

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

JAZZ PHARMACEUTICALS, INC.,

Plaintiff,

v.

AVADEL CNS
PHARMACEUTICALS LLC,

Defendant.

Case No. 1:21-cv-00691-GBW

DECLARATION OF JENNIFER GUDEMAN

I, Jennifer Gudeman, declare:

1. I submit this Declaration in support of Avadel's Opposition to Jazz's Motion for a Stay Pending Appeal. I have personal knowledge of the facts stated herein. If called as a witness in this matter, I could and would competently testify to each of the facts set forth below.

2. I am the Vice President, Medical and Clinical Affairs at Avadel Pharmaceuticals. I joined Avadel in December 2020 in that position.

3. I have over twenty years of experience in the pharmaceutical industry. I am a pharmacist by training and received a bachelor's degree in pharmacy and a doctorate in pharmacy from St. Louis College of Pharmacy in 1999 and 2000, respectively.

NARCOLEPSY, LUMRYZ, AND THE NEED FOR A ONCE-NIGHTLY OXYBATE

4. Narcolepsy is a chronic sleep disorder. Patients with narcolepsy suffer from a number of serious symptoms, including excessive daytime sleepiness. Some narcolepsy patients also suffer from "cataplexy," which is a sudden muscle weakness, typically occurring in response to an emotion, such as laughter, surprise, or anger. Cataplexy can present as a full-body collapse, where a patient is conscious the entire time, but cannot move, or it may present with milder

features, such as drooping face, dropping items, or knee buckling. Cataplexy can be an incredibly isolating symptom of narcolepsy, as patients will remove themselves from social situations where they may experience an emotion that can cause an attack. As one profound example, a patient with narcolepsy chose not to attend his daughter's wedding, as he knew the emotions of the day could cause him to have an episode. Cataplexy can occur in situations that pose danger, such as while the patient is driving, in a swimming pool, or holding a baby. We have also heard an anecdote of a college student who experienced full-body collapse on campus, and did not return to school, because of embarrassment.

5. Despite these patients' need for sleep, narcolepsy patients taking one of Jazz's twice-nightly oxybate products never get a night of sleep without interruption, because Jazz's products require that the patient take two doses overnight: one at bedtime, and another 2.5 to 4 hours later. Patients must be forced awake in the middle of the night every night to take their second dose of oxybate. Avadel is seeking approval to treat narcolepsy patients with a product—LUMRYZ™, also known as FT218—that is taken only once nightly, at bedtime.

6. LUMRYZ is tentatively approved by FDA. FDA's tentative approval included tentative approval of a proposed package insert for LUMRYZ (that is, the Prescribing Information for LUMRYZ, often referred to as the "label"). Once approved, LUMRYZ will be "indicated for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy," which is the same as the indication that Jazz has for narcolepsy in the adult patient population. Unlike patients taking Jazz's oxybate products, patients taking LUMRYZ will not need to be forced awake in the middle of the night to take their second dose.

7. For many patients with narcolepsy, being forced awake every night (typically by an alarm clock or a loved one) night after night to take a second dose of oxybate poses a significant

challenge. As a part of my job at Avadel, I interact with physicians and other clinicians who treat patients with narcolepsy, with patients themselves, with the families of narcolepsy patients, and with patient advocacy groups. From those sources, I have come to understand that there are many narcolepsy patients who are currently taking a twice-nightly oxybate product who have challenges waking up in the middle of the night to take the second dose, and that there are also narcolepsy patients who have discontinued a twice-night oxybate product or have never started in the first place over concerns about the middle of the night second dose. A once-nightly option for patients in these categories will be transformational.

8. Avadel has commissioned research to ensure that Avadel understands patient needs. Last Monday, November 21, 2022, I received the results from one such research project in the form of a letter with attached reports from a company called TREND Community providing additional information regarding the tangible benefits associated with LUMRYZ's proposed once-nightly dosing. The letter is intended to be submitted to FDA. It and its accompanying reports are attached here as **Exhibit A**. TREND is not affiliated with Avadel and although Avadel commissioned this research, it was TREND who performed it.

9. TREND is a digital health analytics company that works to give a voice to underserved rare and chronic disease communities. TREND examined unprompted social media posts and comments in addition to conducting a survey and interviews of narcolepsy patients. The bottom line, as relayed by TREND, is that there is an "urgent need for a once-at-bedtime sodium oxybate therapy." TREND Letter, at 1. The information gathered in that letter and reports is a powerful endorsement of the need for once-nightly oxybate.

10. I agree with the ultimate conclusions that TREND drew from the evidence, which parallels my own experience. I too have been repeatedly approached by patients and patient

caregivers who have the same concerns that were reported to TREND. The burden on both patients and caregivers alike to be forced awake every night in the middle of the night in order to take a twice-nightly oxybate product cannot be understated.

11. As but one example, I have recently been in touch with the mother of a narcolepsy patient whose adult son currently takes a twice-nightly oxybate but struggles with the second dose. The son, who is an engineer, frequently misses his second dose and as a result, his job performance is suffering and he is in danger of losing his job. During college, his mother woke him up for his second dose, which was a hardship on her. Without the assistance of another person to force him awake in the middle of the night each and every night, he wakes up late, leaving him the choice of skipping the second dose and being compromised the next day from his narcolepsy or taking the second dose late and being late to work. Both mother and son are desperately anxious for the son to be able to try a once-nightly option. These individuals are not alone, and we have heard from many other patients and caregivers about similar concerns.

I declare under penalty of perjury under the laws of the United States of America that the foregoing declaration is true and correct.

Executed on November 29, 2022

Chesterfield, Missouri

A handwritten signature in black ink, appearing to read "Jennifer Gudeman", is written over a solid horizontal line.

