New Medicine Recommendation

Sodium Oxybate Oral Solution 500mg/ml (Xyrem®)

For Treatment of Narcolepsy with Cataplexy

Recommendation: Black

Sodium oxybate is not recommended for use as a treatment of narcolepsy with cataplexy. The evidence demonstrates sodium oxybate's efficacy when used for the treatment of narcolepsy with cataplexy. There are however significant concerns, as follows:

- The only UK based cost effectiveness estimate, which was provided by the SMC, estimated sodium oxybate's cost per QALY to be between £49,590 and £65,980. These figures and concerns that the potential costs of adverse events are not included in the costing model and that the clinical resource savings may not be realised, led the SMC to conclude that the drug was not cost effective. [1]
- Safety issues and side effects, particularly respiratory depression are significant [2]
- Sodium oxybate is a schedule 2 Controlled Drug with an abuse potential [3]

Summary of supporting evidence:

- Eight RCT studies have been published and two systematic reviews and meta-analyses are available to support sodium oxybate
- The eight published RCT studies are derived from data of only four study populations

Efficacy

- In 2002, a multi-centre, 136 patient, double blind trial, cataplexy attacks reduced from a median of 21 per week at baseline to 11.8 per week for the 9 g sodium oxybate group [4]
- In 2004, a double blind, 55 patient withdrawal study, of patients who had their sodium oxybate replace with placebo showed increased weekly cataplexy attacks from the treatment 'baseline' of 15.8 to 46.4, equivalent to an increase of 30.6 attacks per week. This contrasts with the group continuing on sodium oxybate where attacks rose by 2.9 per week. [5]
- In 2005, a 228 patient double blind, placebo controlled study, showed that Epworth sleepiness scale scores reduced from 18 to 15 in the 6g sodium oxybate group and from 19 to 12 in the 9g group (both $p < 0.001$) (normal < 10). Patients receiving the 9gram dose of sodium oxybate, but not the 4.5g or 6g groups, displayed a median increase of 10minutes in the maintenance of wakefulness test (MWT) ($p < 0.001$) [6]
- In 2005 an additional analysis of the study group from 2005, above, [6] showed that the frequency of cataplexy attacks reduced by a median for each dose group of: 4.5gram 57% ($p = 0.003$), 6gram 65% ($p = 0.002$) and 9gram 84.7% ($p < 0.001$). The within-group change in cataplexy between weeks four and eight of treatment was only significant for the 9gram sodium oxybate group when compared to placebo (weekly numbers of cataplexy attacks 17.79 at baseline, 8.00 at week four and 3.00 at week eight; $p < 0.001$ compared to placebo). [7]
- In 2006, a second additional analysis was performed on the data from the 2005 study, above. [6]. The primary outcome was the Functional Outcomes of Sleep Questionnaire (FOSQ). Compared to placebo, the group treated with 9.0gram sodium oxybate had

significant improvement in all FOSQ categories at the end of the study except for intimacy and sexual relationships ($p < 0.001$). A dose related effect was observed increasing from 6.0gram to 9.0gram. [8]

- In 2010, there was a third additional analysis using data from 2005 study, above. [6] A median increase of 52.5minutes of stage three and four sleep was observed in the group receiving 9gram sodium oxybate ($p < 0.001$ compared to placebo). A dose related reduction in nocturnal awakening was also observed; -8.00 ($p = 0.005$ compared to placebo) and -12.00 ($p = 0.009$ compared to placebo) for the 6gram and 9gram groups respectively. [9]
- In 2006, a 231 patient, double-blind, placebo-controlled, multicentre study investigated the effectiveness of sodium oxybate therapy, modafinil therapy and the combination of the two for excessive daytime sleepiness (EDS).
  - for 20-minute MWT score, the placebo/placebo group averaged 6.87minutes after 8 weeks, compared with 11.97minutes for sodium oxybate/placebo ($p < 0.001$) and 13.15minutes for sodium oxybate/modafinil ($p<0.001$).
  - In the sodium oxybate group, sleeps attacks decreased from a mean of 10.05 (SD +/- 12.9) at baseline to 7.10 (+/- 9.1) by the end of the study ($p < 0.001$) and the sodium oxybate/modafinil group demonstrated a decrease from 11.82 (+/- 11.3) to 5.55 (+/- 5.9) ($p < 0.001$).
  - In the placebo/placebo group sleep attacks increased from a mean of 15.23 (+/- 19.7) at baseline to 19.75 (+/- 32.6) by the end of the study. [10]
- In 2009, an additional analysis of the 2006 study, above, showed [10]:
  - compared to placebo the sodium oxybate/placebo and sodium oxybate/modafinil groups each demonstrated increases in total non-REM sleep (for both $p < 0.001$) in stages three and four ($p < 0.001$).
  - compared to placebo no changes in sleep composition were observed in the modafinil group.
  - Patients treated with sodium oxybate/modafinil showed an increase in the MWT score compared to baseline modafinil treatment, whereas patients that received either sodium oxybate or modafinil alone did not. [11]
- A 2012 systematic review and meta-anaylsis was conducted to evaluate the effectiveness of sodium oxybate on the clinical and neurological features of narcolepsy. [12] The anaylsis found that:
  - Compared to placebo, sodium oxybate (4.5gram per night) significantly reduced cataplexy attacks (median -8.5 95% CI -15.3 to -1.6; two of four trials) measured using participant diaries
  - Compared to placebo, sodium oxybate 9gram at night significantly increased wakefulness (median increase 5.18, 95% CI 2.59 to 7.78; two trials), and significantly increased the proportion of patients who were much improved or very much improved as measured on the Clinical Global Impression of Change (median 2.42, 95% CI 1.77 to 3.32; three trials).
- The Centre for Reviews and Dissemination (CRD) at the University of York published a critical abstract of the analysis reported above, concluding that the review was generally well conducted, but given the limited evidence base and uncertain long-term effects of sodium oxybate, the authors' conclusions should be interpreted with caution as the findings may not be reliable. [13]

Safety

- Sodium oxybate has an abuse potential and is classified as a Schedule 2 Controlled Drug

[14]

