

London New Drugs Group APC/DTC Briefing Document

Sodium oxybate December 2005

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Summary

- In June 2005 the CHMP adopted a positive opinion recommending granting a marketing authorisation for sodium oxybate (Xyrem) for the treatment of cataplexy in adult patients with narcolepsy.
- The prevalence of narcolepsy with cataplexy in European populations has been estimated at 3-5 per 10,000, and if patients without cataplexy were included this would increase by a third.
- Cataplexy is the abrupt, reversible decrease in muscle tone caused by emotion, such as laughter, elation or anger.
- Sodium oxybate is the sodium salt of gamma hydroxybutyrate (GHB). GHB is a schedule 4 (part 1 CD Benz) controlled drug in the UK. It was originally used as an anaesthetic and later gained popularity as a recreational drug and nutritional supplement for body building. GHB has also been used as a 'date-rape' drug.
- Trials carried out by the US Xyrem Multicenter Study Group have evaluated a range of doses of sodium oxybate (3g-9g/day) for controlling the cataplexy symptoms in patients with narcolepsy.
- Sodium oxybate use was associated with dose-related improvements in the symptoms of narcolepsy and reductions in the number of attacks of cataplexy. The most significant improvements/reductions were seen in patients taking 9g/day.
- Trial results demonstrate that after stabilisation on sodium oxybate therapy, abrupt withdrawal leads to a gradual increase in the number of cataplexy attacks.
- Sodium oxybate should be taken at bedtime whilst in bed, and then again 2.5 - 4 hours later while sitting in bed. The effective dose is 6g-9g/day, in two divided doses, though some patients may respond to 4.5g/day. The elimination half life of sodium oxybate is short and patients with narcolepsy who administer nocturnal doses of medication to themselves awaken with minimal or no measurable plasma oxybate until their next night-time dose.
- No withdrawal effects from sodium oxybate were seen in the trials. Trial results demonstrate that after stabilisation on sodium oxybate therapy, abrupt withdrawal leads to a gradual increase in the number of cataplexy attacks.

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Points for consideration

- Sodium oxybate does not cause rebound cataplexy upon discontinuation, like antidepressants, but a gradual increase in the number of attacks.
- Patients must take the second dose 2.5-4 hours after the first dose and therefore may need to set an alarm clock in order to ensure they wake up. However, since one hallmark of narcolepsy is sleep disruption & frequent awakenings, waking once to take the second dosage is not really inconvenient in this population.
- Sodium oxybate may be sufficient to control cataplexy but a stimulant may still be required to control the excessive daytime sleepiness (EDS). Sodium oxybate has an effect on EDS through the reduction of Epworth Sleepiness Scale scores in several of the trials used for registration.
- In the US, sodium oxybate is a Schedule III drug under the Controlled Substances Act, and only available via the Xyrem Success Program. A number of procedures must be followed in order for Xyrem to be prescribed and supplied, and detailed surveillance must be provided every three months.
- Although sodium oxybate is metabolised into GHB, there are less expensive, albeit illicit, sources. Sodium oxybate is judged to have moderate potential for abuse and diversion.

Background

In June 2005 the Committee for Medicines Products for Human Use (CHMP) adopted a positive opinion recommending to grant a marketing authorisation for sodium oxybate (Xyrem) 500mg/ml solution for the treatment of cataplexy in adult patients with narcolepsy.¹ In February 2003 Xyrem was designated an Orphan medicinal product. Due to its potential for abuse, sodium oxybate is under special prescription.

Narcolepsy

The term narcolepsy was first used in 1880 to describe a syndrome comprising of four main characteristic symptoms: sleep attacks, cataplexy, hypnagogic hallucinations and sleep paralysis; these are known as the narcolepsy tetrad (see table 1).² The prevalence of narcolepsy with cataplexy in European populations has been estimated at 3-5 per 10,000, and if patients without cataplexy were included this would increase by a third. The incidence among first degree relatives is higher (1-2%). The disorder commonly starts in the teens but can be present earlier or in middle age.³

Cataplexy is an abrupt, reversible decrease in muscle tone caused by emotion, such as laughter, elation or anger and is reported by approximately 75% of pa-

tients with narcolepsy. The main muscles affected are the face and neck, leading to a sagging jaw, inclined head and slurred speech. Extremities can also be affected, such as buckling of the knees. Complete cataplexy (sudden and severe loss of muscle tone causing collapse to the ground) is experienced by ~1/3 of narcoleptics with cataplexy. Attacks can last up to 30 minutes.⁴

Narcolepsy may have a number of etiologies and may be partially genetic. In the 1980s Japanese workers discovered that many people with narcolepsy have the tissue type human leucocyte antigen (HLA) DR2³, and 95% of people with narcolepsy and cataplexy have the HLA DQB1*0602.³ In the year 2000 it was reported that concentrations of hypocretins were markedly reduced in the cerebrospinal fluid of narcoleptic patients with cataplexy.³ Hypocretin-containing neurons are found in the hypothalamus and project to various parts of the brain believed to regulate sleep:⁴ their depletion explains both the rapid transition between wakefulness and rapid eye movement sleep, and the tendency for these states to fragment in narcolepsy.³

