

## Plain Language Summary of Publication

# Effects of oxybate dose and regimen on disrupted nighttime sleep and sleep architecture: A Plain Language Summary

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## Summary

### What is this summary about?

This is a plain language summary of a review article that looked at how different forms of a medicine called **oxybate** impact sleep in people with **narcolepsy**. People with narcolepsy often struggle with their sleep. They experience issues like **sleep fragmentation** or reduced **sleep efficiency** that may lead to poor **sleep quality** and **disrupted nighttime sleep** (DNS). To help people with these challenges, oxybate is used to improve sleep and also treat daytime symptoms of narcolepsy (such as excessive daytime sleepiness and cataplexy). Sodium oxybate (SXB; Xyrem®) was first approved in 2002, as a twice-nightly treatment. Newer versions of this medicine have been developed including once-nightly sodium oxybate (ON-SXB; Lumryz™) that contains the same amount of sodium and is taken once per night, and low-sodium oxybate (LXB; Xywav®), which is taken twice per night and has 92% less sodium than SXB. There have not been any direct studies comparing these different oxybate medicines. Information gathered from 5 clinical studies, along with additional supporting research, shows that taking oxybate at night can improve sleep quality and reduce sleep disturbances during the night for people with narcolepsy.

### What were the conclusions?

Nighttime sleep patterns are disturbed in people with narcolepsy. Oxybate medicines can improve sleep quality by making deep sleep last longer and reducing sudden wakeups and shifts between **sleep stages**. These benefits are noticeable whether oxybate is taken once or twice per night. In studies that looked at SXB taken twice nightly, use of the medication tended to show greater improvement in sleep quality later in the night.

### What do the conclusions of the study mean?

Although no clinical studies have directly compared different oxybate medicines, SXB, ON-SXB, and LXB are effective for improving sleep quality and reducing disturbances at night in people with narcolepsy. Future studies should look at the safety and effectiveness of different oxybate products and dosing regimens (once and twice per night) to better understand their advantages and disadvantages. Comparing these medicines can help doctors choose the best treatment for each person's needs.

## Keywords

- Narcolepsy
- Excessive daytime sleepiness
- Sodium oxybate
- Low-sodium oxybate

## How to say (click to play sound)

- 🔊 **Narcolepsy:** NAAR-kuh-lep-see
- 🔊 **Oxybate:** AAK-see-bayt

### Sleep fragmentation

*Repetitive, short interruptions of sleep or between different sleep stages such as between deep and light sleep*

### Sleep efficiency

*Time spent asleep as a percent of time spent in bed*

### Sleep quality

*Can be impacted by the time it takes to fall asleep, how stable different stages of sleep are throughout the night, sleep fragmentation, and sleep efficiency; no single definition has been agreed upon*

### Disrupted nighttime sleep (DNS)

*Usually includes feelings of poor sleep quality, waking up many times during the night, and findings of sleep fragmentation during a sleep study; no single definition has been agreed upon*

### Sleep stages

*Different types of sleep that are defined based on brain activity. From lightest to deepest sleep, these are N1, N2, and N3. A fourth stage, REM sleep, is when dreaming occurs*

## Who is this article for?

This plain language summary is for individuals with narcolepsy, or who know/care for someone with narcolepsy, and want to know more about the different oxybate medicines and how they improve sleep.

Who sponsored this study?

Jazz Pharmaceuticals **sponsored** this study.

Sponsor

A sponsor is a company or organization that oversees and pays for a clinical research study. The sponsor also collects and analyzes the information that is generated during the study.

What is narcolepsy?

- Narcolepsy is an uncommon sleep disorder where people feel extremely tired during the day, often needing to take naps.
- Symptoms usually start during childhood or adolescence.
- In the United States, narcolepsy affects 1 person out of every 2000 annually.
- There are 2 types of narcolepsy, narcolepsy type 1 and narcolepsy type 2. They are similar, but narcolepsy type 1 also involves a symptom called cataplexy.
  - Individuals with narcolepsy type 1 experience cataplexy while awake, and their muscles suddenly weaken temporarily. This usually happens during moments of intense emotions.
- People with narcolepsy might have poor sleep quality and trouble sleeping through the night, which is called DNS. They might also experience hallucinations or feel like they cannot move when they are waking up or falling asleep, which is called sleep paralysis.
- There is no known cure for narcolepsy.