- The US Federal Drug Administration approved sodium oxybate for the treatment of cataplexy associated with narcolepsy in 2002 with provision of a risk management programme (RMP) to mitigate the risks associated with the use of sodium oxybate both historically as a drug of abuse or potential co-administration with CNS depressants. It places additional controls on supply and patient/prescriber education. [15]
- Xyrem (sodium oxybate) has a black box warning in its SPC as follows: 'Xyrem has the potential to induce respiratory depression' [2]
- Apnoea and respiratory depression have been observed in a fasting healthy subject after a single intake of 4.5 g. Patients should be questioned regarding signs of Central Nervous System (CNS) or respiratory depression. Special caution should be observed in patients with an underlying respiratory disorder. Because of the higher risk of sleep apnoea, patients with a BMI ≥40 kg/m^2 should be monitored closely when taking sodium oxybate. [2]
- A randomised, 4-way crossover safety study for sodium oxybate which was conducted in accordance with a post-marketing safety commitment by the manufacturer. 42 patients completed the study. [16]
  - The number of central apnoeas at baseline was 4.5 +/- 10.1 and was significantly higher following sodium oxybate and sodium oxybate/modafinil (11.7 and 9.4 respectively; p = 0.0054) compared to both zolpidem and placebo.
  - Mean apnoea-hypopnea index (AHI)[1] at baseline was 24.7 +/- 9.2 and the mean change from baseline was not significantly different among treatments.
  - Comparison of oxygen SATS between the treatment groups showed no significant difference. [16]
- There are two further case reports that associate the use of sodium oxybate and de-novo sleep apnoea in the literature. [17] [18]
- In 2009 Zvosec et al published a case report of three deaths that had been associated with the use of sodium oxybate, one of which was associated with overdose. All 3 cases included concomitant CNS active drugs. [19]
- Adverse effects from the illicit use of sodium oxybate have included: vomiting, drowsiness, hypotonia, respiratory depression and involuntary movements. Seizure-like activity, bradycardia, hypotension and respiratory arrest have also been reported. Deaths have been reported in several countries. The severity of symptoms following the illicit use of sodium oxybate is dependent on dose and, usually, the co-ingestion of other drugs such as alcohol and benzodiazepines. [20]

[1] AHI relates to number of pauses in breathing per hour of sleep; normal score < 5

Details of Review

Name of medicine (generic & brand name)**:**

Sodium Oxybate Oral Solution 500mg/ml (Xyrem®)

Strength(s) and form(s):

Oral solution 500mg/ml

Dose and administration:

Over 18 years, initially 2.25 g on retiring and repeated 2.5–4 hours later, increased according to response in steps of 1.5 g daily in 2 divided doses at intervals of 1–2 weeks; max. 9 g daily in two divided doses.

BNF therapeutic class / mode of action

4.1.1 Hypnotics. Central nervous system depressant.

Licensed indication(s):

Treatment of narcolepsy with cataplexy in adult patients. Treatment should be initiated by and remain under the guidance of a physician experienced in the treatment of sleep disorders.

Proposed use (if different from, or in addition to, licensed indication above):

Patients with inadequate response to, or have developed side effects from modafinil for excessive sleepiness or antidepressants for cataplexy.

Course and cost:

18ml daily is required at the maximum and most efficacious adult dose of 9gram. 180ml = £360 [14] . A 28 day supply at the maximum dose would cost £1,008. This is equivalent to £13,104 per annum for one patient at maximum, 9g daily dose. The lowest dose is 2.25g per day costing £3,276 per year.

Current standard of care/comparator therapies:

Modafinil is licensed for excessive sleepiness associated with narcolepsy with or without cataplexy. Clomipramine is licensed for adjunctive treatment of cataplexy associated with narcolepsy. Dexamfetamine and methylphenidate (unlicensed indication) are listed in the Lancashire Care Foundation Trust Joint Formulary for Psychotropic Medication for the treatment of narcolepsy [21].

The European Academy of Neurology guidelines for the management of narcolepsy in adults [22] recommend the following for **excessive daytime sleepiness** and irresistible **episodes of sleep**:

- In cases when the most disturbing symptom is excessive daytime sleepiness, **modafinil** should be prescribed based on its efficacy, limited adverse effects, and easiness of manipulation.
- When excessive daytime somnolence coexists with cataplexy and poor sleep, **sodium oxybate** may be prescribed; vigilance should be held for the possible development of

sleep - disordered breathing; depressed patients should not be treated with this drug.

- **Supplementation with modafinil** is generally more successful than **sodium oxybate alone**.
- **Methylphenidate** may be an option in case modafinil is insufficiently active and sodium oxybate is not recommended.

Cataplexy:

- First line - pharmacological treatment of cataplexy is **sodium oxybate**. The drug should not be used in association with other sedatives, respiratory depressants, and muscle relaxants. Vigilance should be held for the possible development of sleep - disordered breathing, and depressed patients should not be treated with the drug.
- Second line – **tricyclic antidepressants**, particularly **clomipramine** (10 – 75 mg), are potent anticataplectic drugs.
- **SSRIs** are slightly less active but have fewer adverse effects.
- The norepinephrine/serotonin reuptake inhibitor **venlafaxine** is widely used today but lacks any published clinical evidence of efficacy.
- The norepinephrine reuptake inhibitors, such as **reboxetine** and **atomoxetine**, also lack published clinical evidence.

Relevant NICE guidance:

None

Background and context

Narcolepsy is a debilitating lifelong rapid eye movement (REM) sleep disorder. The main symptoms of this condition include: excessive daytime sleepiness (EDS) with irresistible sleep attacks, cataplexy (sudden bilateral loss of muscle tone), hypnagogic hallucinations and sleep paralysis. Other symptoms can include loss of concentration and memory. The two main groups of patients with narcolepsy are patients suffering narcolepsy with cataplexy and patients who do not suffer cataplexy. [21]

Narcolepsy is diagnosed according to the international classification of sleep disorders (ICSD-2). Diagnostic methods include a combination of history taking, polysomnography and multiple sleep latency tests alongside the measurement of hypocretin levels in cerebrospinal fluid. [21]

Conventional treatments aim to control symptoms and are not curative. Modafinil is used first line for the treatment of excessive sleepiness associated with narcolepsy with or without cataplexy. Dexamphetamine and methylphenidate (unlicensed) can also be used to treat narcolepsy. [14] None of these treatments reduce the frequency of cataplexy attacks. Antidepressants are often prescribed for patients with narcolepsy with cataplexy as an adjunct. For example, clomipramine is licensed as an adjunctive treatment of cataplexy associated with narcolepsy. [14]

Modafinil is a wake-promoting drug similar in structure to amphetamine [21] that is effective in the treatment of excessive daytime sleepiness, but not cataplexy. [23] A Cochrane review in 2010 found that there was insufficient evidence to support antidepressants for the treatment of cataplexy despite being widely used for this purpose (despite European guidelines that support use). [24] [25] The evidence supporting the use of existing combination therapy, e.g. modafinil and clomipramine, is mixed.