Jennifer Gudeman

EXHIBIT A



Food and Drug Administration
10903 New Hampshire Avenue
Building 32, Room 2346
Silver Spring, MD 20993

Dear FDA,

My name is Maria Picone, and I am the Chief Executive Officer of TREND Community, a digital health analytics company that works to give a voice to underserved rare and chronic disease communities. We have been engaging with the narcolepsy community in this capacity since 2017.

TREND Community learns through listening, and we spark progress through insight. This community-centric approach fills an important gap between patient-reported outcomes in a clinical setting and the real-world experiences that are often underreported because of stigma, fear of losing access to treatments, and other communication barriers.

Following the FDA's decision to grant tentative approval to LUMRYZ, also known as FT218, earlier this year, we began documenting patient experiences with sodium oxybate by surveying and interviewing community members and analyzing their shared stories and experiences on social media. Through this work, ***we have realized the urgent need for a once-at-bedtime sodium oxybate therapy***. This work was funded by Avadel Pharmaceuticals as part of their ongoing effort to quantify the need for a once-nightly sodium oxybate therapy; however, Avadel Pharmaceuticals did not influence the analysis or output in any way. We thank PWN4PWN, a patient-led narcolepsy advocacy organization, for supporting this initiative. The perspectives shared within this letter are those of TREND Community and the narcolepsy community members who participated.

Our first step was to listen to the community. What were people saying—unprompted—on social media on the topic of sodium oxybate? We analyzed more than 25,000 posts and comments contributed by more than 15,000 participants over a span of approximately 11 years. The results show that the need to take a second dose of sodium oxybate creates disruptions and various other issues for the patients and their caregivers. These issues range from challenges with waking up to take the second dose to struggling with getting back to sleep in some cases or dealing with daytime sleepiness in other instances. The community also spoke of the physical side effects and their impact on their mental health. The full report, [*Data Exploration: Social Listening and Sodium Oxybate*](#), is provided as an appendix.

Next, we fielded a survey prompting the community for input, and 87 qualified patients and caregivers responded. Fifty of 85 survey respondents (59%) reported taking the second dose of oxybate therapy more than 4 hours after the first dose, with 74% reporting that this occurs once per month or more often. Eighteen respondents reported taking the second dose less than 2.5 hours after the first dose once a month or more often. When asked about accidentally missing a second dose of oxybate therapy, three-quarters (75%) reported this type of experience. The full report, [*Understanding Patient Experience With Oxybate Therapy*](#), is provided as an appendix. Notable impacts reported include the following:



- 32% have experienced injuries after waking to take the second dose
- Other impacts and issues reported with missing the second dose include poor sleep quality, brain fog, increased daytime sleepiness, decreased awareness, migraines, and worsening symptoms
- For some, taking the second dose more than 4 hours after the first dose has resulted in missing/being late to school or work, including disciplinary action or termination

Finally, keeping in mind that these data represent real people navigating life with a narcolepsy diagnosis, we interviewed 4 community members and asked them to share their experiences (in their own words) with sodium oxybate therapy and the challenges they face while taking the medication. I close this letter with their messages to the FDA. You can read more about [Brian](#), [Brittany](#), [Leo](#), and [Kristen](#) at the end of this report.

Brian is a 53-year-old husband and father who was diagnosed with narcolepsy at age 22, following a 12-year journey to diagnosis:

“I passionately urge the FDA to consider an immediate approval of Avadel Pharmaceuticals’ investigational formulation of sodium oxybate, LUMRYZ™. Greater predictability and consistency in [a] medication regimen is vital to the successful management of this lifelong chronic condition, especially during the night when people with narcolepsy need restful sleep the most.”

Brittany is a 36-year-old woman who was diagnosed with narcolepsy at age 33, following a 7-year journey to diagnosis:

“Sodium oxybate is invaluable to the quality of lives of people with narcolepsy. Providing more options can help with compliance and help people have a better structured nighttime sleep. The decision to delay treatment is unfair to the patient community.”

Leo is a 24-year-old man who was diagnosed with narcolepsy at age 15, following a 2-year journey to diagnosis:

“The benefits of sodium oxybate are so profound and have made my life possible. While I’m incredibly grateful to have this support and access to the medication, I think more formulations and options are needed.”

Kristen is a 33-year-old woman who was diagnosed with narcolepsy at age 23, following a 10-year journey to diagnosis:

“Inaction is not harmless! Why is it taking so long to bring this medication to market? Not approving this medication is causing real-world consequences. The safety and effectiveness of the medication are established. With the current twice-nightly option, many people can’t maximize the benefits of oxybate therapy. These delays are resulting in familial and employment consequences. We deserve to have options.”

The narcolepsy community is asking for your leadership in addressing their unmet medical needs and approving LUMRYZ™ without further delay. With the promise of a once-nightly sodium oxybate therapy



on the horizon, we expect a reduction in the number of injuries that result from missing the second dose and improved quality of life for many living with narcolepsy. I appreciate you taking the time to read the letter.

Best,

Maria Picone, CEO
TREND Community



Community Letters to the FDA

Brian is a 53-year-old husband and father who was diagnosed with narcolepsy at age 22, following a 12-year journey to diagnosis:

"I don't remember much beforehand, but excessive daytime sleepiness was a 'normal' part of my life in middle school. It was a daily struggle for me to stay awake on the school bus and in my classes. Even though I wasn't very good in athletics, I looked forward to Phys Ed because it was the one class I was not sitting and falling asleep."

Sodium oxybate has been a part of Brian's treatment protocol for narcolepsy; however, it is not easy to manage taking it:

"It's been difficult for me to maintain routine usage with Xyrem. It is not uncommon for me to believe I woke to take my second dosage only to realize in the morning that this, too, was just part of my dream and it's still sitting on the nightstand."