What is normal sleep architecture?

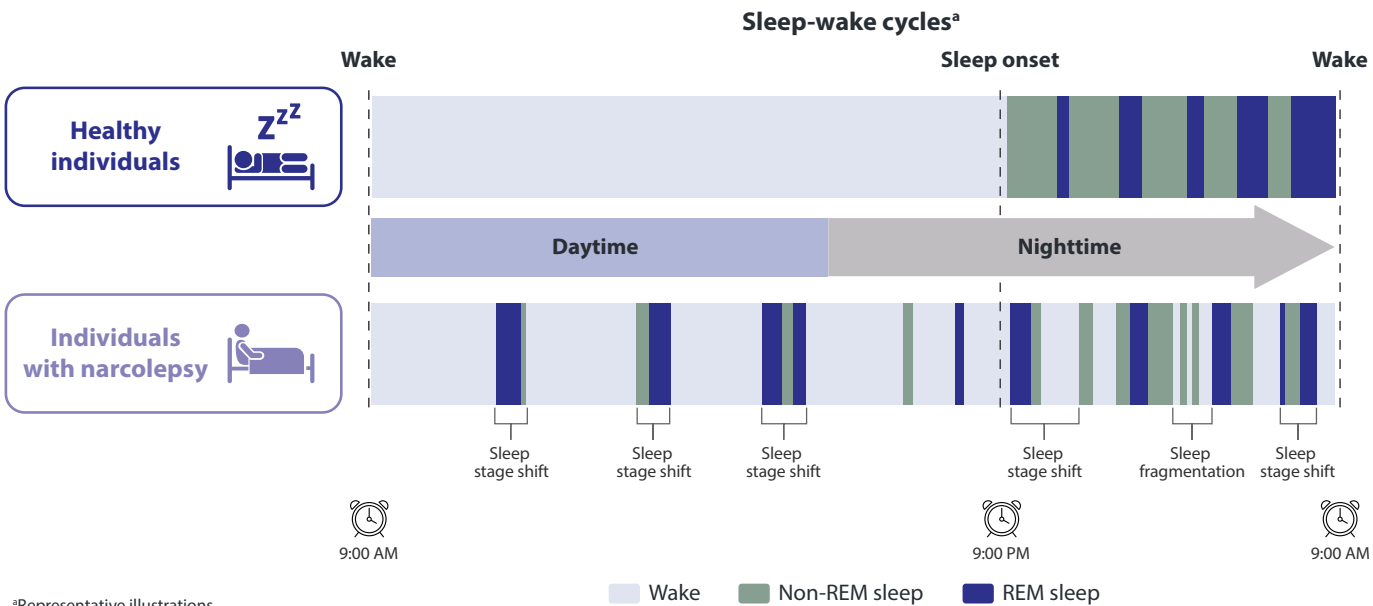
Throughout the night, healthy people move between light sleep, deep sleep, and rapid eye movement (REM) sleep on regular cycles. These cycles are made up of a number of sleep stages that include REM sleep and non-REM sleep stages known as N1, N2, and N3. N1 is the lightest stage of sleep, while N3 is the deepest stage of sleep and is known as “deep sleep” or “slow wave sleep.” Brief interruptions in sleep are normal, even in healthy people. As people get older, they tend to experience more interruptions in sleep and spend less time asleep—around 10 minutes less every decade.

Sleep architecture and disrupted nighttime sleep in narcolepsy

People with narcolepsy do not have normal **sleep architecture**. Instead, they wake up unexpectedly and repeatedly—this is called DNS. Because people with narcolepsy cannot transition through the stages of sleep normally, they do not find sleep as restful.