Sodium oxybate was licensed in the European Union in 2006 for the 'treatment of cataplexy in adult patients with narcolepsy'. [25] In 2007, the EMEA accepted an application to change the product's indication to its current wording of 'treatment of narcolepsy with cataplexy in adult patients'. [26] The precise mechanism by which sodium oxybate produces an effect on cataplexy is unknown although its effect on sleep architecture and sedative producing effects are well documented. [25] [2] In addition to its sedative properties, sodium oxybate is a potent CNS depressant and may increase growth hormone secretion. [25] [27]

Sodium oxybate has been approved for the treatment of cataplexy associated with narcolepsy in the US since 2002. However, a condition of approval was the implementation of a risk management programme (RMP). The RMP was implemented to mitigate the risks associated with the use of sodium oxybate both historically as a drug of abuse or potential co-administration with alcohol and any other CNS depressants. [28]

The pharmacokinetics of sodium oxybate are non-linear due to saturation in both absorption and elimination mechanisms. [25] The area under the plasma concentration (AUC) versus time curve increases 3.8 fold as the dose is doubled from 4.5 to 9grams. The pharmacokinetics of sodium oxybate remain unchanged despite repeated dosing. [2] Sodium oxybate is metabolised by gamma-hydroxybutyrate dehydrogenase, therefore there is potential for interaction with drugs that inhibit this enzyme e.g. sodium valproate for which a 20% dose reduction is recommended. [25] [2]

The recommended starting dose of sodium oxybate is 4.5gram per day divided into two equal doses of 2.25gram. The first is given at bedtime and the second is usually given 4 hours later. The dose should be titrated by a maximum of 1.5gram per day based on efficacy and tolerability up to a maximum of 9gram daily divided into two equal doses. A minimum of one or two weeks is

recommended between dose increments. [2]

The use of sodium oxybate as a drug of abuse significantly predates its current clinical application. Used recreationally sodium oxybate is more commonly referred to by the chemical name GHB (gamma-aminobutyric acid). It is usually supplied illicitly as the sodium salt and has been promoted for body building, weight loss, as a psychedelic substance and as a sleep aid. [20]

Summary of evidence

Summary of efficacy data in proposed use:

Eight key randomised controlled trials (RCTs) and two meta-analyses were identified for sodium oxybate. Additionally, there are several descriptive studies outlining potential safety issues.

Clinical efficacy studies were conducted by members of the US and international Xyrem Multicentre Study Groups.

The first, in 2002, was a multicentre, double-blind, placebo controlled trial evaluating the efficacy and safety of three doses of sodium oxybate and placebo for the treatment of narcolepsy symptoms. The primary outcome measure was the change from baseline in weekly cataplexy attacks. 120 of 136 patients completed the study. Participants were randomised to: sodium oxybate 3gram, 6gram, 9gram or placebo at night for four weeks. Any existing hypnotics were discontinued before study start. Stimulant medication was allowed if the dose was stable. [4]

Baseline numbers of cataplexy attacks were measured in each treatment group before receiving the study drug. At least three cataplexy attacks per week had to be recorded during the last two weeks of the baseline period. The median weekly number of cataplexy attacks was 21 (range 3 to 249). The 9gram sodium oxybate group showed greatest reduction of 11.8 cataplexy attacks per week (4.3 vs. 16.1 respectively). [4] The range of decrease in the 9gram group was 5 to 35 cataplexy attacks per week. The study concluded that sodium oxybate significantly improved symptoms in patients with narcolepsy and was well tolerated. [4]

The next RCT, published in 2004, was a double-blind treatment withdrawal study which aimed to demonstrate the long-term efficacy of sodium oxybate for the treatment of cataplexy in 55 patients with narcolepsy who had received continuous treatment with sodium oxybate for periods ranging 7 – 44months (mean 21 months). [5] Participants were a cohort selected from a previous long-term safety study. [29] The 12-month safety study was an extension of the study conducted in 2002. [4] This introduces significant population selection bias into the 2004 study and could have led to under reporting of adverse events. [29] [5]. This was rationalised by the authors who stated that the study more closely mirrored clinical practice in a way previous studies did not. [5]

The primary outcome measure was the change in number of weekly cataplexy attacks from the baseline period to the double-blind treatment phase. In the first two week phase of the study, patients continued taking sodium oxybate in a patient-blinded manner. Daily diaries were used to record the baseline frequency of cataplexy attacks. During the second phase of the study, half of the participants were randomly assigned to continue sodium oxybate at their current dose and half received a placebo administered in a double-blinded manner for two weeks. [5]

For placebo the mean number of cataplexy attacks per week increased from 15.8 to 46.4 For sodium oxybate the mean increased from 9.9 to 12.8. It was concluded that the trial provided evidence supporting the long-term efficacy of sodium oxybate for the treatment of cataplexy. [5]

A 401 patient RCT reported in 2005 was a multicentre, double-blind, placebo-controlled design.

Its objective was to assess the efficacy of sodium oxybate for the treatment of narcolepsy with an emphasis on excessive daytime sleepiness. 228 adult participants with narcolepsy with cataplexy entered the double-blind phase of the study. 21 patients discontinued the trial due to adverse events. [6]

The participants had antidepressants withdrawn and then randomly assigned to receive 4.5gram, 6.0gram or 9gram sodium oxybate at night or placebo for eight weeks. [6] CNS stimulants for the treatment of excessive daytime sleepiness (EDS) were maintained for the duration of the study. [6]

The primary outcome measure was the improvement of EDS. [6] Baseline Epworth sleepiness scale scores ranged from 17 – 19 (normal < 10) across the 4 treatment groups. The 6gram dose group reduced from a median ESS score at baseline of 18.0 to 15.0 at the end of the study ($p < 0.001$). [6] The 9gram dose group reduced from a median ESS score of 19.0 at baseline to 12.0 ($p < 0.001$). Patients receiving the 9gram dose of sodium oxybate displayed a median increase of 10minutes in the maintenance of wakefulness test (MWT), [16] significant when compared with baseline for the 9gram group and the end-of-study result for the placebo group ($p < 0.001$ for both) [6] Patients in the 4.5gram and 6.0gram groups displayed little or no significant difference in the median MWT time.

The median frequency of weekly sleep attacks decreased in a dose related fashion both compared with baseline ($p < 0.001$ for all dose groups) and against the end-of-study result for the placebo group for the 6gram and 9gram dose groups ($p < 0.001$ and 0.002 respectively). The group concluded that sodium oxybate demonstrates efficacy for the two major symptoms of narcolepsy. [6]

A study from 2005 used the same population from the third study by the same group. [6] [7] It presented efficacy data for the treatment of cataplexy. [7] At weeks four and eight of sodium oxybate treatment, the frequency of cataplexy attacks decreased from baseline. At week eight the frequency of cataplexy attacks reduced by a median for each dose group of: 4.5gram 57% ($p = 0.003$), 6gram 65% ($p = 0.002$) and 9gram 84.7% ($p < 0.001$). The within-group change in cataplexy between weeks four and eight of treatment was only significant for the 9gram sodium oxybate group when compared to placebo (weekly numbers of cataplexy attacks 17.79 at baseline, 8.00 at week four and 3.00 at week eight; $p < 0.001$ compared to placebo). [7]

