Lancashire & South Cumbria Medicines Management Group

NHS
Midlands and Lancashire
Commissioning Support Unit

New Medicine Assessment

Sodium Oxybate

For the treatment of narcolepsy with cataplexy in adults

Recommendation: RED

Restrictions:

- Medicine is supplied by the hospital for the duration of the treatment course.
- Primary care initiation or continuation of treatment is not recommended unless exceptional circumstances such as specialist GP.
- Sodium oxybate is only considered as a final treatment option for patients
- Treatment should be initiated by and remain under the guidance of a physician experienced in the treatment of narcolepsy. Physicians should strictly adhere to the contraindications, warnings and precautions.
- The RMOC Criteria for Commissioning of sodium oxybate in adult patients should be met (see below).
- Discontinue if there is inadequate response at 3 months for both cataplexy and narcolepsy. Measurements should ideally be compared to scores prior to sodium oxybate treatment. Expert clinical review and patient history will also contribute to this assessment.
- Patients on established therapy should be reviewed at least annually if stable (more frequently if not) to ensure continued benefit.

RED medicines are those where primary care prescribing is not recommended. These treatments should be initiated by specialists only and prescribing retained within secondary care. They require specialist knowledge, intensive monitoring, specific dose adjustments or further evaluation in use. If however, a primary care prescriber has particular specialist knowledge or experience of prescribing a particular drug for a particular patient it would not always be appropriate for them to expect to transfer that prescribing responsibility back to secondary care. There should be a specific reason and a specific risk agreement, protocol and service set up to support this.

Primary care prescribers may prescribe RED medicines in exceptional circumstances to patients to ensure continuity of supply while arrangements are made to obtain on going supplies from secondary care.

Summary of supporting evidence:

- All the published evidence confirms sodium oxybate's efficacy when used for the treatment of narcolepsy with cataplexy.
- Sodium oxybate in adults has a RED rating in neighbouring geographies (which may lead to cross border issues)

Date: September 2021

- An RMOC statement states that NHS England Specialised Commissioning, together with NHS Improvement, will develop a framework for adult services clinicians to consider when children on sodium oxybate transition to adult services. In the interim, adult patients with narcolepsy with cataplexy who have transitioned from paediatric care should continue to receive sodium oxybate, providing there is a demonstrable ongoing clinical need; continuity of care should not be compromised.

Details of Review

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

Sodium Oxybate (Xyrem)

Strength(s) and form(s):

500 mg/ml oral solution (available as branded and generic)

Dose and administration:

The recommended starting dose is 4.5 g/day sodium oxybate divided into two equal doses of 2.25 g/dose. The dose should be titrated to effect based on efficacy and tolerability up to a maximum of 9 g/day divided into two equal doses of 4.5 g/dose by adjusting up or down in dose increments of 1.5 g/day (i.e. 0.75 g/dose). A minimum of one to two weeks is recommended between dose increments. The dose of 9 g/day should not be exceeded due to the possible occurrence of severe symptoms at doses of 18 g/day or above.

Single doses of 4.5 g should not be given unless the patient has been titrated previously to that dose level.

Sodium oxybate should be taken orally upon getting into bed and again between 2.5 to 4 hours later. It is recommended that both doses of sodium oxybate should be made up at the same time upon retiring to bed. Sodium Oxybate is provided for use with a graduated dosing pipette and two 90 ml dosing cups with child resistant caps. Each measured dose of Sodium Oxybate must be dispensed into the dosing cup and diluted with 60 ml of water prior to ingestion. Because food significantly reduces the bioavailability of sodium oxybate, patients should eat at least several (2-3) hours before taking the first dose of sodium oxybate at bedtime. Patients should always observe the same timing of dosing in relation to meals. Doses should be taken within 24 hours after preparation or else discarded.

Treatment should be initiated by and remain under the guidance of a physician experienced in the treatment of sleep disorders.