Sleep architecture

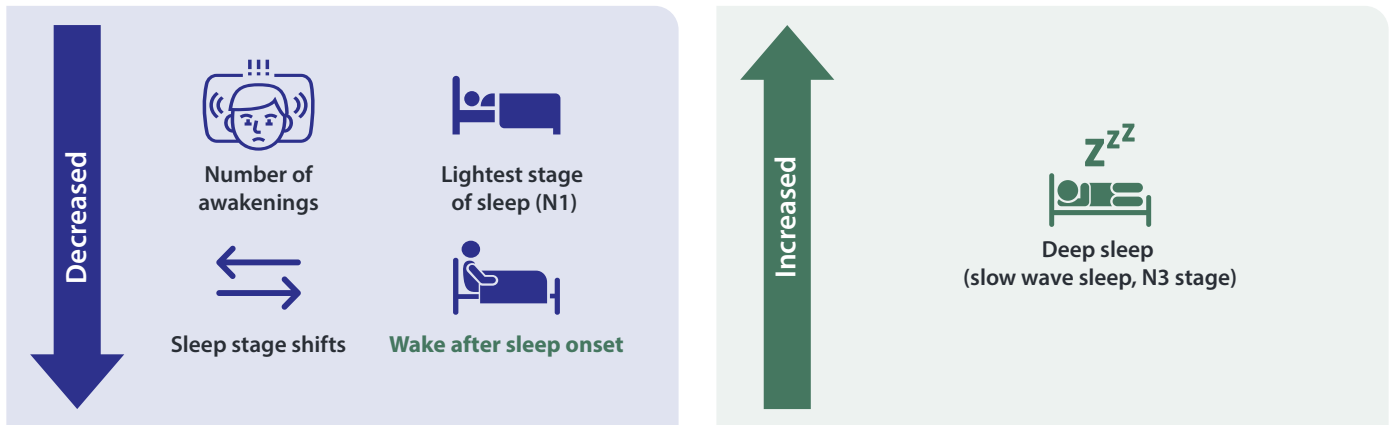
When and how often different sleep stages happen throughout the night