Jed Black from the Stanford Sleep Disorders Clinic led the publication of three RCTs primarily focussing on the treatment of EDS and nocturnal sleep disruption with sodium oxybate. [10] [11] [9]

In 2006, Black and Houghton conducted a double-blind, placebo-controlled, multicentre study investigating the effectiveness of sodium oxybate therapy, modafinil therapy and the combination of the two for EDS in 231 patients (ITT 222) with narcolepsy previously taking modafinil (200-600mg daily). Patients were randomly assigned to one of four treatment groups:1. placebo plus placebo, 2. sodium oxybate plus placebo, 3. modafinil plus placebo or 4. sodium oxybate plus modafinil. The participants randomised to the latter two groups received their usual dose of modafinil in a blinded manner. Patients assigned to the second and fourth groups received sodium oxybate 6gram at night in two divided doses for four weeks, increased to 9gram at night for a further four weeks. [10]

For the primary endpoint of the study, which was the 20-minute MWT score, the placebo/placebo group averaged 6.87minutes after 8 weeks, compared with 11.97minutes for sodium oxybate/placebo ($p < 0.001$) and 13.15minutes for sodium oxybate/modafinil ($p<0.001$). End-of-study ESS scores were reduced compared to placebo/placebo in both the sodium

oxybate/placebo and sodium oxybate/modafinil groups (16, 12 and 11 respectively; $p < 0.001$). ESS scores decreased from baseline in the sodium oxybate and sodium oxybate/modafinil groups (15 to 12 and 15 to 11 respectively; $p < 0.001$). [10]

In the sodium oxybate group, sleeps attacks decreased from a mean of 10.05 (SD +/- 12.9) at baseline to 7.10 (+/- 9.1) by the end of the study ($p < 0.001$) and the sodium oxybate/modafinil group demonstrated a decrease from 11.82 (+/- 11.3) to 5.55 (+/- 5.9) ($p < 0.001$). In the placebo/placebo group sleep attacks increased from a mean of 15.23 (+/- 19.7) at baseline to 19.75 (+/- 32.6) by the end of the study. The authors concluded that sodium oxybate and modafinil are both effective for treating EDS in narcolepsy, producing additive effects when used together. [10]

In 2009 Black et al published a double-blind, placebo-controlled trial to characterise reduction in nocturnal sleep disruption in narcolepsy during treatment with sodium oxybate as monotherapy or in combination with modafinil. The primary outcome measure was effect on nocturnal sleep disruption. A secondary outcome measure defined as EDS was also measured using the ESS. [11]

The population and outcome data was derived from the 2006 study, reported above, [10] a different outcome measure reported. Polysomnography parameters were measured after eight weeks there were no significant changes in total sleep time. Compared to placebo, the sodium oxybate/placebo and sodium oxybate/modafinil groups each demonstrated increases in total non-REM sleep (for both $p < 0.001$) in stages three and four ($p < 0.001$). Compared to placebo, no changes in sleep composition were observed in the modafinil group. [11] Patients treated with sodium oxybate/modafinil showed an increase in the MWT score compared to baseline modafinil treatment, whereas patients that received either sodium oxybate or modafinil alone did not. [11]

In 2010, Black et al published a double-blind, placebo-controlled, parallel group trial to explore the effects of sodium oxybate administration on nocturnal sleep in patients with narcolepsy. [9] The population and outcome data was derived from the 2005 study [6] with a different outcome measure reported. Patients were taking existing medication for narcolepsy with cataplexy, the dosage of stimulant medication being constant during the trial. Patients had antidepressant and sedative/hypnotic medication withdrawn during the study. Participants were randomised to receive 4.5gram, 6gram or 9gram sodium oxybate at night (in divided doses) or placebo for eight weeks. [9]

The primary outcome measure was effect of sodium oxybate on sleep architecture. A median increase of 52.5minutes of stage three and four sleep was observed in the group receiving 9gram sodium oxybate ($p < 0.001$ compared to placebo). A dose related reduction in nocturnal awakening was also observed; -8.00 ($p = 0.005$ compared to placebo) and -12.00 ($p = 0.009$ compared to placebo) for the 6gram and 9gram groups respectively. [9]

Weaver et al reported a multicentre, double-blind, placebo-controlled trial in 2006, [8] re-framing and re-reporting from a previously established study. [6] The aim of the Weaver study was to evaluate the efficacy of sodium oxybate vs. placebo in improving quality of life in patients with narcolepsy, a secondary outcome of the 2005 study. The primary outcome in the Weaver evaluation was the Functional Outcomes of Sleep Questionnaire (FOSQ). Compared to placebo, the group treated with 9.0gram sodium oxybate had significant improvement in all FOSQ categories at the end of the study except for intimacy and sexual relationships ($p < 0.001$). A dose related effect was observed increasing from 6.0gram to 9.0gram. [8]

Systematic Reviews and Meta-Analyses

Alshaikh et al published a systematic review and meta-analysis in 2012 to evaluate the effectiveness of sodium oxybate on the clinical and neurological features of narcolepsy. [12]

Eligibility for inclusion of a study in the analysis included RCTs that compared the safety and efficacy of sodium oxybate to any comparator in adults with narcolepsy with cataplexy. The primary outcome of interest was elimination of excessive daytime sleeping. Secondary outcomes included quality of life and adverse effects. The quality of each study was assessed using the Cochrane risk of bias tool criteria. [12]

Six RCTs (741 participants; range 20 – 278) were included in the review. All studies were blinded and all reported that incomplete outcome data had been addressed. Five studies reported freedom from selective reporting, but all other criteria were not addressed or it was unclear whether they had been addressed. Compared to placebo, sodium oxybate (4.5gram per night) significantly reduced cataplexy attacks (median -8.5 95% CI -15.3 to -1.6; two of four trials) measured using participant diaries. Compared to placebo, sodium oxybate 9gram at night significantly increased wakefulness (median increase 5.18, 95% CI 2.59 to 7.78; two trials), and significantly increased the proportion of patients who were much improved or very much improved as measured on the Clinical Global Impression of Change (median 2.42, 95% CI 1.77 to 3.32; three trials). The authors concluded that sodium oxybate significantly reduced cataplexy and daytime sleepiness and adverse events were mild to moderate in severity. [12]

The Centre for Reviews and Dissemination (CRD) at the University of York published a critical abstract of this analysis, concluding that the review was generally well conducted, but given the limited evidence base and uncertain long-term effects of sodium oxybate, the authors' conclusions should be interpreted with caution as the findings may not be reliable. [13]

The CRD analysed another review by Boscolo-Berto et al. which is not presented as part of this new medicine review as the CRD found limited assessment of study quality, substantial heterogeneity and an absence of trial population details made the reliability of the authors' conclusions uncertain. [30] [31]