Normal sleep comprises of two separate sleep states: rapid eye movement (REM) sleep (vivid dreaming, muscle atonia, desynchronized activity on an electroencephalogram (EEG), and episodic bursts of REM) and non-REM sleep (muscle relaxation, slow/

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delta wave activity on EEG, less frequent dreaming). In narcolepsy both onset and offset of REM- and non-REM sleep are impaired and narcoleptics are unable to maintain either type of sleep, leading to frequent arousals and disturbed nocturnal sleep.⁴ The excessive sleepiness of narcolepsy comes from a background feeling of sleepiness present much of the time and a strong, sometimes irresistible urge to sleep recurring at intervals during the day. Naps at inappropriate times, such as during meals, are characteristic.³ In the UK, people with narcolepsy are required by law to let the DLVA know and are advised to refrain from driving until the DVLA has reached a decision on their case. Driving will be permitted when satisfactory control of symptoms has been achieved, then a 1, 2 or 3-year licence will be granted with regular medical review.⁵

The differential diagnosis of excessive daytime sleepiness (EDS) occurring in isolation is wide: narcolepsy is an important cause but by no means the only one. Others include insufficient sleep at night which improves with extended sleep during weekends and holidays, obstructive sleep apnoea, depression and circadian rhythm disturbances such as jet lag and shift work. EDS occurring with cataplexy is almost always due to narcolepsy.³ The severity of EDS can be determined using the Epworth Sleepiness Scale, a self administered test consisting of eight questions.⁴ The questions are scored from 0 (would never doze) to 3 (high chance of dozing). A normal score is 6-8, with a score over 12 indicating an abnormally high degree of sleepiness. A history of cataplexy can be revealed by asking whether strong emotion elicits muscle weakness.

Narcolepsy is generally treated with a central nervous system (CNS) stimulant to reduce EDS and an antidepressant to control cataplexy and other REM sleep-related symptoms.⁴ These are only partly effective and can have serious adverse reactions on the cardiovascular, gastrointestinal and central nervous systems.

Dexamphetamine, a CNS stimulant, is licensed for the treatment of narcolepsy.⁶ This increases alertness, elevates mood and prevents sleep. Dexamphetamine has a large number of side effects though, such

as insomnia, restlessness, irritability and tachycardia. Modafinil is also licensed in the UK for daytime sleepiness associated with narcolepsy.⁶

Stimulants do not treat cataplexy effectively and tricyclic or SSRI antidepressants, which suppress REM sleep are used, generally at lower doses than those used for depression.⁴ Clomipramine is licensed for the adjunctive treatment of cataplexy in patients with narcolepsy at a lower dose than that used for depression.⁶ Sodium oxybate is a new therapy for the treatment of cataplexy associated with narcolepsy.

Gamma hydroxybutyrate (GHB)

Sodium oxybate is the sodium salt of gamma hydroxybutyrate (GHB).¹

GHB is a schedule 4 (part 1 CD Benz) controlled drug in the UK.⁷ It was first synthesized in France in 1960 as an anaesthetic and later gained popularity as a recreational drug and nutritional supplement for body building.⁸ By the early 1990s GHB had gained notoriety as a substance of abuse at raves, the popular all-night dance parties. Those who took the drug claimed to experience disinhibition, sexual arousal and euphoria similar to that associated with alcohol, but without the hangover effect.⁹

GHB (also known Liquid Ecstasy¹⁰) has also been implicated in drug-facilitated sexual assault, as a "date-rape" drug.^{9;11} It is odourless and colourless but may have a distinct salty taste. When combined with alcohol the sedative effects are synergistic.¹⁰ After inducing an anaesthetic-like sleep the person who has taken GHB does not have the ability to consent or refuse to take part in a sexual act.¹¹ GHB can be mixed with a number of drinks, exerts its effect within 15 minutes¹⁰ and has drugging effects lasting up to 8 hours.¹¹ Of 1,179 specimens collected from victims of alleged assault, 38% were positive for alcohol, 8% for benzodiazepines and 4% for GHB: although flunitrazepam has the reputation of being the date-rape drug, in a study of 578 date rape victims GHB was found six times more frequently than flunitrazepam in urine samples.¹⁰