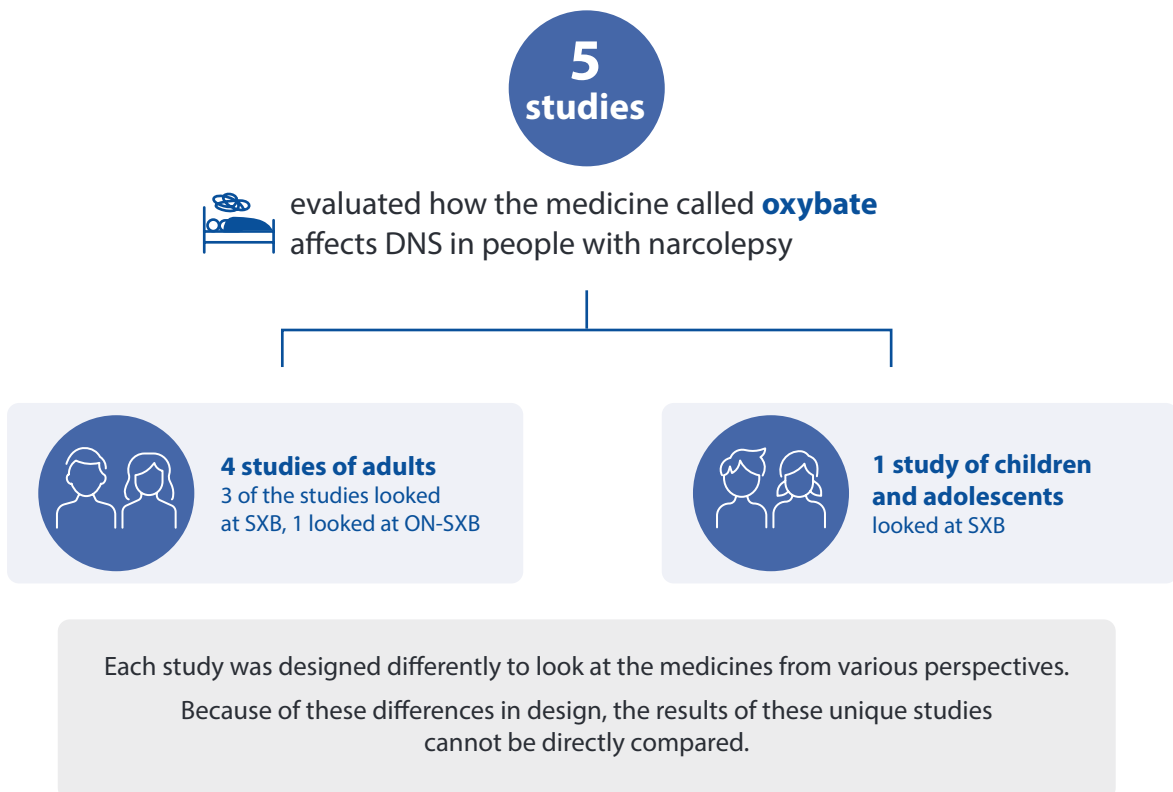
## Early oxybate studies

Gamma-hydroxybutyrate (GHB) is the part of oxybate that makes it work as a treatment for narcolepsy. Several small studies on the use of GHB for the treatment of narcolepsy were published in the 1980s and 1990s. These studies found that GHB decreased the number of awakenings in people and increased slow wave sleep (deep sleep).

**Wake after sleep onset**  
All wake activity, including time out of bed




## Larger scale clinical studies of oxybate



Study 1 (SXB)

How was this study done?



This study included individuals **16 years of age or older** with current symptoms of narcolepsy, including excessive daytime sleepiness and cataplexy.

- To compare which dosage of SXB (in grams [g]) would work best, people were randomly divided into 4 groups.



**4.5 g**  
(nightly)



**6 g**  
(nightly)




**9 g**  
(nightly)




**Placebo**  
(nightly)

Researchers and people in the study did not know who was taking SXB or **placebo**. For the first 4 weeks, the dosage was adjusted to the target dose. For the second 4 weeks, participants took the same dose every day.


What did the study look at?




The study looked at 228 people.




Researchers looked at whether taking SXB at night would relieve people's symptoms of nighttime sleep disruption.



Changes in sleep were measured at night using **polysomnography**.



People reported their sleep quality on a 4-point scale: 0 for excellent, 1 for good, 2 for fair, and 3 for poor.



Sleep and wakefulness tests were performed at the beginning of the study, after 4 weeks, and at the end of the study.

**Placebo**  
*Treatment that does not contain any real medicine. Often used in clinical studies to see if the actual medicine works better than something without real medicine*


**Polysomnography**  
*Also called a "sleep study"; measures the activity in your body over time while you sleep, including your brain waves or activity, sleep stages, eye movements, how much you move around, how much oxygen is in your blood, your heart rate, and your breathing rate*


**Delta power**  
*A measure of the strength of the slowest brain waves, which are most active during deep sleep*

**Tolerability**  
*How well an individual can manage taking a medicine without experiencing too many unpleasant side effects*


**Common side effects**  
*Side effects of a medication or treatment that are frequently seen, generally in at least 5% of people who use it*

What were the conclusions?







**Wake after sleep onset**  
Time spent awake after falling asleep decreased at 8 weeks in people taking SXB 9 g.




**Number of awakenings**  
The number of times people woke up in the night decreased after 8 weeks in all SXB groups.




**Lightest stage of sleep (N1) and REM sleep**  
The amount of time spent in light sleep and in REM sleep decreased in the SXB groups.




**Sleep stage shifts**  
People taking SXB 6 g and 9 g had fewer shifts between sleep stages. People taking SXB 9 g had the biggest decreases.







**Total sleep**  
Total sleep time increased. After 8 weeks of treatment, people taking SXB 9 g increased their total sleep time by an average of 18.0 minutes.



**Sleep quality**  
People taking SXB felt like the quality of their sleep improved.








**Deep sleep (slow wave sleep, N3 stage)**  
Deep sleep increased in the SXB groups.



**Delta power**  
Delta power increased with SXB, particularly during the second half of the night.

Tolerability

- The most **common side effects** were:  Nausea  Dizziness  Headache  Nasal passage/ throat inflammation  Bedwetting
- Of these, nausea and dizziness occurred more often in people taking SXB compared with those taking placebo.
- 21 people left the study because of side effects. Most of them were taking SXB 9 g.

What do the conclusions mean?

- This study showed that taking SXB nightly increased the hours people slept and the hours of deep sleep. It also decreased nighttime awakenings.
- In general, people taking higher doses of SXB had better improvements in their symptoms.
- This study suggests that SXB relieves some of the sleep disturbance that is common in narcolepsy.

## Study 2 (SXB)

### How was this study done?



This study included **adults 18 years of age or older** with narcolepsy who may or may not have cataplexy.