For Brian, the challenge of taking Xyrem goes beyond missed second doses; he also battles increased sleep inertia and brain fog from doses after 4 hours:

"I was unable to take the second dose of Xyrem the same time every night, and sometimes not at all. While staying awake during the day is difficult, waking up is the hardest thing I do all day. Sometimes, the brain fog during oxybate therapy lasted longer than anticipated, and a few times, this resulted in my driving impaired and damaging my vehicle."

Brian has experienced more losses than just an automobile accident. His inability to work through the grogginess from late doses impacted his employment and family relationships:

"After initially being understanding, my employer withdrew my accommodation and ultimately terminated me because I could not consistently arrive on time for early morning meetings. As if being 'fired' wasn't enough to turn away prospective employers, the stigmas associated with a person with narcolepsy (lazy, rude, etc.) makes it even harder. This left me unemployed for just over a year."

Narcolepsy has had a profound effect on Brian's daily life. The related impact on his family weighs heavy on him as a husband and father:

"After more than 25 years of living with narcolepsy, it has broken and continues to ravage what remains of my marriage, my family, my jobs, my body, my mind, and my life."

Brian's message to the FDA:

"I passionately urge the FDA to consider an immediate approval of Avadel Pharmaceuticals' investigational formulation of sodium oxybate, LUMRYZ™. Greater predictability and consistency in [a] medication regimen is vital to the successful management of this lifelong chronic condition, especially during the night when people with narcolepsy need restful sleep the most."



Brittany is a 36-year-old woman who was diagnosed with narcolepsy at age 33, following a 7-year journey to diagnosis:

“I believe that my narcolepsy gene was triggered in 2003 when I had a long hospital stay with meningitis that turned into encephalitis.”

Narcolepsy has had a profound impact on Brittany and her family’s life:

“Narcolepsy affects my life daily and is always on my mind. I need to remember my daytime meds, monitor my water intake, [and] watch for mood shifts, which are often the first indicator that I need a nap or an afternoon medication to get through the day. I rely heavily on my mom/family to help me remember appointments and get there, as many are too far for me to safely drive.”

Confusion and even injuries have occurred as a result of Brittany awakening for the second dose of Xyrem:

“I have gotten confused while preparing my nighttime meds because I am tired, and that automatic behavior kicks in for all of us when we are doing our routine, but especially for a person with narcolepsy, as we might actually be microsleeping.”

“On multiple occasions, I have fallen asleep while on the toilet in between doses. I already touched on how brain fog can hinder and be dangerous when mixing and preparing nighttime doses of medication, but I have also experienced injuries and extreme confusion. A few examples are stumbling through doorways and hallways while trying to get up to take my second dose. I have also been so completely sure that I heard my alarm (an auditory hallucination) and gotten up to take my second dose when I already had. On a few occasions, I awoke the next day to see the full bottle was on the floor—realizing I had missed my dose.”

Brittany also shared the impact of missing or mis-timing doses:

“Missing doses makes people feel sick. Mis-timing doses leaves you ‘seasick’... My world seems wobbly, and my head is cloudy afterwards.”

For Brittany, the benefit of a once-nightly formulation is apparent:

“Avoiding a midnight alarm clock will allow my sleep cycle to be less disruptive. People with narcolepsy experience disrupted sleep already, and adding another nighttime awakening is unnecessary and more disruptive.”

Brittany’s message to the FDA:

“Sodium oxybate is invaluable to the quality of lives of people with narcolepsy. Providing more options can help with compliance and help people have a better structured nighttime sleep. The decision to delay treatment is unfair to the patient community.”



Leo is a 24-year-old man who was diagnosed with narcolepsy at age 15, following a 2-year journey to diagnosis:

"I consider myself fortunate to have been diagnosed after only 2 years. Most of my friends living with narcolepsy had to look for answers for 5 to 10 years before getting a diagnosis."

Narcolepsy has had a profound impact on Leo's daily life:

"One of my greatest passions is the overseas mission work I did in Vietnam (my family's home country) between graduating high school and returning to college. While it was a joy and an honor to help others as an English tutor, I couldn't fully engage because of being undermedicated. I'm currently pursuing a nursing degree to help others find answers."

Leo has struggled with awakening for the second dose and spilling doses in the process:

"There are times when I don't wake up to take the second [dose], and there are other times when I spill the vial or only take part of a dose."

Leo also shared the impact of missing or mis-timing doses:

"When I miss doses or miss the timing, I must weigh the benefit of taking the full amount or only part of it. If I don't take the second, then I might not be able to make it to school or work. If I do take the second dose later than 4 hours, then I might be late or have really bad brain fog."

The impact of brain fog resulting from missed or mis-timed doses is overwhelming for Leo:

"I don't drink anymore, but from what I remember, the impact of late doses is worse than a hangover. A cloud of confusion sets in, and I feel disoriented, dehydrated, and nauseous. Normally my sleep schedule is fairly consistent; however, when sleep time is variable, the missed doses are increased. This makes enjoying time off even more of a challenge."

For Leo, the benefit of a once-nightly formulation is about compliance and convenience:

"The convenience of taking a once-nightly sodium oxybate formulation means it will be easier to stay compliant on my doses. Measuring out 1 prepackaged dose takes the guesswork out of dosing and possibly missing a dose. Another advantage of prepackaged packets is not having to carry liquids around during travel. During a trip to Vietnam, I had the bottle top become slightly loose and ended up having some of the liquid medication leak out into my luggage."

Leo's message to the FDA:

"The benefits of sodium oxybate are so profound and have made my life possible. While I'm incredibly grateful to have this support and access to the medication, I think more formulations and options are needed."