Other efficacy data:

There are additional studies identified that could have provided more information about the efficacy of sodium oxybate. These include one cohort study, one retrospective cohort study and two open label trials; all were either too small, had potential bias or were not of sufficient quality to include in any detail in this new medicines review. [29] [32] [33] [34]

Regulatory Information

Sodium oxybate has an abuse potential and is classified as a Schedule 2 Controlled Drug which is subject to the full controlled drug requirements relating to prescriptions, safe custody, the need to keep registers, etc. [14]

The US Federal Drug Administration (FDA) approved sodium oxybate for use in the US for the treatment of cataplexy associated with narcolepsy in 2002 with provision of a risk management programme (RMP). The RMP consisted of the following:

- implementation of restricted distribution
- patient and physician education programme developed
- initial prescription will only be dispensed when the patient and prescriber have completed

the education programme and maintain a register of all prescribers and patients. [15]

The RMP was implemented to mitigate the risks associated with the use of sodium oxybate both historically as a drug of abuse or potential co-administration with alcohol and any other CNS depressants.

The European Medicines Agency (EMA) licensed sodium oxybate for use within the European Union in 2006. In the first iteration of the drug's licensing documents, the EMA concluded that sodium oxybate was efficacious in reducing cataplexy attacks and the 9gram dose is the most efficacious at the cost of increased side effects. [25] They also found that sodium oxybate has a positive effect on daytime sleepiness when higher doses are used and the effect on daytime sleepiness is paired with less sleep attacks and less awakenings during the night. [33] The authors stated that the evidence that supports the effect on daytime sleepiness is not as strong as the evidence for use in cataplexy. In 2006 EMA did not consider that the effect on daytime sleepiness had been demonstrated. [25] This was partially addressed when the product's manufacturer supplied new clinical evidence showing improvements in daytime sleepiness requesting a change in licensed indication granted in 2007 from:

- 2006 licensed indication: 'treatment of cataplexy in adult patients with narcolepsy'. [25] to
- 2007 licensed indication: 'treatment of narcolepsy with cataplexy in adult patients' [26]

The updated indication is wider than the original but still did not fulfil the extent of change the manufacturer suggested, which was as follows:

- Drug Company suggested indication, 2007: 'treatment of narcolepsy in adult patients' [26]

Other Reviews

The Scottish Medicines Consortium (SMC) reviewed sodium oxybate for use in NHS Scotland in 2006 and 2007, [35] [1] in both cases not recommending the drug's use in Scotland due to cost effectiveness issues. The SMC did acknowledged that sodium oxybate has been shown to reduce the frequency of cataplexy attacks, but concomitant stimulants are likely to be required. [35]

In 2008 the All Wales Medicines Strategy Group published an appraisal notice stating that sodium oxybate in not recommended for use with NHS Wales for the treatment of cataplexy associated with narcolepsy as the manufacturer failed to make a submission. [36]

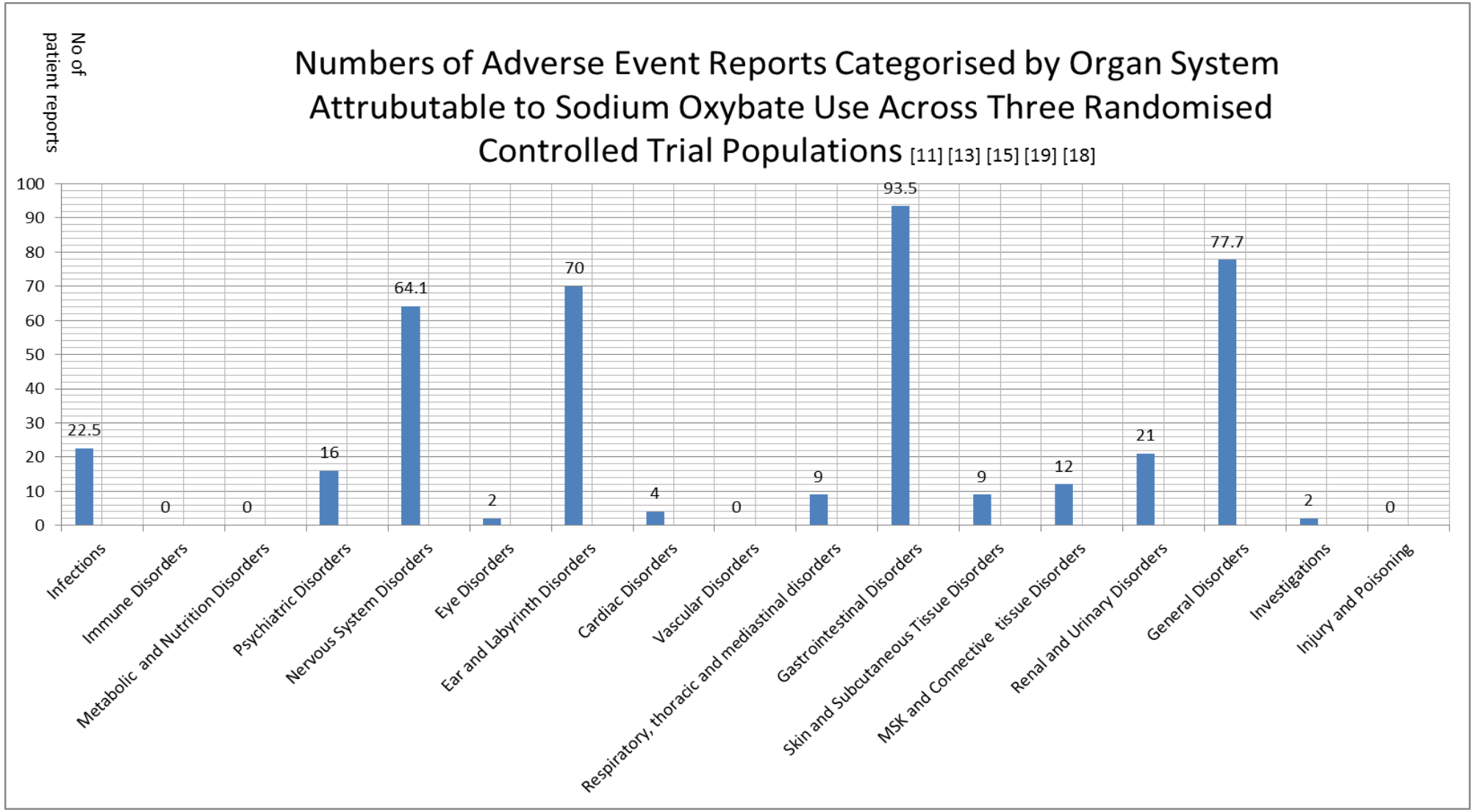
The Canadian Agency for Drugs and Technologies in Health (CEDAC) published a final recommendation on the use of sodium oxybate in 2009. CEDAC did not recommend the use of sodium oxybate in Canada as, although sodium oxybate reduced the incidence of total cataplexy attacks relative to placebo, statistical significance was not demonstrated versus placebo for complete attacks. [37]