- Everyone had been taking regular doses of the wake-promoting medicine modafinil 200–600 mg/day for at least 1 month.
- People were randomly divided into 1 of 4 different groups depending on the medications they were taking:
  - Placebo SXB and placebo modafinil (placebo group)
  - Modafinil and placebo SXB (modafinil group)
  - SXB and placebo modafinil (SXB group)
  - SXB and modafinil (SXB/modafinil group)
- People in the modafinil and SXB/modafinil groups stayed on their usual doses of modafinil.
- People assigned to the oxybate groups took 2 doses of SXB:



Researchers and people in the study did not know who was taking SXB, modafinil, and/or placebo.

### What did the study look at?



The study looked at 222 people.

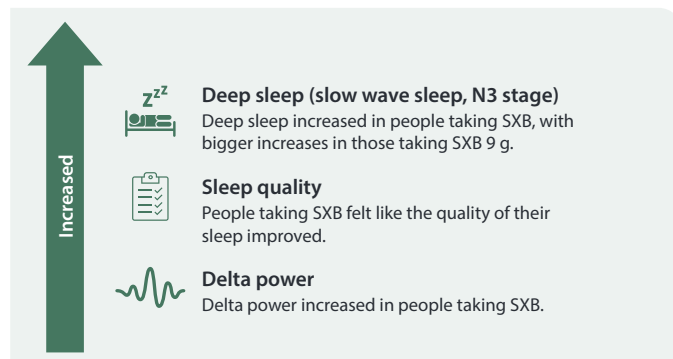
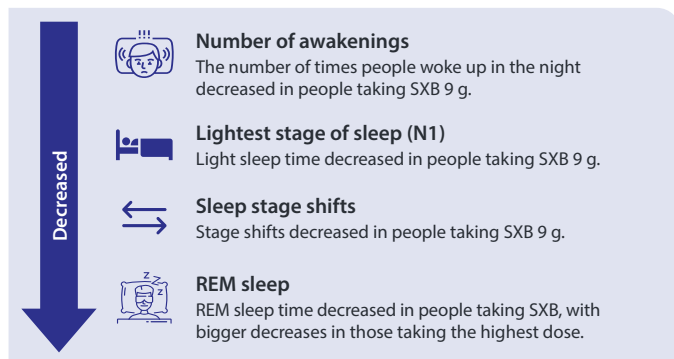


Researchers looked at how well taking SXB, modafinil, or a combination of both would relieve people's symptoms of nighttime sleep disruption and daytime sleepiness.



Sleep was measured at night using polysomnography before and after the start of the study, and after 4 and 8 weeks of treatment.

### What were the conclusions?



### Tolerability


- Side effects were generally more frequent in people taking SXB in combination with modafinil than in those treated with SXB alone, modafinil alone, or placebo.
- The most common side effects were:
  - Nausea
  - Dizziness
  - Headache
  - Nasal passage/throat inflammation
  - Vomiting
  - Drowsiness
- Of these, nausea, vomiting, and dizziness occurred more often in people taking SXB and/or modafinil compared with those taking placebo.
- 13 people left the study because of side effects.

### What do the conclusions mean?

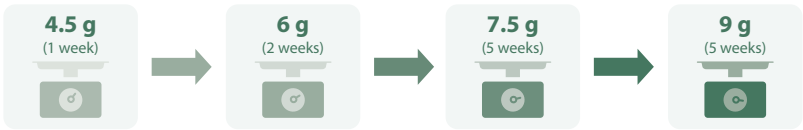
- SXB alone and in combination with modafinil improved nighttime sleep, but modafinil alone did not.
- This study showed that people taking SXB, either alone or in combination with modafinil, had more deep sleep and fewer awakenings and sleep disturbances after 4 weeks of treatment.
- After an additional 4 weeks of treatment with SXB 9 g, people experienced no change in total sleep but an improvement in deep sleep.

Study 3 (ON-SXB)





How was this study done?

 This study included individuals **16 years of age or older** with a diagnosis of narcolepsy type 1 or narcolepsy type 2.


- The study began with a 3-week screening period, followed by a 13-week treatment period.
- People were randomly assigned to ON-SXB or placebo once a day at bedtime in increasing doses:
- Researchers and people in the study did not know who was taking ON-SXB or placebo.