Kristen is a 33-year-old woman, who was diagnosed with narcolepsy at age 23, following a 10-year journey to diagnosis:

“I’ve been labeled ‘sleepy’ for as long as I can remember. My symptoms began to become overwhelming during my teen years and into early college. In addition to being diagnosed with narcolepsy, I have also been diagnosed with depression, ADHD, and learning disabilities. It’s hard to separate the impacts of the conditions, but at the foundation is sleepiness and narcolepsy.”

Narcolepsy has had a profound impact on Kristen’s daily life:

“Prior to getting the diagnosis, I was sleeping through exams, and keeping up seemed nearly impossible.”

Medication provided Kristen with a new look on life:

“I often compare receiving my diagnosis and being medicated to putting on glasses for the first time. Medication opened my eyes to a world I didn’t realize was possible; however, even with current treatments, the outlook is foggy.”

Kristen has difficulties making sure she takes both doses of oxybate:

“Making sure I get the second dose has been a huge hurdle for me. When I don’t get in both doses, it disrupts my schedule. This leads to waking up late or in a cloud of brain fog. This creates a cycle of missed doses causing more missed doses. Trying to measure out both doses at night and figure out timing is made more difficult because of the sleepiness.”

For Kristen, taking Xyrem is often like balancing a mathematical equation:

“The process of figuring out the ‘Xyrem Math’ is a big part of my routine. My work and school schedules require flexibility. I need to have the medication out of my system to drive safely and function. Calculating how much medication to take and when to take the second dose is critical. Solving the ‘Xyrem Math’ problem when I have sluggish thinking complicates the decision.”

Kristen also shared the impact dosing on her family:

“In order to wake up for my second dose, I have a ‘sonic boom’ alarm clock. Even though the noise is very disruptive to my partner, oftentimes I don’t wake up without his help.”

For Kristen, the benefits of a once-nightly formulation are apparent:

“My physician and I came up with workarounds due to frequently missing my second dose. I take a higher amount during my first dose (6 g) in case I miss my second. Creating a once-nightly, premeasured dose would allow me to get the full benefit of the medication. Equally as important, this once-nightly dose would not disrupt my partner’s sleep as well, reducing these unnecessary awakenings.”



Kristen's message and question to the FDA:

"Inaction is not harmless! Why is it taking so long to bring this medication to market? Not approving this medication is causing real-world consequences. The safety and effectiveness of the medication are established. With the current twice-nightly option, many people can't maximize the benefits of oxybate therapy. These delays are resulting in familial and employment consequences. We deserve to have options."



TREND Community
Turning Anecdotes Into Evidence

Data Exploration

Social listening and sodium
oxybate

November 16, 2022



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Purpose

The purpose of this report is to understand the treatment impact of sodium oxybate (SO) in the narcolepsy community via social listening. The data sources being used in this report are two online support groups: **Facebook and a subreddit, r/Narcolepsy**.

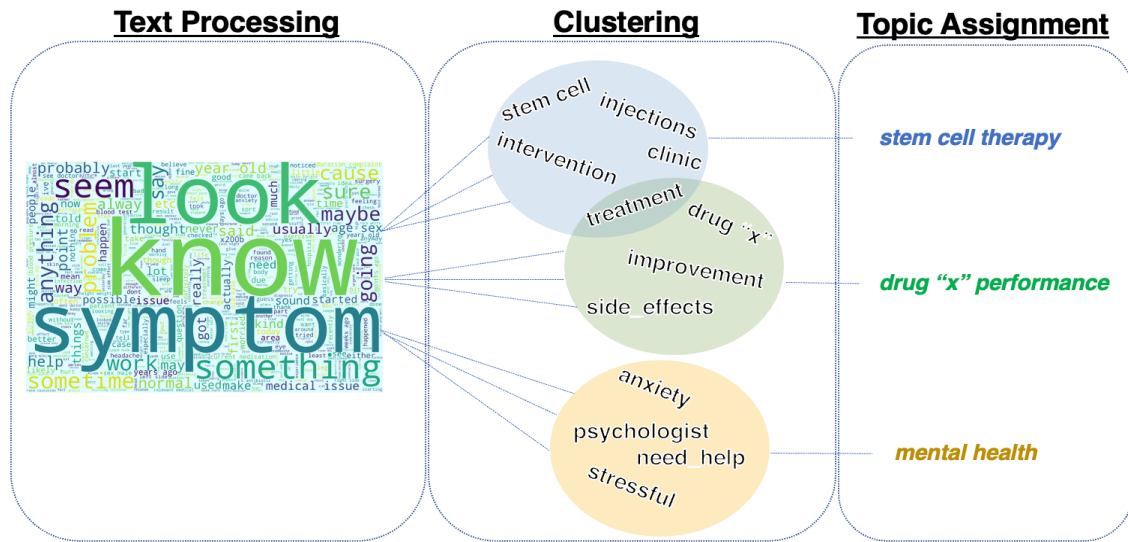
TREND Community Technology

TREND Community harnesses machine learning and natural language processing techniques with Krystie™, our proprietary analytics engine to capture the perspective and experiences shared online by people living with rare and chronic diseases. Krystie was the daughter of one of our community members and the inspiration driving everything we work towards. Krystie—and the millions of others facing rare, chronic, and emerging diseases—is always at the heart of TREND Community.

Our Methodology

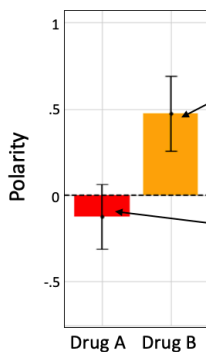
Krystie™ enables TREND to identify conversations in domains that tend to be prevalent in social media-based discussions regarding chronic and rare diseases (e.g., disease burden, management, mental health). After isolating conversations within domains of interest, we leverage a variety of analytical techniques to characterize the language and emotions associated with patient experiences and perspectives. These techniques are implemented both independently and in conjunction with one another to offer converging support for discoveries. We offer a summary of the key methodologies:

TOPIC MODELING



TREND implements various topic modeling approaches to determine language that tends to cluster together. These machine learning techniques rely on statistical probabilities and pre-trained knowledge of words, phrases, and their meanings to identify significant groupings.