Table 1: Symptoms of narcolepsy⁴

Symptoms of narcolepsy	
Excessive daytime sleepiness (EDS)	<ul style="list-style-type: none"> • Daytime sleep episodes occurring at inappropriate or unexpected times. • Has major social implications • First clinical symptom to emerge.
Cataplexy	<ul style="list-style-type: none"> • Abrupt, reversible decrease in muscle tone caused by emotion, such as laughter, elation or anger. • Reported by ~75% of narcoleptics. • Mainly affect facial/neck muscles (sagging jaw, inclined head, slurred speech). Can also affect extremities (e.g. buckling of knees). • Complete cataplexy (sudden and severe loss of muscle tone causing collapse to the ground) is experienced by ~1/3 of narcoleptics with cataplexy. • Attacks can last up to 30 minutes.
Sleep paralysis	<ul style="list-style-type: none"> • Inability to move for seconds to minutes during sleep onset or offset. • Breathing is unaffected but patients are unable to move their extremities, or speak. • Up to 80% of narcoleptics report sleep paralysis episodes.
Hypnagogic hallucinations	<ul style="list-style-type: none"> • Occur during the transition between waking and sleep, and in addition to nocturnal sleep onset, may occur during daytime naps or sleep attacks. • Often bizarre or frightening visual experiences but may also have auditory or other sensory involvement. • Patients are aware they are hallucinating and remain conscious of their surroundings. • Experienced by nearly 70% of narcoleptics.
Automatic behaviours	<ul style="list-style-type: none"> • Experienced by ~50% of narcoleptics. • Occurs when sleep has partially overtaken the brain but body continues to perform familiar tasks with complete retrograde amnesia. • Brief lapses during conversation or routine activities, such as walking or driving.
Other	<ul style="list-style-type: none"> • Symptoms have negative impact on the quality of life of patients. • Risk of serious motor accidents is real. • Fear of public embarrassment and injury resulting from cataplexy episodes, resulting in suppressed emotions to lessen the attacks. • May be viewed as poorly motivated or depressed. • Secondary psychological symptoms such as alienation, shame, low self-esteem or depression.

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Sodium oxybate

The formal development of sodium oxybate for the treatment of cataplexy began in 1994 by Orphan Medical Inc.⁹ Sodium oxybate is metabolised to GHB, which occurs naturally in vivo as a metabolite as well as a precursor of GABA (gamma amino butyric acid).² The mechanism of action of sodium oxybate is not fully understood but probably involves systems other than central GABAergic systems.² It has anti-cataplectic activity in patients with narcolepsy.¹²

Sodium oxybate should be taken at bedtime whilst in bed, and then again 2.5 – 4 hours later while sitting in bed. The starting dose is 4.5g a day in two divided doses (2.25g bd). This can be increased to a maximum of 9g a day in increments of 1.5g/day (0.75g/dose) at two-weekly intervals in order to evaluate clinical response and minimise side effects. The effective dose is 6 – 9g/day.¹²

In the US sodium oxybate is a Schedule III drug under the Controlled Substances Act*, and only available via the Xyrem Success Program.¹² Under this Program, sodium oxybate is made available to prescribers via a single centralised pharmacy following a number of procedures. Both the prescriber and the patient must sign that they have read the supplied educational material explaining the risks and proper use of the drug. The patient is then supplied with sodium oxybate and must provide detailed surveillance at least every three months. All serious adverse events must be reported.¹²

[* Schedule III drugs are those that have a potential for abuse less than the drugs or substances in schedules I and II, and it has a currently accepted medical use in treatment in the US. Abuse of it may lead to moderate or low physical dependence or high psychological dependence. Other Schedule III drugs include amphetamines, methylphenidate and anabolic steroids.¹³]

Pharmacokinetics

Sodium oxybate undergoes significant hepatic first-pass metabolism. In patients who have compromised liver function, the starting dose should be halved as the elimination half life is increased. No dose adjustment is required in

patients with renal insufficiency, as less than 5% of the dose is renally excreted.¹²

Sodium oxybate is rapidly absorbed with an absolute bioavailability of ~25%. Absorption is delayed and decreased by a high fat meal: patients should eat several hours before taking the first dose. The average time to peak concentration after oral administration is 0.5-1.25 hours. The half life is 0.5-1 hour and blood levels increase 3.7-fold when the dose is increased from 4.5g to 9g.¹²

Precautions and contraindications

Due to its rapid onset of CNS depressant effects sodium oxybate should only be taken at bedtime and whilst in bed. Patients should not take alcohol whilst taking sodium oxybate and should also be warned against the concurrent administration of sedatives or other CNS depressants.¹²

In clinical trials 9% of patients experienced either a single episode or sporadic nocturnal urinary incontinence. Less than 1% of patients discontinued due to incontinence, which occurred at all doses tested. Sleepwalking has also occurred during trials (in 7% of patients) but refers to confused behaviour occurring at night and, at times, associated with wandering. It is unclear whether some or all of the episodes corresponded to true somnambulism or to any other specific medical disorder. All episodes should be fully evaluated.¹²

Sodium oxybate contains 0.5g of sodium in a 3g dose and 1.6g in a 9g dose. This should be taken into account in patients with heart failure, hypertension or compromised renal function.¹²

Sodium oxybate should not be used in patients with succinic semialdehyde dehydrogenase deficiency. It should also not be used in combination with sedative hypnotics or other CNS depressants.¹²