Summary of Safety Data

Table 1 - Types of adverse event described in each RCT defined by effected system. Note: *indicates a severe reaction **indicates a reaction which is not listed in the SPC. Both will be discussed in the main text. [a] = estimated number based on prevalence in other RCT populations. [4] [13] [15] [19] [18]

RCT Study Reference	Infections	Immune Disorders	Metabolic and Nutrition Disorders	Psychiatric Disorders	Nervous System Disorders	Eye Disorders	Ear and Labyrinth Disorders	Cardiac Disorders	Vascular Disorders	Thoracic and Mediastinal Disorders	Gastrointestinal Disorders	Skin and Subcutaneous Tissue Disorders	MSK and Connective tissue Disorders	Renal and Urinary Disorders	General Disorders	Investigations	Injury and Poisoning
[4] (n = 120)	√ infection (8)	x	x	√ abnormal thoughts (3), *acute confusional state (1)	√ anxiety (4), confusion (9), dream abnormality (4), sleep disorder (9)	x	√ dizziness (30),	x	x	x	√ vomiting (6), nausea (19), both (4), diarrhoea (4)	√ sweating (6)	x	√ incontinence of urine (7)	√ headache (19), pain (14), **dysmenorrhea (8)	x	x
[5] (n = 55)	Prevalence given but details of ADRs in treatment groups not provided																
[6] [7] [8] [9] (n = 209)	√ *pneumonitis** (1)	x	x	√ disturbance in attention (6), disorientation (5)	√ somnolence (8), feeling drunk (2), tremor (2), hypoesthesia (3)	√**Eye irritation (2)	√ dizziness >5%	√ *chest pain** (3)	x	√ dyspnoea (5), snoring (4)	√ nausea >5%,	√ contusion (3)	√ back pain (5), muscle cramp (4),dysarthria (2), *fractured ankle (fall) (1)	√ enuresis >5%	√ sleep walking (3)	√ *raised ALT** (1)	x
[10] [11] (n = 222)	√ 6.1% nasopharyngitis	x	x	√ *psychotic disorder (1)	√ 5.6% somnolence and tremor 4.8%	x	√ 9.1% dizziness	√ *palpitations (1)	x	x	√ 11.7% nausea and 6.1% vomiting *abdominal pain (1)	x	x	x	√ 15.2% headache	√ *deranged LFTs** (1)	X
Total across 3 RCT Populations (n = 551)	22.5	0.0	0.0	16	64.1	2.0	70.0 (estimate)[a]	4.0	0.0	9.0	93.5 (estimate)[a]	9.0	12.0	21.0	77.7	2.0	0.0

Figure 1 - Graphical representation of adverse effects from RCT data



There is one randomised, 4-way crossover safety study for sodium oxybate which was conducted in accordance with a post-marketing safety commitment by the manufacturer. [16] Additionally, several descriptive studies were identified providing safety information for sodium oxybate.

RCT Safety Data

George et al published a randomised, 4-way crossover study investigating the effects of sodium oxybate and sodium oxybate in combination with modafinil on sleep disordered breathing and sleep architecture in patients with obstructive sleep apnoea syndrome (OSAS) in comparison with zolpidem and placebo. [16]

60 patients with a history of mild to moderate OSAS were enrolled in the study and received one of four treatments in a randomised, crossover manner for four consecutive nights. The four treatments were: sodium oxybate 9gram in divided doses, sodium oxybate 9gram plus modafinil 200mg, zolpidem 10mg and placebo. [16].

42 patients completed the study. [16] The number of central apnoeas at baseline was 4.5 +/- 10.1 and was significantly higher following sodium oxybate and sodium oxybate/modafinil (11.7 and 9.4 respectively; p = 0.0054) compared to both zolpidem and placebo. [16] Mean apnoea-hypopnea index (AHI)[2] at baseline was 24.7 +/- 9.2 and the mean change from baseline was not significantly different among treatments. [16] The sodium oxybate and sodium oxybate/modafinil groups saw the greatest change at -6.1 and -3.3 respectively (p = 0.0558). [16] Comparison of oxygen SATS between the treatment groups showed no significant difference. [16]

The 2002 Study by the US Xyrem Multicentre Study Group highlighted one severe adverse drug reaction (ADR) and one ADR which is not listed in the SPC. The severe ADR was a patient that experienced an acute confusional state in a patient taking a 6gram dose. The patient recovered and the study medication was discontinued. 8 out of 67 patients experienced dysmenorrhoea. [4].

The International Xyrem Study group study published in 2005 and its associated studies [13] [15] [19] [18] reported the following severe ADRs and ADRs not listed in the SPC: pneumonitis, eye irritation, chest pain, fall (resulting in a fractured ankle) and deranged AST/ALT levels being 2 to 3 x ULN .

Safety Case Reports

Seven descriptive studies were identified presenting severe adverse reaction associated with the therapeutic use of sodium oxybate.

In 2009 Zvosec et al published a case report of three deaths that had been associated with the use of sodium oxybate:

- a 52year-old woman with a history of narcolepsy with cataplexy. Blood toxicology detected sodium oxybate, phentermine, paroxetine and zolpidem at thearapeutic levels.
- a 44year-old man with a history of hypertension and mood disorder, mild OSAS and gastric by-pass. Prescribed sodium oxybate 2gram twice a day at night. The deceased was not wearing his continuous positive airway pressure (CPAP) mask when he was found. Post-mortem blood toxicology tests found: sodium oxybate alprazolam, nordiazepam and quetiapine all at therapeutic levels.
- a death that appeared to be secondary to an overdose of sodium oxybate. The patient had previously presented twice at hospital with drug overdoses which had involved sodium oxybate. Toxicology tests detected: methamphetamine, amphetamine, grossly elevated sodium oxybate levels and trace levels of chlorphenamine. [19]

The SPC for Xyrem states that sodium oxybate should not be used in combination with sedative

[2] AHI relates to number of pauses in breathing per hour of sleep; normal score < 5

hynotics or other CNS depressants and used with special caution in patients with respiratory disorders. [2] There are two further case reports that associate the use of sodium oxybate and de-novo sleep apnoea in the literature. [17] [18] There is one case report of dose related sodium oxybate-induced sleep driving and sleep-related eating disorder. [38]

Adverse effects from the illicit use of sodium oxybate have included: vomiting, drowsiness, hypotonia, respiratory depression and involuntary movements. Seizure-like activity, bradycardia, hypotension and respiratory arrest have also been reported. Deaths have been reported in several countries. The severity of symptoms following the illicit use of sodium oxybate is dependent on dose and, usually, the co-ingestion of other drugs such as alcohol and benzodiazepines. [20]