What did the study look at?




-  The study looked at 190 people.
-  Researchers looked at whether a single bedtime dose of ON-SXB would help treat people with narcolepsy and improve their sleep.
-  Sleep patterns were measured using polysomnography at the start of the study and at week 3, week 8, and week 13.
-  People reported quality of sleep and the refreshing nature of sleep daily using a visual rating scale from 0 to 100.

What were the conclusions?








-  **Number of awakenings**  
The number of nighttime awakenings decreased in people taking ON-SXB, with bigger decreases as the dose went up.
-  **Lightest stage of sleep (N1)**  
Duration of light sleep decreased in people taking ON-SXB, with bigger decreases as the dose went up.
-  **Sleep stage shifts**  
The number of sleep stage shifts decreased in people taking ON-SXB, with bigger decreases as the dose went up.
-  **REM sleep**  
REM sleep duration decreased in people taking ON-SXB.



-  **Deep sleep (slow wave sleep, N3 stage)**  
Deep sleep increased in people taking ON-SXB, with bigger increases as the dose went up.
-  **Sleep quality**  
Sleep quality improved in people taking ON-SXB, with bigger improvements as the dose went up.
-  **Delta power**  
Delta power during NREM increased in people taking ON-SXB.

Tolerability

- The most common side effects were:  Nausea  Dizziness  Headache  Vomiting  Bedwetting
- 17 people in the ON-SXB group and 2 people in the placebo group left the study because of side effects.

What do the conclusions mean?

- This study showed that people taking ON-SXB experienced better sleep quality and spent more time in deep sleep compared with people not taking any treatment.
- People taking ON-SXB also had fewer sleep stage shifts and nighttime awakenings and less time in REM sleep.
- The improvements seen with ON-SXB were greater when people took higher doses.

## Study 4 (SXB)

### How was this study done?



This study included individuals **18 years of age or older** with a diagnosis of narcolepsy.

- The study took place over 14 weeks.
- People in this study took increasing doses of SXB:



### What did the study look at?



The study looked at 25 people.



Researchers looked at whether taking SXB at night improves sleep quality and daytime narcolepsy symptoms.

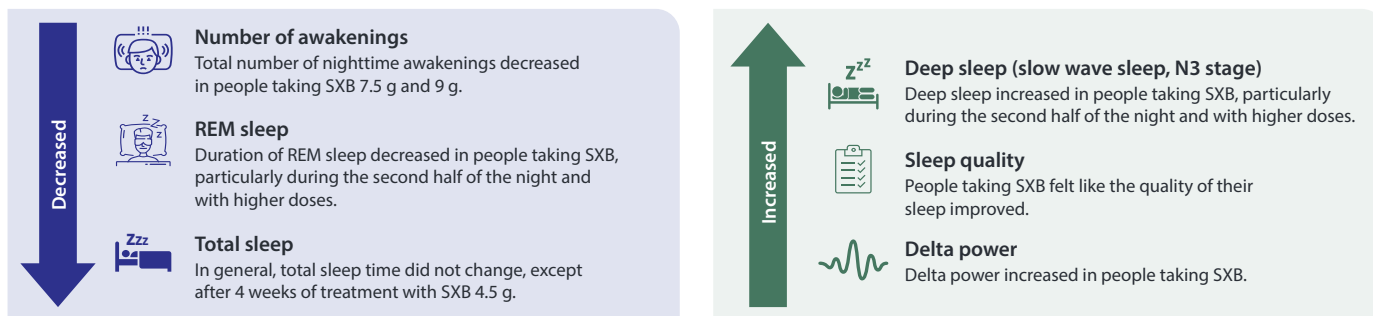


An overnight polysomnography was performed at the first visit and then at the end of each of the 2-week periods.



People reported whether they had any improvements or worsening in their sleep quality.

### What were the conclusions?



### Tolerability

- The most common side effects were:



Nausea



Back pain



Loss of appetite



Vomiting



Swelling



Another sleep disorder



Drowsiness

- 18 people reported at least 1 side effect.
- 2 people left the study because of side effects.