Adverse events

The most common adverse events seen in the trials were headache (25% of patients), nausea (21%), dizziness (17%), pain (16%), somnolence (13%), pharyngitis (11%) and infection (10%). Others included diarrhoea (8%), urinary incontinence (8%), vomiting (8%), nervousness (7%), confusion (7%), sleepwalking

(7%), depression (6%) and abnormal dreams (6%). In the trials 13% of patients discontinued due to adverse events, with the most common reasons being nausea (2%) and headache (1%).¹²

Abuse potential

Although sodium oxybate is metabolised into GHB, there are less expensive, albeit illicit, sources. It is judged to have moderate potential for abuse and diversion.²

Sodium oxybate was not specifically studied in trials for its abuse potential, although illicit use and abuse have been reported. The onset of the effects of sodium oxybate (sedative-hypnotic) is rapid and makes it a desirable drug of abuse or misuse. When combined with alcohol the effects have been proven to be dangerous to the voluntary and involuntary (assault victim) user.¹²

Clinical efficacy

Scrima et al¹⁴ evaluated the use of gamma hydroxybutyrate (GHB) in a small double-blind, placebo-controlled, crossover trial (n=20) in patients, aged between 16 and 65 years of age, with narcolepsy. The trial was in five stages:

- Baseline (14 days)
- First treatment (29 days)
- First washout (6 days)
- Second treatment (29 days)
- Second washout (6 days)

Patients took 25mg/kg GHB at bed time and 25mg/kg 3 hours later. No alcohol, sleeping pills or central nervous stimulants were taken during the study and caffeine-containing drinks were not taken after 6pm. Each subject had an 8-hour polysomnogram on the last night of the baseline period and on the first and last nights of both of the treatment periods (starting at the usual bedtime, immediately after taking the dose). Multiple sleep latency tests (MSLT) were performed the day following each polysomnogram. Methylphenidate was not allowed after 5pm on the days of the polysomnogram or on the following day until after the MSLTs were completed; otherwise up to 30mg/day was allowed.

The use of GHB was associated with improved sleep depth and continuity. Patients taking GHB (day 1 and 29, vs. placebo) had decreased light sleep (stage 1) (p=0.012), increased stage 3 (p=0.008) and increased delta (deep) sleep (stages 3 and 4) (p=0.049). They also had longer sleep latency (p=0.029), few sleep stage shifts (p=0.002), significantly fewer awakenings (p=0.006) but significantly increased minutes of wakefulness (p=0.040). In the last two hours of sleep there was a significant decrease in sleep efficiency (p=0.017) and significant increase in wakefulness (p=0.019). There would be little influence of GHB on the last two hours of the eight hour polysomnogram since it is only detectable in the blood for 2.5-3 hours after administration. The number of nocturnal myoclonus arousals was reduced but not the number of nocturnal myoclonus events.

The results of the MSLT data indicate that GHB causes a decrease in objective sleepiness. By day 29, wakefulness was significantly increased. Females (n=10) had significantly fewer REM naps whilst taking GHB compared with placebo on day 29 (p=0.020) but not on day 1. No difference was seen in males (n=10). There were no significant treatment effects on non-REM sleep.

It has been suggested that some treatments for narcolepsy may improve the quality of alertness for patients without altering their propensity for sleep. GHB might decrease the patients' tendency for sleep without improving their state of alertness. It is possible that higher doses or longer treatment periods are needed to cause a more pronounced and subjectively noticeable decrease in sleepiness in patients with narcolepsy. In this small study the results support the theory that GHB reduces REM sleep and improves night-time sleep in narcoleptics.

A double-blind, placebo-controlled trial was carried out by the **US Xyrem Multicenter Study Group¹⁵** in order to evaluate and compare the efficacy and safety of three doses of sodium oxybate and placebo for treating the symptoms of narcolepsy. Patients aged 18 years and older with a diagnosis of narcolepsy for at least 6 months based on the American Sleep Disorders Association criteria and a valid polysomnogram within the previous 5 years were eligible for trial entry (n=136).

The trial was divided into a number of phases:

- Gradual withdrawal from medications previously used to treat cataplexy symptoms to avoid rebound phenomena, over a 4 week period. Stimulant medication could continue provided stable doses were used five days prior to baseline and until the end of the trial. Of 136 patients, 113 remained on stimulants.
- A five day washout period, or five times the half-life of the discontinued medication up to 28 days, which was longer. Daily diary use (to record number of cataplexy attacks, nocturnal awakenings, total amount of sleep each night, number of hypnagogic hallucinations, incidence of sleep paralysis and adverse events) was started in this period.
- A four week treatment period in which patients received 3g, 6g or 9g sodium oxybate or placebo, without any dose titration. The dose was given in two equally divided doses at bedtime and 2.5-4 hours later. This was followed by a 3-5 day washout period.¹⁶
- Patients could then enter a long-term open label study after completing this double-blind phase.