POLARITY ANALYSIS



Drug B has an overall positive average sentiment (above 0).

Example comments:

- "drug b improved my symptoms"
- "I would recommend drug b".

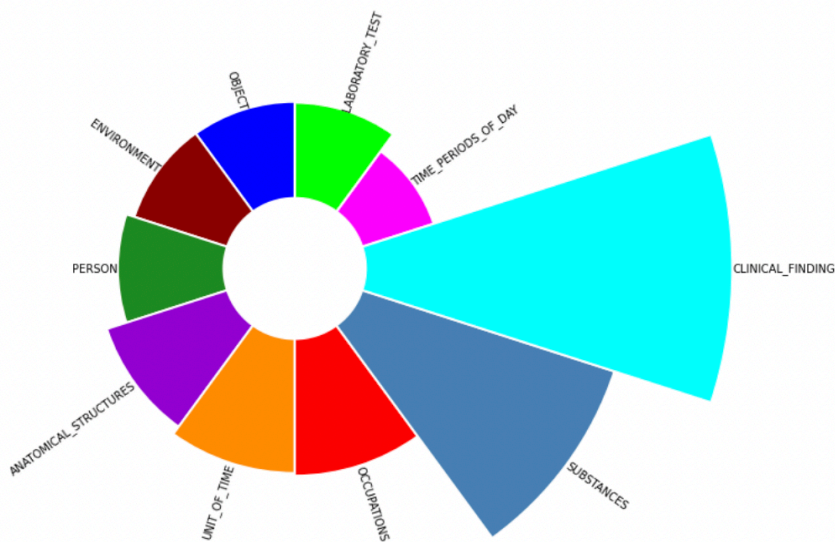
Drug A has a negative average sentiment (below 0).

Example comments:

- "drug a does not help me much"
- "my symptoms were worse with drug a".

We use a variety of polarity and sentiment analysis techniques to broadly understand user emotions and feelings on given topics. These include both word and conversation level analyses.

CLINICAL ENTITY RECOGNITION



We use a custom clinical entity recognition (CER) tagger to mark language based on its membership to 10 clinical domains: clinical findings, substances, occupations, units of time, anatomical parts, persons, environments, objects,

Data Set

Data Sources:

**Facebook
r/Narcolepsy**

15,280

People
Participating

25,018

Posts
Shared

229,626

Comments
Elicited

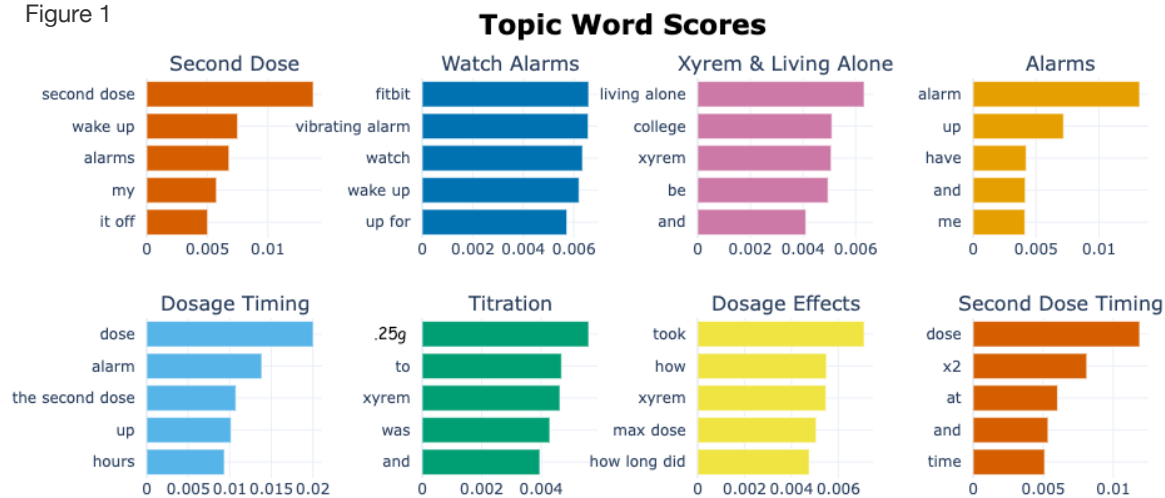
August 2011 - October 2022

Date Range

Topic Modeling

First, we extracted the conversations that mention sodium oxybate from the entire data set. To be more inclusive, we used multiple names and synonyms to perform the extraction, including sodium oxybate, Xyrem, and Xywav, etc. The complete list can be found in Appendix A. The total number of conversations that mentioned sodium oxybate is 26,088 and the total number of reddit users who mentioned sodium oxybate is 4,275. We applied topic modeling on this filtered data set to get a general understanding of the topics being discussed and the results are meant to be taken in aggregate. The model identified several topics related to the sodium oxybate doses. The takeaway is that these topics are all highly related and represent "sodium oxybate and second doses" overall and are used for further analysis as a composite. Figure 1 below shows eight topics and their word representation (top five words).

Figure 1



From the topic model, we identified the following issues related to taking sodium oxybate in the community.