BNF therapeutic class / mode of action

Sodium oxybate is a central nervous system depressant which reduces excessive daytime sleepiness and cataplexy in patients with narcolepsy and modifies sleep architecture reducing fragmented night-time sleep. The precise mechanism by which sodium oxybate produces an effect is unknown, however sodium oxybate is thought to act by promoting slow (delta) wave sleep and consolidating night-time sleep. Sodium oxybate administered before nocturnal sleep increases Stages 3 and 4 sleep and increases sleep latency, whilst reducing the frequency of sleep onset REM periods (SOREMPs)

Licensed indication(s): Treatment of narcolepsy with cataplexy in adult patients.

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

Licensed indication

Course and cost:

180ml (90g) = £360.00at a dose of 4.5g / day = 20 days supply, at maximum dose of 9g/day = 10 days supply. [1]

30 days supply at maximum dose = £1,080.

Ongoing course

Current standard of care/comparator therapies:

Modafinil[2] is licensed for excessive sleepiness associated with narcolepsy with or without cataplexy.

Pitolisant[3] is indicated in adults for the treatment of narcolepsy with or without cataplexy.

Clomipramine[4] 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, sodium oxybate is listed as non- formulary.[5]

The European Academy of Neurology guidelines for the management of narcolepsy in adults recommend the following:

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 – 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.[6]

Relevant NICE guidance:

Narcolepsy with or without cataplexy in adults: pitolisant. Evidence summary [ES8]. Published: 14 March 2017.[7]

Other Guidance:

Sodium oxybate is recommended as a standard of care for the treatment of narcolepsy symptoms by the American Academy of Sleep Medicine,[8] European Federation of Neurological Societies,[9] and the French consensus group.[10]

RMOC Advisory Statement : Sodium oxybate commissioning on adult patients with narcolepsy with cataplexy, Clinical decision criteria, October 2019 is outlined, below:[11]

NHS England Specialised Commissioning, together with NHS Improvement, will develop a framework for adult services clinicians to consider when children on sodium oxybate transition to adult services. In the interim, adult patients with narcolepsy with cataplexy who have transitioned from paediatric care should continue to receive sodium oxybate, providing there is a demonstrable ongoing clinical need; continuity of care should not be compromised.

Adult patients currently receiving sodium oxybate should also be reviewed to ensure that the treatment remains effective and that there is an ongoing need.

Criteria for Commissioning of sodium oxybate in adult patients

The following criteria have been drawn up in consultation with specialist sleep clinicians and NHS England Specialised Commissioning. They are offered as the basis for local commissioning decisions for adult patients.

- Patients presenting with narcolepsy with cataplexy according to International Classification of sleep disorders 3 (ICSD) criteria for Narcolepsy Type 1 AND
- Patients≥ 19 years old AND
- Where patients have co-morbidities, which are also affecting sleep, these should be managed and adequately treated (for example moderate to severe obstructive sleep apnoea or restless legs syndrome) AND
- Failure to respond to non-pharmacological treatments consisting of behavioural and environmental adaptations, for example planned naps AND
- Inadequate response (within 3 months) to, or intolerable adverse effects from, or contra-indicated use of, more than one stimulant for narcolepsy, and more than one anticataplectic agent AND
- Assessed as being able to benefit from sodium oxybate via a specialist sleep centre.

Sodium oxybate is generally considered as a final treatment option for patients. Therefore, consideration needs to be given to the consequences of not allowing a patient access to sodium oxybate, how the patient will be managed in the future, and the impact this might have on the patient's quality of life.

The patient should be fully consulted at all stages of the process and should be fully involved in the decision on appropriate treatment options.

Assessing need for ongoing treatment

- Patients who show signs of serious adverse events should discontinue therapy.