Strengths and limitations of the evidence:

Strengths

- Eight RCT studies have been published and two systematic reviews and meta-analyses are available to support the drug
- 9g dosage of sodium oxybate is associated with a statistically significant reduction in incidence of weekly cataplexy attacks, reducing attacks by around 10 attacks per week compared to placebo
- For the treatment of cataplexy, the only other licensed drug is clomipramine

Weaknesses

- The eight published RCT studies are derived from data of only four study populations
- Exclusion criteria for inclusion in study population of some of the RCTs is significant
- The adverse event profile of sodium oxybate is considerable and includes respiratory depression

Summary of evidence on cost effectiveness:

The Scottish Medicines Consortium evaluated sodium oxybate for the treatment of cataplexy in adult patients with narcolepsy. The manufacturer submitted a cost-utility analysis to the SMC of sodium oxybate compared to clomipramine. The patient group was those with a diagnosis of narcolepsy and at least one cataplexy attack per week at baseline. The estimation of the clinical benefits came from a 6 month open-label trial that used a generic SF-36[3] [39] instrument to measure changes in quality of life. The cost per QALY was estimated to be £65,980 for sodium oxybate 6g daily dose, falling to £49,590 per QALY at 9g doses. The choice of comparator, form of model and presentation of results and sensitivity analyses were adequate. The main weaknesses were:

- The utility values for standard care may not be representative of clomipramine- treated patients because 60% of the patients in the open label trial were not taking a TCA or SSRI;
- The assumed clinical resource savings, particularly in the hospital setting, are unlikely to be realised from the treatment of cataplexy only. However, additional analysis suggested that the result was relatively insensitive to changes in this parameter;
- No costs for the treatment of adverse events were included; and
- Non-responders may be on sodium oxybate for more than three months before reverting

[3] SF-36 is a set of generic, coherent, and easily administered quality-of-life measures. These measures rely upon patient self-reporting and are now widely utilized by managed care organizations and by Medicare for routine monitoring and assessment of care outcomes in adult patients.

to standard care.

The economic case was considered not demonstrated due to the high reported cost per QALY, concerns that the potential costs of adverse events are not included in the model and that the clinical resource savings may not be realised. [1]

Prescribing and risk management issues:

Sodium oxybate is a Schedule 2 Controlled Drug. Special storage and prescription writing requirements are necessary for safe custody and supply respectively.

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Cost per patient per course/ per year (ex VAT)
Sodium oxybate	4.5g - 9g daily	£6,552 - £13,104
Clomipramine	10mg - 75mg daily	£20.02 -£72.54
Modafinil	200-400mg daily	£1,262-£2,525
Dexamfetamine	10-60mg daily	£644-£3,861
Methylphenidate (unlicensed)	10-60mg daily [40]	£65.88-£395

Associated additional costs or available discounts:

Sodium oxybate's manufacturer offers a rebate scheme where 3 months of the drug can be trialled by a patient. If this trial is unsuccessful, the cost of the three months drug treatment is refunded.

Productivity, service delivery, implementation:

Sodium oxybate is a specialist medicine which will need to be monitored by the specialist Sleep Service. Sodium oxybate has the potential to interact with commonly prescribed medicines therefore non-specialist prescribers will need to have awareness of its availability and have a point of contact within the specialist service to field queries, etc. Sodium oxybate is a controlled drug which will require safe storage and has associated prescribing requirements.

Anticipated patient numbers and net budget impact:

The applicant estimates that, using experience in the Mersey region, around 1-2 patients per CCG would be eligible each year. At this relatively low level of eligibility for treatment, it is not possible to accurately assess the impact at a CCG or Lancashire level as there may be pockets of eligible patients within certain CCGs and none in others.

The drug's manufacturer offers a non-responder programme and will reimburse the cost of treatments for patients who do not adequately respond in the first three months of treatment. The applicant estimates that around 1 in 5 patients would qualify for the nonresponder programme. Sodium oxybate will cost between £6,552 and £13,104 per year per patient, based on the dosage being between 4.5g and 9g daily.

Innovation, need, equity:

Sodium oxybate is used when currently available treatments have failed; it offers a new treatment option for patients who may otherwise not have their symptoms controlled.

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Table: Summary of key sodium oxybate RCTs relevant to use in adults with narcolepsy with cataplexy.

Ref	Trial design	Patients / Trial subjects	Trial intervention and comparison	Outcomes: Primary endpoint (mITT)	Outcomes: Key secondary / exploratory endpoints	Grading of evidence / risk of bias
[9] *The nightly use of sodium oxybate is associated with a reduction in nocturnal sleep distruption: a double blind, placebo-controlled study in patients with narcolespy.* **Black et al.** 6, 2010, Journal of Clinical Sleep Medicine , Vol. 6, pp. 596 - 602.	Randomised Controlled Trial – double-blind, placebo controlled, parallel-group design	401 patients consented to enter the study. After screening, 353 were enrolled and 285 were randomised to treatment. 246 received at least one dose of study drug and 228 entered the double-blind phase of the trial. 206 patients completed the trial and polysomnographic data was available at weeks 4 and 8 for 191 and 103 patients respectively. Of the patients randomised to treatment 78% were taking stimulants, 14.7% were taking tricyclic antidepressants and 14% were taking selective serotonin reuptake inhibitors.	Patients were withdrawn from antidepressants and sedative/hypnotics, and then randomized to receive 4.5, 6, or 9 g sodium oxybate or placebo nightly for 8 weeks. Patients receiving 6 and 9 g/night doses were titrated to their final dose in weekly 1.5 g increments, while patients receiving placebo were randomised to undergo a similar mock dose titration. The use of stimulant therapy continued unchanged. Methods of comparison between the groups included polysomnography and maintenance of wakefulness tests.	Effect of sodium oxybate on sleep architecture	Polysomnographic parameters.	Patient-oriented outcome measure? Yes Allocation concealment? Yes Blinded if possible? Yes Intention to treat analysis? Yes. However, not all patients that were randomised were included in the final analysis. Patients that were received at least one drug were included. Adequate power/size? No sample size calculations obvious. P was set at 0.05. Adequate follow-up (>80%)? 285 patients were randomised and 206 completed the study (72.3%). 191 and 193 had polysomnography data collected at weeks 4 and 8 respectively. Level I evidence based on RCT, blinding. However, level II – potential high risk of

