administer a second dose. Some people miss the second dose entirely, and then lastly, some have grogginess in the morning after taking the second dose, particularly if they take it at the wrong time. So these are some highlights from the data in the RESTORE trial.

Now, the efficacy and safety data associated with the once-nightly sodium oxybate formula will be discussed in Chapter 3, but you asked the question about maybe the Orange Book discussion. So the 3 standard formulations of sodium oxybate are listed as approved drug products with therapeutic equivalent evaluations. In theory, this means they all work in an equivalent way. And the 3 current formulations on the market are Xyrem, which came out first, then Xywav, and now Lumryz.

For reference, a class of medications, such as GLP-1 receptor agonists, are listed as pharmaceutical equivalent medications to treat diabetes and help with weight loss. These are all equivalent, and they may have different side effect profiles, but their efficacy equivalency is stated in the Orange Book, much like the efficacy of the 3 oxybates on the market. So clinicians should have appropriate equipoise and comfort when considering the use of any of these oxybate drug agents, including the once-nightly formulation of sodium oxybate.

Dr. Kushida, do you have any final comments?

Dr. Kushida:
Perfect. And thank you, Dr. Ibrahim, especially for highlighting that clinicians should have appropriate equipoise and comfort when considering use of any of these oxybate preparations.

Dr. Ibrahim:
Thank you, Dr. Kushida, for joining.

Remember to stay tuned for Chapter 3, where we'll be discussing accidental dosing errors with immediate-release sodium oxybate in narcolepsy.

Chapter 3
Dr. Kushida:
Welcome back. In this chapter, we're addressing accidental dosing errors associated with immediate-release formulations of sodium oxybate in the treatment of narcolepsy.

Dr. Ibrahim, what are the patient-related dosing errors and adverse events that are commonly associated with this formulation?

Dr. Ibrahim:
Thank you for your question, Dr. Kushida. Middle-of-the-night dosing errors associated with twice-nightly dosing of sodium oxybate are a real concern. We can first review the process of taking these medications that you and I both know we counsel on during patient care experiences.

For twice-nightly oxybates, both Xyrem and Xywav, patients are instructed to prepare 2 doses before bedtime. They use a syringe to dose and extract the prescribed dose from 180-mL bottle, which contains 500 mg/mL, and it requires a dilution into water. So they prepare these 2 separate containers; they're made, and they're left at the bedside. Once the patient is in the bed, they're instructed to take their first dose at bedtime, after getting into bed, most falling asleep within 5 to 10 minutes. Then they wake up and take the second dose at least 2.5 hours but no more than 4 hours after the first bedtime dose.

So now that we've reviewed how to take these medications, we can take a look at how patients are generally doing with this regimen by looking at some of the data.

We'll look first at the FDA adverse event reporting system data. This data was used to assess dosing errors related to twice-nightly dosing of sodium formulations, Xyrem and Xywav.

For data available through the end of March 2022, there were a total of 541 reports that included the preferred term of inappropriate schedule of product administration as a reaction with the twice-nightly oxybates.

Of this, there were nearly a third, 178 in total, in which immediate-release twice-nightly oxybate was the suspect product and the patient had a serious outcome. Forty-one reports classified as serious described patients accidentally taking their second dose of Xyrem less than 2.5 hours after the first dose and experiencing an adverse event as a result. All these 41 reports of interest were submitted to the FDA by the manufacturer, Jazz Pharmaceuticals, between August 2011 and November of 2020. This was published by Gudeman et al. in 2023.

Furthermore, the authors examined timing of dosing errors, which varied as follows: 20% took their 2 doses at the same time or almost the exact same time, 39% consumed their second Xyrem dose less than 1 hour after the first dose, and 61% took the second dose between 1 and 2.5 hours after the first dose.

So this doesn't match how they should be taking the medication.