- Improvements in narcolepsy and/ or cataplexy should be determined by expert clinical review, which will include the use of the Epworth Sleepiness Scale and an assessment of symptomatic/quality of life improvements.
- Discontinue if there is inadequate response at 3 months for both cataplexy and narcolepsy. Measurements should ideally be compared to scores prior to sodium oxybate treatment. Expert clinical review and patient history will also contribute to this assessment.
- Patients on established therapy should be reviewed at least annually if stable (more frequently if not) to ensure continued benefit.
- Trial withdrawal periods can be considered if this is clinically appropriate.

GMMMG Sodium Oxybate RAG rating is RED, for Narcolepsy with cataplexy in adult patients.

Criterion 2 - Only for use in adult patients who have received and benefited from treatment with sodium oxybate as commissioned by NHS England, i.e. continuing treatment in those >19 years old. [12]

Pan Mersey Area Prescribing Committee recommends sodium oxybate 500mg/ml oral solution as a treatment option for narcolepsy with cataplexy in adult patients only when recommended by a consultant in a specialist commissioned sleep service. RED RAG rating.[13]

NARCOLEPSY - University Hospital Aintree Sleep Service Pathway

Positions sodium oxybate as 4th line therapy or as 3rd line therapy in favour before pitolisant. Indications to favour sodium oxybate:

- Previous adverse reaction to or lack of clinical response to pitolisant
- Narcolepsy specific issues: Significant (i.e. multiple nightly) REM intrusion phenomena, greater frequency of cataplexy e.g. >15 episodes a week
- Coexisting insomnia
- Obesity

All patients commenced on pitolisant or sodium oxybate MUST be followed up every 3 months in the specific Narcolepsy clinic.[14]

Derbyshire Joint Area Prescribing Committee (JAPC) Nov 2019: The JAPC have classified Sodium oxybate as RED – CCG commissioned for adult patients with narcolepsy with cataplexy, through specialist sleep centres. Commissioning criteria adapted from RMOC statement.[15]

The East of England Priorities Advisory Committee (PAC)[a]: Guidance statement for sodium oxybate in the management of narcolepsy with cataplexy in adults aged 19 and over. Recommendation:

1. Sodium oxybate for the treatment of narcolepsy with cataplexy is recommended for funding for adult patients who meet the following criteria:-

Adults aged 19 and over where attempts to try to control symptoms of narcolepsy with cataplexy have failed despite a trial of first and second line medications for each symptom group for at least 3 months. Specifically:

[a] Hosted by PrescQipp

- Patients presenting with narcolepsy with cataplexy according to International Classification of sleep disorders 3 (ICSD) criteria for Narcolepsy Type 1 AND

Adequately treated co-morbid sleep disorders (such as sleep apnoea and restless legs syndrome) as assessed clinically and by polysomnogram as appropriate AND

Failure to respond to non- pharmacological treatments consisting of behavioural and environmental adaptations, for example planned naps AND

Inadequate response (within 3 months) to, or intolerable adverse events from, or contra-indicated use of, more than one stimulant for narcolepsy and more than one anticataplectic agent AND

Assessed as being likely to benefit from sodium oxybate by a specialist sleep centre

- Continuation treatment for children transitioning to adult services where sodium oxybate has been commissioned by NHS England. Children transitioning to adult services should be reviewed by a consultant sleep physician and assessed for suitability for continued treatment.

2. Treatment should be initiated and monitored by a consultant sleep physician or under the direct supervision of a consultant sleep physician.

3. Responsibility for prescribing and supplying sodium oxybate should remain with the specialist centre.

4. Treatment should only be continued if patients show evidence of an adequate response to treatment

5. Adult patients currently receiving sodium oxybate should also be reviewed to ensure that the treatment remains effective and that there is ongoing need

6. These recommendations will be reviewed in the light of new evidence on clinical and cost effectiveness and safety.

PAC therefore recommend that sodium oxybate is commissioned for adult patients in line with the criteria funded by NHSE for children, to ensure equity of access to treatment.[16]

Background and context

LSCMMG was asked to review the current Black RAG rating for sodium oxybate when used in adults (≥19 years) for the treatment of narcolepsy with cataplexy. There are inconsistencies across England regarding access to sodium oxybate when a child transitions to adult services, the former having funding arrangements in place with NHS England allowing access to the drug.