- Having difficulties taking second dose, including:
 - Hard to wake up for second dose
 - Sleeping through the alarm(s) for second dose
 - Dreaming that had taken the second dose
 - Need help from parents/partners to wake up for second dose
 - Worry the second dose alarm will wake up other people
- Issues on scheduling the doses

- Insomnia after doses
- Skipped doses because of drinking
- Binge eating or craving foods after taking a dose
- Timing meals with the medication

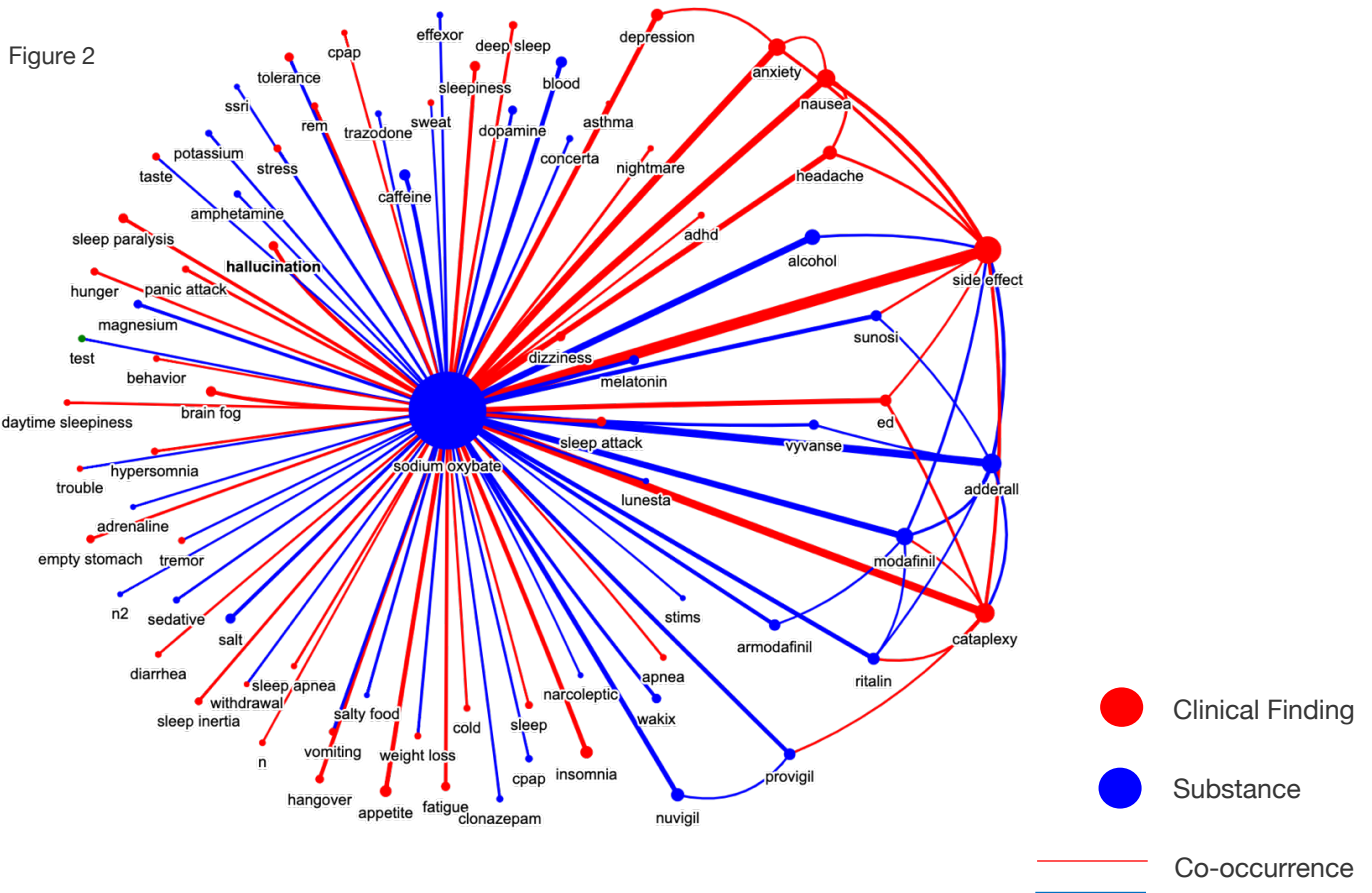
By using the state-of-the-art deep learning language model, we are able to extract the posts and sentences discussing the above issues. The table below shows the statistics of each issue identified. The second column lists the number of occurrences and frequency out of all sodium oxybate discussions (N=26,088). The third column is the number of distinct reddit users and its frequency out of all reddit users who have mentioned sodium oxybate (N=4,275).

Issue	Entry Count (Frequency) N=26,088	User Count (Frequency) N=4,275
Difficulties taking the second dose	635 (2.43%)	398 (9.31%)
Issues scheduling the two doses	14 (0.05%)	4 (0.33%)
Insomnia after doses	161 (0.62%)	134 (3.13%)
Skipped doses due to drinking	3 (0.01%)	3 (0.07%)
Binge eating or food craving after doses	13 (0.05%)	13(0.3%)
Timing meals	27 (0.1%)	26 (0.61%)
Total	715 (2.74%)	439 (10.29%)

The data show that there are 715 posts (2.74% of all sodium oxybate conversations) mentioning an issue when taking sodium oxybate. There were 439 distinct users (10.29% of total users) who mentioned sodium oxybate in their conversations. Please refer to Appendix B for comments from these patients.

Network Analysis

Using our CER tagger, we can build the co-occurrence network and examine the relationships between entities. We filtered conversations that mentioned (1) second dosage (e.g., second dose, 2nd, etc) and (2) sodium oxybate (e.g., xyrem, SO, etc) to build a unique co-occurrence network for all conversations discussing second doses of sodium oxybate. The sub-network is shown in Figure 2 below. The red nodes are clinical findings and blue nodes are substances. The size of the nodes corresponds to the total number of occurrences. Entities mentioned together in the same post/comments are connected by edges. The width of the edges corresponds to the number of co-occurrences; thicker edges imply stronger relationships.