The primary efficacy variable was the change in frequency of cataplexy attacks and analysis from baseline to endpoint was carried out on the intention-to-treat (ITT) population. No power calculation was carried out. Day-time somnolence was assessed with the Epworth Sleepiness Scale (ESS) at baseline and endpoint. Overall disease severity was assessed with the Clinical Global Impression of Severity (CGIS) and the change in severity was assessed with the Clinical Global Impression of Change (CGIC). For all measures a level of significance was established at $p < 0.05$.

Results are shown in table 2. The median change in the number of cataplexy attacks was significant across the doses ($p = 0.0021$), indicating a dose related effect. The median change from baseline to endpoint was only significant in the 9g group (see table 2 for further details on the 6g group). The greatest improvement in the reduction in the number of cataplexy attacks occurred during the first two weeks of therapy. The reduction in the ESS score in the 9g group indicated that for some patients at this dose the

subjective measure of sleepiness fell into the normal range (< 10). In the 9g group 24 of 30 patients (80%) were either 'much improved' or 'very much improved' after 4 weeks of therapy, compared with 11 out of 34 (32.4%) in the placebo group. There were significant improvements across the treatment groups with respect to sleep paralysis and hypnagogic hallucinations ($p = 0.05$) but these were not significant compared with placebo.

Most of the adverse reactions occurred during the first few days of treatment and decreased over time. Ten of the 16 patients who withdrew from the trial did so because of adverse effects. A number of adverse events were believed to be related to sodium oxybate and occurred in a dose related fashion. Nausea and vomiting occurring significantly more frequently in the sodium oxybate groups than placebo (19 vs. 2, $p = 0.0045$ and 6 events vs. 0, $p = 0.0475$ respectively). Dizziness and urine incontinence events also occurred more frequently in the sodium oxybate groups (30 events vs. 2, $p = 0.0178$, and 7 events vs. 0, $p = 0.0143$).

During the washout period at the end of the trial there was an increase in the number of attacks of cataplexy in each treatment group, including placebo. A significant increase was seen in the 6g group where the median number increased from 8 to 16.3 ($p = 0.0001$) but did not approach the mean baseline value of 23. A similar change was seen in the 9g group, with an increase from 8 to 14 ($p = 0.0017$, baseline median 23.5).

Overall clinical improvements in the symptoms of narcolepsy, which were statistically significant in the 9g group (and in the 6g group when the single patient who experienced an increase in the number of attacks was removed), were seen when sodium oxybate was given at a twice nightly dose. Day-time somnolence as well as inadvertent naps/sleep attacks was improved in the 6g and 9g groups. These improvements occurred whilst the patients were on stable doses of stimulant medications. The adverse events, which occurred at a greater frequency at higher doses, occurred at the beginning of the study and abated over time.

Table 2: Baseline to endpoint changes¹⁵

Variable	Placebo (n=34)	3g (n=34)	6g (n=33)	9g (n=35)
Median change in weekly cataplexy attacks	-4.3	-7.0	-9.9*	-16.1 (p=0.0008)
Median % change from baseline for cataplexy attacks per week	-28	-49	-49	-69 (p=0.0008)
Epworth Sleepiness Scale (ESS)	ESS improved in all treatment groups, becoming significant at the 9g dose (p=0.0001 when compared with placebo). Median score at 9g fell from 17.0 to 12.0.			
CGIC	Significance difference across the doses was seen (p=0.0014). Dose related responses became significant at 9g (p=0.0002).			
Reduction in number of inadvertent naps	Significant reduction with both 6g (p=0.0497) and 9g (p=0.0122) doses. 9g dose also produced significant decrease in nocturnal awakenings (p=0.0035).			
Sleep paralysis	Incidence ranged from 74%-76%			
Hypnagogic hallucinations	Incidence ranged from 74%-85%			
* One patient experienced 249 attacks at baseline which rose to 332 and 346 after 2 and 4 weeks of therapy (REM re-bounce following discontinuation of prior anticataplectic medication). When the data was re-evaluated and this patient removed, the median number of cataplexy attacks was 7.75 (p=0.0327).				

The **US Xyrem Multicenter Study Group** then evaluated the long-term safety and efficacy of nightly sodium oxybate in 118 of the patients from the previous study in a 12 month, open-label extension.¹⁶ Protocol amendments allowed patients to continue in the study for up to 24 months. Efficacy measurements included reports of the change in frequency of cataplexy, attacks, daytime sleepiness, frequency and duration of inadvertent naps or sleep attacks, number of nocturnal sleep awakenings, total amount of sleep, incidence of hypnagogic hallucinations and sleep paralysis.

Treatment of 6g sodium oxybate nightly (in two divided doses) was started after a 3-5 day washout period at the end of the previous double-blind trial. Doses could be increased or reduced according to effectiveness or adverse events, at two-weekly intervals in 1.5g increments. A stable dose of stimulant medication was allowed during the duration of the trial. Concomitant stimulant medications, such as methyl-

phenidate, amphetamines, pemoline and mazindol, were taken by 104 of 118 patients. Efficacy was measured using the ESS, the CGIS and the CGIC. Clinical response information was recorded in personal diaries on a daily basis, including data on the frequency of cataplexy events, number and duration of hypnagogic hallucinations and the incidence of sleep paralysis. Patients were assigned to a treatment group by calculating the average dose used over the study period and rounding to the nearest dose category (3/4.5/6/7.5/9g).