NHS England currently commission sodium oxybate for post-pubescent children weighing ≥40kg and up to their 19th birthday if they meet the strict criteria within their policy. Once a patient passes their 19th birthday, commissioning responsibility transfers to local CCGs, which has led to variation across England. Sodium oxybate is not included within the National tariff payment system.

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.

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.

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. Pitolisant is indicated in adults for the treatment of narcolepsy with or without cataplexy. Clomipramine is licensed for adjunctive treatment of cataplexy associated with narcolepsy. Dexamphetamine and methylphenidate (unlicensed) can also be used to treat narcolepsy.

Sodium oxybate was licensed in the European Union in 2006 for the 'treatment of cataplexy in adult patients with narcolepsy'. 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'[17]. Sodium oxybate is a central nervous system depressant which reduces excessive daytime sleepiness and cataplexy in patients with narcolepsy and modifies sleep architecture reducing fragmented nighttime sleep. The precise mechanism by which sodium oxybate produces an effect is unknown, however sodium oxybate is thought to act by promoting slow (delta) wave sleep and consolidating night-time sleep. Sodium oxybate administered before nocturnal sleep increases Stages 3 and 4 sleep and increases sleep latency, whilst reducing the frequency of sleep onset REM periods (SOREMPs). Other mechanisms, which have yet to be elucidated, may also be involved. In the clinical trial database, greater than 80 % of patients maintained concomitant stimulant use.

Summary of evidence

Evidence from original LMMG review

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.[18]

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). 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.[18]

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).[19] Participants were a cohort selected from a previous long-term safety study. The 12-month safety study was an extension of the study conducted in 2002.[18] This introduces significant population selection bias into the 2004 study and could have led to under reporting of adverse events.[20] This was rationalised by the authors who stated that the study more closely mirrored clinical practice in a way previous studies did not.[19]

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.[19]

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.[19]

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.[21]

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. CNS stimulants for the treatment of excessive daytime sleepiness (EDS) were maintained for the duration of the study.[21]

The primary outcome measure was the improvement of EDS. **Invalid source specified.** 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 ($p < 0.001$). **Invalid source specified.** 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) **Invalid source specified.** Patients in the 4.5gram and 6.0gram groups displayed little or no significant difference in the median MWT time.[21]

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.[21]

A study from 2005 used the same population from the third study by the same group.[21,22] It presented efficacy data for the treatment of cataplexy. 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).[22]

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.[23,24,25]

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.[24]

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; $p < 0.001$).[24]

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.[24]

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.[25]

The population and outcome data was derived from the 2006 study, reported above, 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. 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.[25]

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.[24] The population and outcome data was derived from the 2005 study 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.[24]

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.[24]

Weaver et al reported a multicentre, double-blind, placebo-controlled trial in 2006,[23] re-framing and re-reporting from a previously established study.[21] **Invalid source specified.** 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.[23]

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.[26]

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.[26]

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.[26]

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.[27]

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.[28,29]

Evidence since 2016 LMMG review

Summary of efficacy data in proposed use:

For the previous review of Sodium Oxybate conducted by LSCMMG in 2016, eight key randomised controlled trials (RCTs) and two meta-analyses were identified.[30] The evidence in 2016 demonstrated sodium oxybate's efficacy when used for the treatment of narcolepsy with cataplexy. However, there were concerns with regards to costs and safety issues.