Network analysis shows the top 20 most influential clinical finding nodes below, ordered by degree centrality.

- | | |
|--------------------------|------------------------|
| 1. side effect | 11. dizziness |
| 2. cataplexy | 12. appetite |
| 3. nausea | 13. sleepiness |
| 4. anxiety | 14. sleep attack |
| 5. headache | 15. hallucination |
| 6. ed (eating disorders) | 16. medication anxiety |
| 7. depression | 17. sleep paralysis |
| 8. insomnia | 18. tolerance |
| 9. hypersomnia | 19. empty stomach |
| 10. hangover | 20. panic attack |

The results show that the second dose of sodium oxybate results in not only physical issues such as nausea, headaches, dizziness, and hunger but also mental health issues like anxiety, panic, and depression.

Summary

In this report we evaluated the impact of sodium oxybate based on the analysis of social media data. The results show that the need to take the second dose of sodium oxybate creates various issues and disruption for the patients and their caregivers. These issues range from challenges with waking up to take the second dose to then struggling with getting back to sleep in some cases or dealing with daytime sleepiness in other instances. After taking sodium oxybate, patients also experience physical symptoms such as nausea, headaches, dizziness, and hunger as well as mental health challenges like anxiety, panic, and depression.

Appendix A

Words and synonyms used for concept

SO: oxybate, xyrem, xywav, jazz, nighttime med, ghb, gaba, date rape, gamma hydroxybutyrate, gamma-hydroxybutyrate

'Skip' verbs: skip, miss, skips, misses, skiping, missing, skipping, mising, skiped, missed

Alarm: alarm, fitbit, tracker, tracking

First dose: first dose, 1st dose, first xyrem, first xywav, 1st xyrem, 1st xywav, one dose, one-dose, single dose, single-dose

Second dose: second dose, 2nd dose, second xyrem, second xywav, 2nd xyrem, 2nd xywav, double dose, between dose

Slow release: once nightly, once-nightly, slow release, extended release, extend release, once per night, long acting, slow-release, extended-release, extend-release, once-per-night, long-acting

'Wake' verb: wake me up, woke me up, wakes up, wake up, woke up, waking up

'Sleep' verb: sleep over, slept over, sleep through, slept through, sleeping over, sleeping through, sleeps over, sleeps through

Alcohol: alcohol

Titration: titrat

Accident: miss work, miss school, missing work, missing school, missed work, missed school, accident

Appendix B

Quotes from the discussions

Difficulties taking the second dose

“I have difficulty waking up for a second dose too, even if I use an alarm and give myself a full 4 hours of sleep after the first dose (side note: excessive sleeping / oversleeping / hypersomnia has always been a part of my sleep problem / narcolepsy).”

“I cannot for the life of me seem to wake up for the second dose....”

“I struggle immensely with waking up to take a second dose and am at the point where I only take the first one and don't bother preparing the second.”

“Waking up to take a second dose is jarring and I hate the drugged feeling I get.”

“It's been a miracle drug for me. It completely turned my life around but I'm having the darnedest time waking up for the second dose.”

“Part of the problem was a ton of anxiety about waking up for the second dose without disturbing my partner.”

Alcohol and food

“No alcohol with Xyrem unless somebody else is going home with you and will make sure you wait the appropriate amount of time.”

“If I want to drink I skip it that night.”

“I take my first dose, the second it kicks in, I feel like I'm starving so I nibble on my premade meal.”

“Strangely enough, after taking my first dose, if I stay awake for more than a half hour I find myself becoming ravenous, even if I've eaten full meals throughout the day.”

UNDERSTANDING PATIENT EXPERIENCE WITH OXYBATE THERAPY

Survey Results
November 16, 2022



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OBJECTIVES & CRITERIA



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Research Objectives and Screening Criteria

The purpose of this research is to better understand patient experience with taking oxybate therapy (Xyrem® or Xywav®) for narcolepsy.

The following are the criteria to participate in the survey:

- Age \geq 18 years
- Living in the United States
- Patient or caregiver of a patient with a narcolepsy diagnosis
- Currently taking or have previously taken oxybate therapy like Xyrem® or Xywav®

FINDINGS



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Survey Respondent Data

Total Respondents N=87

Group

Patient: 85

Caregiver: 2

Gender (patients)

Female: 64

Male: 19

Intersex: 1

Prefer not to answer: 1

Diagnoses

Type 1 with Cataplexy: 44

Type 2 without Cataplexy: 39

Unsure: 2

Medications

Currently taking Xyrem®: 19

Previously taken Xyrem®: 34

Currently taking Xywav®: 45

Previously taken Xywav®: 11

Frequency of missing the second dose

When asked: during the time you have been on your oxybate therapy (Xyrem or Xywav), have you accidentally missed your 2nd dose, a majority (75%) of the 85 patients who responded reported this experience.

These patients were then asked: approximately how frequently do you experience this issue? Of this group, 65% miss the second dose once a month or more often.

Frequency	% (N=64)
A few times a week	17%
Once a week	20%
Once a month	28%
Every 6 months	25%
Once a year	5%
Less frequently than once a year	5%

Injuries resulting from waking to take second dose

To better understand the patient experience we asked: during the time you have been on your oxybate therapy (Xyrem or Xywav), have you experienced injuries (such as falling) after waking to take your second dose?

Almost one-third (32%) of the survey respondents have experienced injuries after waking to take the second dose of oxybate therapy.

Of this group, the chart to the right shows the frequency of injuries with 33% experiencing issues once a month or more often.