Out of 118 patients, one was excluded due to failure to return diary information and 80 (68.4%) completed the entire 12 months of the study period. Ninety five patients (81.2%) completed three months and 87 (74.4%) completed six months of the study. Eight-six out of the 117 patients reached a stabilised dose (no dose change for at least three consecutive visits [fortnightly visits for two months, then every two months]). Results are in table 3.

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Table 3: results from the 12 month open label study¹⁶

Event	Results
Cataplexy	Number of attacks decreased after one month by an average of 23.65 per week from baseline ($p < 0.001$) and by 35.48 per week at the end of the study period.
Daytime sleepiness	Significant reduction at one month for all but 4.5g group. Overall improvement maximal after 2 months ($p < 0.001$) and significant across all doses. Approximate 30% decrease in mean score.
CGIC	~80% had positive response after 2 months (much or very much improved) – maintained during course of study.
Daily sleep attacks	Change = -0.77 (± 1.28) after one month and -1.03 (± 1.29) after 12 months.
Mean duration of sleep	-20.17 mins (± 39.0) at one month, -29.64 mins (± 47.74) at 12 months.
Hypnagogic hallucinations	Change from baseline was -0.48 (± 1.83) at one month to -0.78 (± 2.38) at endpoint. (not significant)
Sleep paralysis	Change from baseline was -0.38 (± 0.95) at one month to -0.51 (± 1.29) at endpoint. (not significant)

The most commonly reported adverse events were headache, nausea, viral infection, dizziness ($p < 0.05$), pain, enuresis and somnolence. Adverse events occurred in at least 10% of patients for any one of the five average doses during the 12 months. No deaths occurred during the study. Eleven patients chose to discontinue study medication due to adverse effects during the first 12 months of the study.

The data from this study shows that sodium oxybate use was associated with significant and maintained clinical improvement in the frequency of cataplexy attacks and reduced daytime sleepiness. Maximal effects were seen in general after two months of therapy and were maintained. Concomitant stimulant medications were taken by 103 out of the 118 patients in the study, making the reduction in daytime sleepiness more noteworthy. Although the clinical improvements in hypnagogic hallucinations and sleep paralysis were not statistically significant,

they did continue throughout the study. No evidence of tolerance to the effects of sodium oxybate was seen.

The **US Xyrem Multicenter Study Group** carried out a double-blind study to establish the long-term efficacy of sodium oxybate for the treatment of cataplexy with narcolepsy.¹⁷ Patients over the age of 16 years with a current diagnosis of narcolepsy based on the American Academy of Sleep Medicine criteria, and who had a history of five or more cataplexy attacks a week, before any treatment for cataplexy, were entered into the trial ($n=55$).

Study participants were drawn from a pool of patients who had undergone continuous sodium oxybate treatment for at least 6 months (range 7-44 months, mean 21 months) in a long-term, open-label safety trial. Doses that the patients were stabilised on ranged from 3g to 9g nightly (doses were given in equally divided doses upon retiring and then 2.5 to 4 hours later, i.e. 1.5g to 4.5g twice nightly).

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The study was divided into two phases¹⁷:

- Phase 1 was the initial 2 weeks of the study during which the patients continued to take sodium oxybate in a single-blind manner, using the same twice nightly doses as in the open-label study. Daily diaries were used to record attacks of cataplexy and adverse events.
- Phase 2 consisted of a 2 week period when half of the study patients were assigned to continue active treatment (n=26) and the other half were assigned placebo (n=29), in a double-blind fashion. Two weeks was considered adequate to detect a significant change in the frequency of cataplexy attacks without imposing undue hardship on the participants. Daily diary use was continued.

Cataplexy was defined in this trial as sudden, bilateral loss of voluntary muscle control, usually triggered by emotions such as laughter, anger or surprise, of sudden onset and localised to specific muscle groups or parts of the body. The patient should have been aware of the time and place the event occurred.¹⁷

The primary efficacy variable was the change in the number of weekly cataplexy attacks from the baseline to the double-blind phase. Statistical analysis was carried out on the intention-to-treat population. A power analysis indicated that 22 patients per group would have 80% power to detect a 40% difference in increase of cataplexy attacks between the treatment groups at a significance level of

0.05%.¹⁸

In the sodium oxybate group there was no median change in the number of cataplexy attacks between phases 1 and 2. However, in the placebo group the number of cataplexy attacks increased significantly more during the same period ($p < 0.001$), (see table 4). Patients who were previously stabilised on doses of 6-9g at night and who were randomised to receive placebo experienced an increase of 15 or more cataplexy attacks during the double-blind phase.¹⁷