Since the original review an additional network meta-analysis was published in 2018 comparing the efficacy and safety of sodium oxybate, pitolisant and modafinil for the treatment of narcolepsy.[31] This meta-analysis was based on 14 published RCTs which compared the efficacy, safety, and benefit/risk ratio of medical treatments for adult narcolepsy. It concluded that the three drug treatments at specific doses, modafinil (200–400mg/d), sodium oxybate 9g/d, and pitolisant up to 40mg/d were found to have similar clinical efficacy and were significantly more effective than placebo for excessive day time sleepiness. Only sodium oxybate 9g/d and pitolisant up to 40mg/d were shown with a comparable beneficial effect on cataplexy. Overall, pitolisant at a maximal dose of 40 mg/d was shown to have a slightly better safety profile and the highest benefit/risk ratio.

An evaluation of sodium oxybate as a treatment option for narcolepsy was published in 2019. Unfortunately, only an abstract was available. Published results from 11 randomised control trials were reviewed. The evaluation concluded the following for sodium oxybate: 1) it is an effective therapy for excessive daytime sleepiness and cataplexy in adults and children ages 7–17 years, 2) it is also an effective therapy for disrupted nocturnal sleep and 3) sodium oxybate improves narcolepsy symptoms and enhances quality of life in narcolepsy patients.[32]

A double bling label study, *Efficacy and safety of calcium, magnesium, potassium, and sodium oxybates (lower-sodium oxybate [LXB]; JZP-258) in a placebo-controlled, double-blind, randomized withdrawal study in adults with narcolepsy with cataplexy*, was published in 2021.[33] This study evaluated efficacy and safety of 'lower-sodium' oxybate (LXB), a novel oxybate medication with 92% less sodium than sodium oxybate (SXB). Adults aged 18–70 years with narcolepsy with cataplexy were eligible. The study included a ≤30-day screening period; a 12-week, open-label, optimized treatment and titration period to transition to LXB from previous medications for the treatment of cataplexy; a 2-week stable-dose period (SDP); a 2-week, double-blind, randomized withdrawal period (DBRWP); and a 2-week safety follow-up. During DBRWP, participants were randomized 1:1 to placebo or to continue LXB treatment. Efficacy was assessed in 134 participants who received randomized treatment, and safety was assessed in all enrolled participants (N = 201). Statistically significant worsening of symptoms was observed in participants randomized to placebo, with median (first quartile [Q1], third quartile [Q3]) change in weekly number of cataplexy attacks from SDP to DBRWP (primary efficacy endpoint) in the placebo group of 2.35 (0.00, 11.61) versus 0.00 (−0.49, 1.75) in the LXB group ($p < 0.0001$; mean [standard deviation, SD] change: 11.46 [24.751] vs 0.12 [5.772]), and median (Q1, Q3) change in Epworth Sleepiness Scale score (key secondary efficacy

endpoint) of 2.0 (0.0, 5.0) in the placebo group versus 0.0 (−1.0, 1.0) in the LXB group ($p < 0.0001$; mean [SD] change: 3.0 [4.68] vs 0.0 [2.90]). The most common treatment-emergent adverse events with LXB were headache (20.4%), nausea (12.9%), and dizziness (10.4%). The study concluded that the efficacy of LXB for the treatment of cataplexy and excessive daytime sleepiness was demonstrated. The safety profile of LXB was consistent with SXB.

All the evidence published since the last review confirms sodium oxybate's efficacy when used for the treatment of narcolepsy with cataplexy.

Summary of safety data:

The safety profile was qualitatively the same in adult and paediatric studies.

In adults the most commonly reported adverse reactions were dizziness, nausea, and headache, all occurring in 10% to 20% of patients. The most serious adverse reactions are suicidal attempt, psychosis, respiratory depression and convulsion.

In adults the efficacy and safety of sodium oxybate for the treatment of narcolepsy symptoms was established in four multicentre, randomised, double-blind, placebo-controlled, parallel-group trials in patients with narcolepsy with cataplexy except for one trial where cataplexy was not required for enrolment.

Undesirable effects are listed according to MedDRA System Organ Class.