Frequency	% (N=27)
A few times a week	7%
Once a week	7%
Once a month	19%
Every 6 months	22%
Once a year	19%
Less than once a year	26%

Injuries resulting from waking to take second dose

When asked: please provide us with some additional details about this (for example, describe injuries, how the event happened, seriousness, etc.), many patients reported falling or bumping into things resulting in bumps, bruises, and black eyes. Pulled muscles, stitches, and the need for physical therapy due to a neck and shoulder injury have occurred. One person experienced confusion resulting in taking the second dose too soon which led to a trip to the ER. Another suffered multiple concussions thus impacting their ability to function as well as their mental health.

“[I received] frequent minor injuries (mild bumps and bruises). I have had several concussions that caused more serious issues and required treatment from a concussion clinic due to lingering concussion symptoms and periodic re-injury due to additional concussions under the same circumstances. Overall, the concussions have taken a big toll on my overall functioning and mental health.”

“Knocked over CPAP onto floor and walked around confused bumping into the wall and/or stubbing toes looking for second dose & forgetting it was next to the bed all along.”

“I got up to use the bathroom, fell asleep on the toilet and fell off, slamming my head on doorjamb of bathroom door.”

“I’ve fallen out of bed when I sat up to take the 2nd dose. I hurt my neck and shoulder and needed physical therapy.”

Dose Timing: Taking the second dose more than 4 hours after the first

More than half (59%) of the 85 survey respondents have taken the second dose of oxybate therapy more than 4 hours after the first dose. These data were derived when we asked: during the time you have been on your oxybate therapy (Xyrem or Xywav), have you taken your second dose more than 4 hours after your first dose?

Of those taking the second dose more than four hours after the first, this is occurring once a month or more for almost three quarters (74%) of these patients.

Frequency	% (N=50)
A few times a week	6%
Once a week	14%
Once a month	54%
Every 6 months	12%
Once a year	6%
Less than once a year	8%

Dose Timing: Taking the second dose less than 2.5 hours after the first

A smaller group has taken the second dose less than 2.5 hours after the first dose. The information was gleaned by asking: during the time you have been on your oxybate therapy (Xyrem or Xywav), have you taken your 2nd dose less than 2.5 hours after the first dose?

We then asked: you indicated that you have taken your 2nd dose less than 2.5 hours after the first dose. Approximately how frequently do you experience this issue? This is occurring once a month or more often for almost two fifths (39%) of these patients.

Frequency	% (N=18)
A few times a week	6%
Once a week	11%
Once a month	22%
Every 6 months	11%
Once a year	28%
Less than once a year	22%

Impact of taking the second dose less than 2.5 hours after the first

Upon asking: please describe any impact or issues you typically experience due to taking your second dose less than 2.5 hours after the first dose, a few patients expressed fear and anxiety about taking the doses too close together. Another small group spoke of confusion and disorientation when taking the oxybate therapy within 2.5 hours of the first dose. Others shared experiences of physical discomfort or illness, including headaches, dizziness, and upset stomach. For one patient, this impacted their ability to do things the next day and for another, they experienced EDS. Two patients felt the efficacy was decreased which led to them purposely take the second dose within 2 to 3 hours of the first. Another finds it useful and with no negative impact to take the second dose after only 2 hours.

“I was terrified once I looked at the clock and realized what I had done, ended up in the ER courtesy of my mom knocked out and with a respiration rate of 5 breaths per minute.”

“Increased emotions, severe digestive upset, headache, increased EDS, and worsening of symptoms.”

“I always take my first dose at 10 and my second at 12, it works the best for me and I haven’t noticed any bad symptoms. I wake up when I need to and taking the second dose after 2 hours has been the most successful for me to wake up.”

Additional issues reported

In response to the question: please provide details about other issues you experienced during the time you have been on your oxybate therapy (Xyrem or Xywav), a few patients spoke of experiencing serious mental health issues including depression. One person experienced suicidal thoughts and another experienced paranoia. Others mentioned the following issues: bed wetting, racing heart, light sensitivity, night sweats, muscle spasms, acid reflux, hand tremor, and nighttime cravings and eating problems in between doses. A few spoke of the need to experiment with the dosage amounts in order to get the desired effects. And another small group report a decrease in efficacy over time.

“I experienced extreme anxiety/depression for 4-6 hours after awakening from Xyrem. This is an extreme side effect that is not talked about or addressed.”

“The bottles and measuring and diluting and waking up in the middle of the night for dose two just feels so wrong. I'm on a dose now that definitely gives me a better quality sleep and less daytime sleepiness, but all it takes is sleeping through my second dose to screw everything up again. I feel like I'm on a rollercoaster, which then impacts my mental health. There has to be a better way to dose this!!”

“Xyrem made me want to rip my own skin off. Xywav left me feeling very ill in the mornings, so much that I could barely take care of my children.”

Belief that a once-nightly dose would be safer

As a final question, we asked: please indicate the extent to which you agree or disagree with the following statement: "I believe that a single bedtime dose of sodium oxybate, in a pre-measured packet, would be safer for me to take than the currently available versions, due to avoiding a 2nd, middle-of-the-night dose, the majority (76%) of these patients either strongly agree or agree.

	% (N=87)
Top 2 Box	76%
Strongly agree	46%
Agree	30%
Neither agree nor disagree	11%
Disagree	6%
Strongly disagree	7%

"I am awaiting approval of once nightly sodium oxybate because no other medicinal or lifestyle regimens have allowed me to complete my ADLs without significant struggle. I am so sad that I cannot spend the time I would like to with my 4 year old son and husband due to my EDS, and am not able to take Xyrem anymore due to missing the second dose too frequently due to shutting off my alarms, and going back to sleep, or hallucinating and thinking I took my second dose when I really did not."

"Accidentally poured a liquid that wasn't plain water into the cup. Accidentally poured water into another different medication bottle ruining an entire month script."



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