### What do the conclusions mean?

- This study showed that people with narcolepsy who took SXB experienced fewer awakenings during the night, increased deep sleep, decreased REM sleep, and improved sleep quality.
- The improvements seen with SXB were generally more frequent when participants took higher doses.



Study 5 (SXB)

How was this study done?



This study included **children and adolescents (7–16 years of age)** with narcolepsy with cataplexy.

- Children and adolescents taking SXB or receiving no treatment could participate in the study.
- Children and adolescents who were not taking SXB at the start of the study were started on SXB, which was increased to an optimal dose and then kept stable for 2 weeks.
- Children and adolescents taking SXB at the start of the study stayed on their usual, stable dose for 3 weeks.
- After being on stable SXB doses, children and adolescents were randomly assigned to continue SXB or take placebo for 2 weeks.
- Then, children and adolescents were studied for another 47 weeks to look at the safety of SXB.

What did the study look at?



The study looked at 106 children and adolescents.



Researchers looked at whether SXB was effective for the treatment of cataplexy and excessive daytime sleepiness.



Polysomnography was performed before the study started, while individuals were on stable doses of SXB, and during the time that safety was being reviewed.

What were the conclusions?

Decreased

**Number of awakenings**  
Awakenings decreased in people who had not previously taken SXB.  
**REM sleep**  
REM sleep time decreased in people who had not previously taken SXB.  
**Lightest stage of sleep (N1)**  
Light sleep time decreased in people who had not previously taken SXB.

Increased

**Deep sleep (slow wave sleep, N3 stage)**  
Deep sleep increased in people who had not previously taken SXB.

Tolerability

- The most common side effects were: Nausea Headache Vomiting Bedwetting Decreased weight Decreased appetite
- People who were not taking SXB at the beginning of the study were more likely to report side effects than those taking SXB.
- Sleepwalking was reported in 6% of the children and adolescents in the study.
- 1 person who experienced strange thoughts at a higher dose of SXB treatment discontinued this dose. They then took a lower dose of SXB and did not have any more strange thoughts.
- 1 person with suicidal thoughts left the study.

What do the conclusions mean?

- This study showed that SXB treatment reduced awakenings, decreased light sleep, and increased deep sleep in children and adolescents who were not taking SXB at the beginning of the study. There was little further change in sleep for children and adolescents already taking SXB.



## Additional studies of SXB

### Long-term studies

#### How were these studies done?

- These were small studies where people with narcolepsy took SXB and were observed for up to 3 years.

#### What did the studies look at?



- SXB dose
- Sleep parameters using polysomnography:
  - In one 2-year study, sleep parameters were assessed before individuals began taking SXB and at 3, 9, and 14 months after starting SXB.
  - In the 3-year study, sleep parameters were assessed at 6 months, 1 year, and 3 years after starting SXB.



- **Sleep latency** using the Multiple Sleep Latency Test
- Alertness using the Maintenance of Wakefulness Test
- Activity using an **actigraphy device**



#### 2-year study

observed 4 individuals



#### 2-year study

observed 18 individuals



#### 3-year study

observed 23 individuals

#### Sleep latency

*Is the time it takes to fall asleep after going to bed*

#### Actigraphy device

*A wearable device that measures activity and movement and helps assess sleep patterns*

#### What were the conclusions?

##### 2-year studies



- SXB dose varied over time ranging from 5 g to 9 g nightly.
- Deep sleep increased.
- Awakenings and non-REM light sleep decreased.

##### 3-year studies



- The average SXB dose was 4.5 g to 9 g nightly.
- Sleep interruptions increased from 6 months onward.
- Non-REM light and medium sleep increased.
- Number of awakenings generally decreased over time.

#### Tolerability

- Common side effects reported across long-term studies:



Nausea



Dizziness



Bedwetting



Weight loss

### Matched control studies of SXB

#### How were these studies done?

- Individuals with narcolepsy took SXB for 5 consecutive nights.

#### What were the conclusions?

Treatment with SXB was associated with:

- Decreased awakenings and non-REM light and moderate sleep.
- Increased REM sleep and deep sleep.

#### Tolerability

- The only side effect reported was:



Mild drowsiness

#### What did the studies look at?



- The studies looked at sleep parameters using polysomnography.