Frequency estimate: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

<u>Infections and infestations</u>

Common: nasopharyngitis, sinusitis

<u>Immune system disorders</u>

Uncommon: hypersensitivity

<u>Metabolism and nutrition disorders</u>

Common: anorexia, decreased appetite

Not known: Dehydration, increased appetite

<u>Psychiatric disorders</u>

Common: depression, cataplexy, anxiety, abnormal dreams, confusional state, disorientation, nightmares, sleepwalking, sleep disorder, insomnia, middle insomnia, nervousness

Uncommon: suicide attempt, psychosis, paranoia, hallucination, abnormal thinking, agitation, initial insomnia

Not known: suicidal ideation, homicidal ideation, aggression, euphoric mood, sleep-related eating disorder, panic attack, mania / bipolar disorder, delusion, bruxism, irritability and increased libido

<u>Nervous system disorders</u>

Very common: dizziness, headache

Common: sleep paralysis, somnolence, tremor, balance disorder, disturbance in attention, hypoaesthesia, paraesthesia, sedation, dysgeusia

Uncommon: myoclonus, amnesia, restless legs syndrome

Not known: convulsion, loss of consciousness, dyskinesia

Eye disorders

Common: blurred vision

Ear and labyrinth disorders

Common: vertigo

Not known tinnitus

Cardiac disorders

Common: palpitations

Vascular disorders

Common: hypertension

Respiratory, thoracic and mediastinal disorders

Common: dyspnoea, snoring, nasal congestion

Not known: respiratory depression, sleep apnoea, choking sensation

Gastrointestinal disorders

Very common: nausea (the frequency of nausea is higher in women than men)

Common: vomiting, diarrhoea, abdominal pain upper,

Uncommon: faecal incontinence

Not known: dry mouth

Skin and subcutaneous tissue disorders

Common: hyperhidrosis, rash

Not known: urticaria, angioedema, seborrhea

Musculoskeletal and connective tissue disorders

Common: arthralgia, muscle, spasms, back pain

Renal and urinary disorders

Common: enuresis nocturna, urinary incontinence

Not known: pollakiuria / micturition urgency, nocturia

General disorders and administration site conditions

Common: asthenia, fatigue, feeling drunk, oedema peripheral

Investigations

Common: blood pressure increased, weight decreased

Injury, poisoning and procedural complications

Common: fall

Description of selected adverse reactions

In some patients, cataplexy may return at a higher frequency on cessation of sodium oxybate therapy, however this may be due to the normal variability of the disease. Although the clinical trial experience with sodium oxybate in narcolepsy/cataplexy patients at therapeutic doses does not show clear evidence of a withdrawal syndrome, in rare cases, adverse reactions such as insomnia, headache, anxiety, dizziness, sleep disorder, somnolence, hallucination, and psychotic disorders were observed after GHB discontinuation.

Sodium oxybate has the potential to induce respiratory depression. Patients should be assessed before treatment for sleep apnoea and caution should be exercised when considering treatment. Apnoea and respiratory depression have been observed in a fasting healthy subject after a single intake of 4.5g (twice the recommended starting dose). During post-marketing surveillance, it has been observed that the use of sodium oxybate may predispose the patients to choking sensation during sleep. 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. Patients should be monitored for signs of respiratory depression during treatment. Because of the higher risk of sleep apnoea, patients with a BMI ≥40 kg/m2 should be monitored closely when taking sodium oxybate.

Approximately 80% of patients who received sodium oxybate during clinical trials maintained CNS stimulant use. Whether this affected respiration during the night is unknown. Before increasing the sodium oxybate dose prescribers should be aware that sleep apnoea occurs in up to 50% of patients with narcolepsy.

Sodium oxybate, which is as the sodium salt of GHB, is a CNS depressant active substance with **well-known abuse potential**. Prior to treatment physicians should evaluate patients for a history of or susceptibility to drug abuse. Patients should be routinely monitored and in the case of suspected abuse, treatment with sodium oxybate should be discontinued.