						bias. Risk of bias: High/moderate – see above.
[16] *A safety trial of sodium oxybate in patients with obstructive sleep apnea: Acute effects on sleep-disordered breathing.* **George et al.** 2010, Sleep Medicine , Vol. 11, pp. 38 - 42.	Randomised controlled trial – randomised 4 way crossover design	42 completed the study (60 enrolled) 76.7% were male, 90.9% were Caucasian. Median age was 50years. Method of randomisation not defined. Not stated whether blinding occurred. 60 commenced the study, 42 completed it. 10 were withdrawn because they were taking medication outside the protocol and were not included in the final analysis. Nine patients withdrew due to adverse events and one for protocol violation. Adverse events experienced were: Headache and nausea. The most common adverse events leading to withdrawal were nausea, dizziness and hypoesthesia (reduced sensitivity to touch). Significant exclusion	Sodium oxybate 9g, sodium oxybate 9g/modafinil 200mg, zolpidem 10mg and placebo. Respiratory parameters (AHI, central apnoeas and saO2) and sleep architecture	Effect on respiratory parameters	Effect on sleep architecture.	Patient-oriented outcome measure? No Allocation concealment? Yes. Blinded if possible? No Intention to treat analysis? Not referenced. Adequate power/size? No sample size calculations. Small group of patients. 42 completed the study, 60 were recruited. Unsure how many were randomised. Adequate follow-up (>80%)? 60 enrolled, 42 completed (70%) Level II evidence – based on the above factors. Risk of bias: High

		criteria listed. Patients were mainly white males ?population representative.				
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[10] *Sodium Oxybate Improves Excessive Daytime Sleepiness in*	Randomised Controlled Trial – double-blind, placebo-	270 adult patients with narcolepsy taking 200 to 600mg of modafinil daily for treatment of excessive daytime	Sodium oxybate was administered as 6g nightly for 4 weeks and was then increased to 9g nightly for 4 additional weeks. Polysomnogram, maintenance of	Improvement of 20minute mean wakefulness test	Improvement of Epworth Sleepiness scale score, CGI-C scale score and assessment of daily sleep diaries.	Patient-oriented outcome measure? No Allocation concealment? Yes

Narcolepsy. **Black et al.** 7, 2006, Sleep, Vol. 29, pp. 939 - 946.	controlled design	sleepiness. Randomly assigned to 1 of 4 treatment groups: sodium oxybate placebo plus modafinil placebo, sodium oxybate plus modafinil placebo, modafinil plus sodium oxybate placebo or sodium oxybate plus placebo. Significant exclusion criteria. 13 patients withdrew due AE overall. Serious AEs were reported in 4 patients.	wakefulness test, Epworth Sleepiness scale. Dose and regimen of sodium oxybate used was clinically significant.			Blinded if possible? Yes Intention to treat analysis? Yes, although not all patients that were randomised were analysed (231 were randomised and 222 were analysed). However, all those analysed received at least one dose of double-blind medication and provided baseline and efficacy data at visit 4 or 5. Adequate power/size? No sample size calculations or power of sample discussed. P value = 0.05. Adequate follow-up: 8 weeks in total double-blind phase and follow up after 4 weeks and at 8 weeks. Level of evidence: Level I/II based on the above information. Risk of bias: Moderate.
[4] *A Randomized, Double Blind, Placebo-Controlled Multicenter Trial Comparing the Effects of Three*	Randomised Controlled Trial – double-blind, placebo controlled design	136 patients were enrolled in the study. The study was completed by 120.	Sodium oxybate, 3g, 6g or 9g or placebo nocte for 4 weeks. Anti-cataplectic medication was discontinued before commencing the trial. Disease symptoms and adverse effects were recorded in daily	Change from baseline in weekly cataplexy attacks.	Daytime sleepiness using Epworth Sleepiness Scale, inadvertent daytime naps/sleep attacks and night time awakenings.	Patient-oriented outcome measure? Yes Allocation concealment? Yes Blinded if possible? Yes

Doses of Orally Administered Sodium Oxybate with Placebo for the Treatment of Narcolepsy. **The US Xyrem Multicenter Study Group.** 1, 2002, Sleep, Vol. 25, pp. 42 - 49.			diaries.			Intention to treat analysis? No. 136 patient were enrolled in the study, 120 completed it. Unknown if all the patients randomised were included in the analysis. P value = 0.05. Adequate power/size? No sample size calculations or power of sample discussed. Adequate follow-up (>80%)? 88.3% of participants completed the study. Level of evidence: Level II – moderate risk of bias. Risk of bias: Moderate
[5] *Sodium oxybate demonstrates long-term efficacy for the treatment of cataplexy in patients with narcolepsy.* **US Xyrem Multicenter Study Group.** 2004, Sleep Medicine, Vol. 5, pp. 119 - 123.	Randomised Controlled Trial – double-blind treatment withdrawal.	55 patients with narcolepsy with cataplexy who had received continuous treatment with sodium oxybate for 7 – 44 months (mean 21 months).	patients were randomised to receive either placebo or continue sodium oxybate at their previous dose. Patient recorded incidence of cataplexy attacks and adverse events in daily diaries.	The primary endpoint was the change in number of weekly cataplexy attacks from the baseline period to the double-blind treatment phase.	Adverse effects/symptoms of abrupt withdrawal.	Patient-oriented outcome measure? Yes Allocation concealment? Yes Blinded if possible? Yes Intention to treat analysis? No. However, only one patient drop out (56 recruited and 55 completed the study). However, all these patients had completed a previous open label study by the same

						group. Therefore selection bias. Adequate power/size? No sample size calculation or power of sample discussed. Adequate follow-up (>80%)? (98% completed the study) Level of evidence: Level II moderate/high risk of bias – based on the information above. Risk of bias: Moderate/High.
[11] *The nightly administration of sodium oxybate results in significant reduction in the nocturnal sleep disruption of patients with narcolepsy .* **Black et al.** Sleep Medicine : s.n., 2009, Vol. 10, pp. 829 - 835.	Randomised Controlled Trial – double-blind, placebo controlled	278 patients with narcolepsy taking modafinil 200 – 600mg o.d. for the treatment of excessive sleepiness were involved in the study.	Patients were randomised to receive treatment with: placebo sodium oxybate and placebo modafinil, sodium oxybate + placebo modafinil, placebo sodium oxybate and modafinil or sodium oxybate + modafinil. A Polysomnogram and maintenance of wakefulness test was completed at baseline and again at 4 and 8 weeks.	Reduction of nocturnal sleep disruption.	Polysomnographic parameters and maintenance of wakefulness test and Epworth Sleepiness scale scores.	Patient-oriented outcome measure? Yes Allocation concealment? Yes Blinded if possible? Yes Intention to treat analysis? Yes, but not all patients randomised were analysed. Patients that received at least one dose of drug in the double-blind phase and had followed up date was included. Adequate power/size? No sample size calculation or power of sample discussed.

						Adequate follow-up (>80%)? 96.1% 222 completed out of 231 randomised. Level of evidence: Level II – moderate risk of bias. Risk of bias: Moderate – based in the information above.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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