#### Matched control studies

*Compare people who receive a treatment to a similar group who do not. The two groups are matched based on characteristics like age or gender to ensure a fair comparison to help understand if the treatment works*


Additional studies of SXB

Real-world outpatient study of SXB

How was this study done?

- Individuals taking SXB for narcolepsy were studied and observed in their daily life, outside of a clinical study.

What did the study look at?

-  The study looked at sleep parameters using polysomnography.

What were the conclusions?


- The average SXB dose was 5.8 g nightly.
- Deep sleep increased 3 months after starting SXB.

Retrospective study of SXB

How was this study done?

- Information that had already been gathered in the past from people with narcolepsy who took SXB were analyzed.

What did the study look at?

-  The study looked at sleep parameters using polysomnography.

What were the conclusions?

- The average SXB dose was 6.8 g nightly.
- Individuals took SXB for an average of 8.1 weeks.
- Treatment with SXB was associated with decreased awakenings and REM sleep and increased deep sleep.

Retrospective study


A study that looks at information that has already been collected; is observational

Systematic review and meta-analysis of 15 SXB studies

How was this study done?

- Findings from 15 studies that included a total of 2104 individuals who took SXB were reviewed.

What did the study look at?





-  The study looked at sleep parameters using polysomnography.

What were the conclusions?

Treatment with SXB was associated with:

- Decreased number of awakenings, REM sleep, non-REM light sleep, and sleep stage shifts.
- Increased deep sleep and nighttime sleep quality.

Tolerability

- Side effects were:  Nausea  Dizziness  Vomiting  Bedwetting

Systematic review

A detailed summary of all the research on a specific topic in the medical literature. Researchers collect, assess, and combine findings from multiple studies to provide a clear understanding of the research

Meta-analysis

This type of study combines numerical information from several studies to create 1 stronger conclusion

What do the conclusions from these additional studies mean?

- The effects of oxybate medications reported in these studies were generally similar to those reported in the key clinical studies. The only exception was the 3-year study of SXB in individuals with narcolepsy type 1. It is difficult to interpret the results from the 3-year study because sleep parameters were not measured before individuals started taking SXB. In addition, the average dose of SXB in the 3-year study was less than 6 g, indicating that the SXB dose may not have been at the right dose to work adequately.

## Considerations about oxybate treatment



- Oxybate has been known to worsen sleep-related breathing problems, such as sleep apnea. The clinical studies described in this summary excluded anyone with a sleep disorder other than narcolepsy, such as sleep apnea, so the effect of oxybate in people with other sleep disorders should be researched further. Doctors prescribing oxybate should keep that risk in mind on a case-by-case basis.
- Oxybate is linked with episodes of sleepwalking and bed-wetting in adults and children. Doctors should give advice to people with narcolepsy and caregivers on how to handle these events if they happen and consider other supportive ways to treat people.
- Oxybate may increase risk of depression for some adults and children, particularly those with a history of depression or suicidal thoughts. These people should be monitored closely for changes to their mental health.

## Limitations and future directions

A key limitation of oxybate research is that there have been no studies comparing different forms of oxybate within the same study. SXB, ON-SXB, and LXB, all of which are approved for the treatment of cataplexy and excessive daytime sleepiness in people with narcolepsy, have been studied under varying circumstances and measured different factors related to DNS. Therefore, it is difficult to compare these studies directly.

## Conclusions

People with narcolepsy experience DNS, which presents as altered sleep architecture, repeated waking throughout the night, and more shifting between light and deep stages of sleep. Oxybate medicines improve DNS in narcolepsy by increasing the amount of time spent in deep sleep, decreasing the amount of time spent in light sleep, and decreasing awakenings and shifts between stages of sleep. These improvements are observed with both once-nightly and twice-nightly oxybate dosing. However, there have been no direct comparisons to show how much better one schedule might be compared with the other.

## Where can readers find more information on this study?

The original article was published in the medical journal *Sleep Medicine* in 2024. The title is “Effects of oxybate dose and regimen on disrupted nighttime sleep and sleep architecture”.

You can access and read the article for free using the links below:

<https://pubmed.ncbi.nlm.nih.gov/38244463/>

<https://www.sciencedirect.com/science/article/pii/S1389945723015794>

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### Financial & competing interests disclosure

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