In order to assist prescribers, and patients/caregivers about the important information for sodium oxybate, **educational materials** will be provided to them.

Sodium oxybate has **major influence on the ability to drive and use machines**.

For at least 6 hours after taking sodium oxybate, patients must not undertake activities requiring complete mental alertness or motor co-ordination, such as operating machinery or driving.

When patients first start taking sodium oxybate, until they know whether this medicinal product will still have some carryover effect on them the next day, they should use extreme care while driving a car, operating heavy machines, or performing any other task that could be dangerous or require full mental alertness.

Strengths and limitations of the evidence:

Strengths

- Nine 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 nine published RCT studies are derived from data of only five 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:

Sodium oxybate 180ml (90g) = £360.00[1]

At a dose of 4.5g / day = 20 days supply, at maximum dose of 9g/day = 10 days supply.

30 days supply at maximum dose = £1,080.

Modafinil 30 x 100mg tablets = £3.30, 30 x 200mg tablets = £6.50[1]

The recommended starting daily dose = 200mg, maximum recommended daily dose = 400mg.

30 days supply at maximum dose = £13.00

Pitolisant 30 x 4.5mg tablets = £310, 30 x 18mg tablets = £310[1]

The recommended daily dose is 9-36mg

30 days supply at maximum dose = £620

Clomipramine 28 X 10mg capsules = £2.79, 28 x 25mg capsules = £2.95, 28 x 50mg capsules = £5.62[1]

The recommended daily dose is 10-75mg.

30 days supply at maximum dose = £9.18

The only cost effectiveness data available is that from the SMC in 2007 which states:

The manufacturer submitted a cost-utility analysis 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 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. Sensitivity analyses showed the result was sensitive to the utility values and drug costs.

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 to standard care.

NB. The comparator (clomipramine) is only licensed for the adjunctive treatment of cataplexy associated with narcolepsy. Newer drugs ie pitolisant are now available.

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:

Productivity, service delivery, implementation:

Patients will need to have their treatment initiated by and remain under the guidance of a consultant physician experienced in the treatment of sleep disorders.

Potential cross boundary issues

Sodium oxybate is a controlled drug which will require safe storage and has associated prescribing requirements.

Anticipated patient numbers and net budget impact:

The 'healthier Lancashire and South Cumbria' system covers a population of around 1.8 million.[34]

In the NICE evidence summary narcolepsy with or without cataplexy: pitolisant,[35] it was anticipated that pitolisant would initially be used in those patients with narcolepsy who can either not tolerate current treatment or have not responded to these (same patient group as anticipated for sodium oxybate). It was estimated that there were approximately 30,000 people in the UK who suffer from narcolepsy, about 5,000 of who receive treatment. Of these 5,000 patients they estimate that approximately 50% ie 2,500 patients, who are currently being treated may have issues with their current medications.

In mid-2019, the population of the UK reached an estimated 66.8 million.[36]

It can therefore be estimated that approximately 67 patients in Lancashire and South Cumbria may be eligible for treatment, (in December 2016, NHS England estimated that there are around 10 paediatric patients newly diagnosed per year. At the time there were 10 children treated with sodium oxybate nationally).

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.

References

[1] NHS Drug Tariff May 2021. https://www.drugtariff.nhsbsa.nhs.uk/#/00803325-DC/DC00803229/Part%20VIIIA%20products%20S

[2] EMC May 2021 Modafinil 100mg tablets https://www.medicines.org.uk/emc/product/4319/smpc

[3] EMC May 2021 Pitolisant film coated tablets https://www.medicines.org.uk/emc/product/7402

[44] EMC May 2021 Clomipramine 25mg hard capsules https://www.medicines.org.uk/emc/product/2550/smpc

[5] LSCFT Joint formulary for psychotropic medication 2018. https://www.lscft.nhs.uk/media/Publications/Pharmacy/Formulary/Joint%20formulary%20for%20psychotropic%20medication.%20%20April%202018.pdf

[6] N. E. Gilhus, M. P. Barnes and M. Branin, "European Handbook of Neurological Management: Volume 1, 2nd Edition, Chapter 38: Management of narcolepsy in adults.," in European Handbook of Neurological Management, 2nd ed., vol. 1, Blackwell Publishing Ltd., 2011.