So then the authors looked at contributing factors to why the patients consumed the second dose less than 2.5 hours after the first. Those included being distracted, forgetting or restarting routines, sleepwalking, which we know is a side effect, or a potential side effect,

of oxybates in general. Some did not check or readjust their alarm clock to make sure enough time has passed before the first and second dose.

Some just misunderstood the frequency prescribed or misread the directions. And lastly, some did not recognize that 2 doses were added to the same container.

Furthermore, a subsequent study using RESTORE trial data, in which we had twice-nightly participants switch to once-nightly dosing of sodium oxybate and published in 2024, showing some data and errors in timing associated with adverse events in those taking twice-nightly dosing.

So with this background, Dr. Kushida, what are some results of that study that you want to highlight and you think are important? And then, secondly, what are some strategies to reduce the frequency of adverse events related to twice-nightly dosing errors?

Dr. Kushida:
Thank you for your question, Dr. Ibrahim. Now, you mentioned that the RESTORE study was a multicenter, open-label, phase 3 extension/switch study in which preference for extended-release once-nightly sodium oxybate versus twice-nightly immediate-release oxybate was assessed in participants switching from immediate-release oxybate to once-nightly sodium oxybate.

So the RESTORE study design consisted of 3 periods: a titration period of 1 to 2 months, a stable dosing period up to 2 years, and a follow-up period of 1 week. As you had mentioned, the assessments included a nocturnal adverse events questionnaire at baseline to assess participant experiences with a second immediate-release oxybate dose in the 3 months before entering the study, a patient preference questionnaire after 3 months on stable drug, and lastly, an end-of-study questionnaire to capture their experiences on once-nightly sodium oxybate.

Now, regarding the RESTORE findings, of the 129 switch participants who completed the nocturnal adverse events questionnaire at baseline, 69% reported missing their second oxybate dose, and of those participants, 80% thought that control of their symptoms was worse the next day compared to days after which they had taken both doses as prescribed. More than half, or 51% of the 51 participants who took a second nightly oxybate dose more than 4 hours after the first dose reported feeling somewhat to extremely groggy or unsteady the next morning. 92% reported getting out of bed after taking their second dose of oxybate, with 7.5% of those reporting falling after waking up for the second dose and 4.2% reporting injuries. 23% of participants stated that they required another person to wake them up in the middle of the night to ensure that they took the second dose of their twice-nightly oxybate.

Now, of the 98 switch participants who completed the patient preference questionnaire, 94% preferred once-nightly oxybate to twice-nightly oxybate dosing. Of the 68 switch participants who completed the end-of-study questionnaire, 79% were very satisfied with once-at-bedtime oxybate compared to other narcolepsy treatments they had previously taken. 91% said they were better able to sleep through the night since starting treatment with once-nightly sodium oxybate. 91% said they were better able to follow the recommended medication schedule of once-nightly sodium oxybate than their previous oxybate.

So, secondly, strategies that can help reduce the frequency of adverse events related to twice-nightly dosing errors include a risk evaluation and mitigation strategies, or REMS, program. And this program typically entails information and/or training certification provided to healthcare providers. For patients, patient education materials is important so that they are aware of the medication dosing risks.

Now, to conclude, in my own practice, patients prefer the once-nightly sodium oxybate to avoid having to set their alarms to waken for second dosing. This is especially true for my younger patients who are often sleep-deprived due to school or work commitments and have preexisting sleep debt.

Dr. Ibrahim, do you have any final comments, including your own clinical experiences with once-nightly sodium oxidate?

Dr. Ibrahim:
I share in similar experiences with you, Dr. Kushida, in that my parents, in particular, who have to dose sodium oxybate, also prefer the once-nightly dosing.

Dr. Kushida:

Thank you, Dr. Ibrahim.

This concludes the final chapter, and please don't hesitate to check out Chapters 1 and 2, if you haven't already, for other information on additional aspects of sodium oxybates.

Thank you, Dr. Ibrahim, for participating, and thank you, audience, for listening.

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