Treatment-emergent adverse events were not expected to be prevalent as patients had been stabilised on their therapy before trial entry. No adverse event led to discontinuation and none were serious. Only 17 patients reported an adverse event. One patient taking placebo suffered from a broken wrist which was thought to have been due to a cataplectic attack.¹⁷

This was the first placebo-controlled trial to examine the long-term efficacy of sodium oxybate for the treatment of cataplexy in patients with narcolepsy. The results demonstrate that after stabilisation on sodium oxybate therapy, abrupt withdrawal leads to a gradual increase in the number of cataplexy attacks. There was no evidence of an acute withdrawal syndrome upon abrupt discontinuation, indicating a lack of physical dependence.¹⁷

Table 4: Changes in number of attacks of cataplexy¹⁷

	Sodium oxybate (n=26)	Placebo (n=29)
Baseline weekly attacks, mean (range)¹⁷	9.9 ± 21.4 (0-93)	15.8 ± 39.9 (0-197)
End period 1, mean (range)¹⁷	12.8 ± 33.5 (0-158)	46.4 ± 73.8 (0-250)
Median number at week 1, phase 2¹⁷	Not stated	4.2
Median number at week 2, phase 2¹⁷	Not stated	11.7

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The **Xyrem International Study Group**¹⁹ measured the effect of sodium oxybate in 228 patients. Their hypothesis was that the administration of sodium oxybate to patients with narcolepsy nightly for 8 weeks would demonstrate greater efficacy for the treatment of cataplexy compared to a previous 4 week study. This is the largest study conducted with sodium oxybate for the treatment of cataplexy.

Patients over the age of 16 years with a positive history of narcolepsy based on an overnight polysomnogram and multiple sleep latency test within the last 5 years, plus current symptoms of narcolepsy with excessive daytime sleepiness and cataplexy, were included in the trial. Diaries were used to collect daily information about narcolepsy symptoms, trial and concomitant medication use and adverse events.

After a 14 day lead-in period, during which patients recorded symptoms and adverse events in daily diaries, they were then gradually withdrawn from tricyclic antidepressants, SSRIs or any other medication used for the treatment of cataplexy, during a 21-day withdrawal period. This was followed by a washout period lasting 5 days or 5 half-lives of the discontinued drug, whichever was longer, but not exceeding 18 days. Patients were then randomised to receive either sodium oxybate liquid (500mg/ml) or a placebo solution. Medication was administered in two divided doses each night: the first dose was taken immediately before going to sleep and the second dose was taken 2.5 to 4 hours later (woken by alarm clock).

During the 14 day baseline period all patients received placebo. In order to continue to the double-blind phase they must have experienced at least 8 cataplexy attacks during this time: 59 patients were randomised to placebo and 169 to sodium oxybate 4.5g per night. After 7 days 64 patients continued with 4.5g/night and 105 had their dose increased to 6g/night. After another 7 days 58 patients remained on 6g/night and 47 had their dose in-

creased to 7.5g/night. After a further 7 days these patients had their dose increased to 9g/night. After this 4-week dose titration phase patients continued on their final dose for another 4 weeks.

The ITT population was 228 patients who received at least one dose of study medication. For those who did not complete the study the last-observation-carried-forward technique was used. Results are in table 5. At baseline patients were experiencing a median 18.54 weekly cataplexy attacks, which were untreated in 70% of them. Stimulants were used by 80% of patients.

Even though patients taking placebo exhibited a decrease in the number of cataplexy attacks, the improvements seen in the sodium oxybate group were greater at all doses.

Significant improvements in the incidence of hypnagogic hallucinations or sleep paralysis in this patient group were difficult to achieve due to the low baseline frequency of these symptoms. Although there were suggestions of improvement it was only sleep paralysis in the 6g group which was significantly improved ($p=0.005$).

Nausea and dizziness were among the most frequent adverse events and were dose-related. Two of the six serious adverse events were thought to be related to study medication: abnormal ALT and AST levels which decreased over a period of 8 months following discontinuation of study medication in one patient, and in another patient a fractured ankle following an accidental fall occurring 3 hours after the first nightly dose.

This was the largest trial examining the effects of sodium oxybate on the frequency of cataplexy attacks. Improvements were significant at all doses used. The reduction in the number of attacks is both time- and dose-dependent.

Table 5: results from the International Study-Group study

Variable	Placebo (n=58)	4.5g (n=64)	6g (n=58)	9g (n=47)
Median % decrease in cataplexy attacks after 4 weeks	13.8%	44.3% $p=0.006$	51.9% $p<0.001$	61.8% $p<0.001$
Final median % decrease in cataplexy attacks after 8 weeks	21.3% $p=0.02$	57.0% $p<0.001$	65.0% $p<0.001$	84.7% $p<0.001$

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Withdrawal effects

The US Xyrem Multicenter Study Group explained the lack of withdrawal effects in this group of patients in greater detail.¹⁸ There have been reports of a severe withdrawal phenomenon following abrupt cessation of GHB, taken illicitly as a drug of abuse.

Withdrawal has been associated with the chronic use of GHB, with dosing frequency ranging from every 30 minutes to 3 hours, dosing duration of 6 months to 4 years and total daily doses ranging from 25g to 144g. Mild withdrawal has been characterised as anxiety, tremor and insomnia, while severe withdrawal has been described as autonomic instability, psychosis and delirium. Reported symptoms have included nausea, vomiting, agitation, anxiety, confusion, tremor, delirium, psychosis and auditory and tactile hallucinations. Some cases involved polydrug abuse.

When the adverse events of the trial described previously⁽¹⁷⁾ were analysed, few patients experienced adverse events that could be considered possible symptoms of a withdrawal phenomenon. Two reported

anxiety and one each reported insomnia, dizziness and somnolence. These symptoms are consistent with the return of narcolepsy symptoms due to the termination of sodium oxybate therapy.

The elimination half life of sodium oxybate is short (0.5-1 hour) and patients with narcolepsy who administer nocturnal doses of medication to themselves awaken with minimal or no measurable plasma oxybate until their next night-time dose. This contrasts to reports of GHB withdrawal that have been associated with increasing doses and increasing drug frequency, until some reported users were taking it round-the-clock. There appears to be little likelihood of dependence or withdrawal even though the length of exposure of patients in the study (7-44 months) was similar to cases of withdrawal reported following chronic GHB abuse (2-36 months).

Two studies have been published in abstract format only and are described in table 6 overleaf. One showed that improvements in the patients' quality of life were associated with reductions in the number of cataplexy attacks.

Cost implications

The prevalence of narcolepsy with cataplexy in European populations has been estimated at 3-5 per 10,000.³

Drug	Dose	Cost/28 days
Sodium oxybate*	Effective dose is 6g to 9g/day	The cost in the US is approximately \$6000-\$7500 ²² (~£3360 - £4200) per year, which equates to ~£257 - £322 / 28 days. NB: UK price may not match US price.
Clomipramine†	10-75mg/day for cataplexy associated with narcolepsy	10mg capsules: £1.76 25mg capsules: £2.27 50mg capsules: £3.73 75mg MR capsules: £8.83 (Anafranil SR)

* Price based on conversion rate of £1 = \$1.78, 30/8/05 (<http://today.reuters.co.uk/Investing/Currencies.aspx?src=dg>)

† Basic NHS prices (Drug Tariff October 2005 http://www.ppa.org.uk/edt/October_2005/mindex.htm).

Modafinil and dexamfetamine are licensed for the treatment of daytime sleepiness associated with narcolepsy, and not cataplexy associated with narcolepsy.

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Table 6: Details of studies published in abstract format only.

Reference	Trial design	Results
Montplaisir et al²⁰	<p>Nightly doses of 4.5g, 6g, 7.5g and 9g each evaluated for 2-4 weeks, after a 4-week washout period of all anti-cataplectic medications.</p> <p>4.5g given in 2 divided night-time doses for first 4 weeks, followed increases at 2-weekly intervals to 6g, 7.5g and 9g.</p> <p>Stimulants for daytime sleepiness continued at stable doses.</p> <p>Efficacy measures: Maintenance of Wakefulness Test (MWT) (quantifies ability to resist falling asleep). Epworth Sleepiness Scale (ESS).</p> <p>The change in number of cataplexy attacks was not measured.</p>	<p>21 patients completed the full study.</p> <p>MWT – average sleep latency increased from 4.5 mins at baseline to 8.2 mins after 4.5g and 10.6 mins after 9g.</p> <p>Sleep onset REM recorded for 86% of patients at baseline, 62% after 4.5g dose and 30% after 9g dose.</p> <p>Mean ESS total score was 19.8 at baseline. Decreases were 2.4 (4.5g), 3.8 (6g), 4.8 (7.5g) and 5.8 (9g).</p> <p>Dose-related objective and subjective improvements in excessive daytime sleepiness (EDS) in patients already taking stimulants for EDS.</p>
Hayduk et al²¹	<p>Impact of treating patients with narcolepsy with sodium oxybate on patient quality of life was evaluated with the SF-36 Survey questionnaire, administered in conjunction with a 6 month open-label trial of sodium oxybate (3g-9g titrated to optimal efficacy).</p> <p>SF-36 questionnaire has 8 different scales corresponding to various facets of the patients quality of life [physical functioning; role limitations – physical; bodily pain; general health; vitality; social function; role limitations – emotional; mental health].</p>	<p>Nightly administration of sodium oxybate significantly decreased the incidence of cataplexy.</p> <p>A statistically significant improvement was seen in every SF-36 scale ($p < 0.05$) except bodily pain ($p = 0.088$).</p> <p>Improvements in quality of life were associated with significant reductions in cataplexy attacks and other symptoms of narcolepsy.</p>

This document reflects the views of the LNDG. Orphan Medical Ltd have commented on this review.

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