[7] Narcolepsy with or without cataplexy in adults: pitolisant. NICE Evidence summary [ES8]Published: 14 March 2017. https://www.nice.org.uk/advice/es8/chapter/Key-points

[8] American Academy of sleep medicine. Guideline for treatment of narcolepsy and hypersomnias of central origin.

https://j2vjt3dnbra3ps7ll1clb4q2-wpengine.netdna-ssl.com/wp-content/uploads/2017/07/PP_Narcolepsy.pdf

[9] Billiard M et al; EFNS guidelines on management of narcolepsy. Eur J Neurol. 2006 Oct;13(10):1035-48. https://onlinelibrary.wiley.com/doi/full/10.1111/j.1468-1331.2006.01473.x

[10] Lopez R et al; French consensus. Management of patients with hypersomnia: Which strategy? Rev Neurol (Paris). Jan-Feb 2017;173(1-2):8-18. https://pubmed.ncbi.nlm.nih.gov/27865546/

[11] RMOC: Sodium oxybate in adult patients. https://www.sps.nhs.uk/articles/rmoc-sodium-oxybate-in-adult-patients/

[12] GMMMG RAG list May 2021 http://gmmmg.nhs.uk/html/rag_dnp_adult.php

[13] Pan Mersey APC ,Sodium Oxybate solution. https://www.panmerseyapc.nhs.uk/media/2179/sodiumoxybate.pdf

[14] NARCOLEPSY -University Hospital Aintree Sleep Service Pathway https://www.panmerseyapc.nhs.uk/media/2178/narcolepsy.pdf

[15] Derbyshire Joint Area Prescribing Committee (JAPC) Nov 2019 – prescribing guideline: sodium oxybate for adult patients with narcolepsy with cataplexy. http://www.derbyshiremedicinesmanagement.nhs.uk/assets/High_cost_drugs/JAPC%20Briefing%20Sodium%20Oxybate.pdf

[16] The East of England Priorities Advisory Committee (hosted by PrescQipp) : Guidance statement for sodium oxybate in the management of narcolepsy with cataplexy in adults aged 19 and over. https://medicines.blmkccg.nhs.uk/wp-content/uploads/2021/01/sodium-oxybate-pac-doc.pdf

[17] European Medicines Agency., "Scientific Discussion - Sodium Oxybate (Xyrem)," European Public Assessment Report, 2007. https://www.ema.europa.eu/en/medicines/human/EPAR/xyrem

[18] The US Xyrem Multicenter Study Group, "A Randomized, Double Blind, Placebo-Controlled Multicenter Trial Comparing the Effects of Three Doses of Orally Administered Sodium Oxybate with Placebo for the Treatment of Narcolepsy," Sleep, vol. 25, no. 1, pp. 42 - 49, 2002.

[19] US Xyrem Multicenter Study Group, "Sodium oxybate demonstrates long-term efficacy for the treatment of cataplexy in patients with narcolepsy," Sleep Medicine, vol. 5, pp. 119 - 123, 2004.

[20] US Xyrem Multicentre Study Group, "A 12-month, Open-Label, Multicentre Extension Trial of Orally Administered Sodium Oxybate for the Treatment of Narcolepsy," Sleep, vol. 1, pp. 31 - 35, 2003.

[21] Xyrem International Study Group, "A Double-Blind, Placebo-Controlled Study Demonstrates Sodium Oxybate is Effective for the Treatment of Excessive Daytime Sleepiness in Narcolepsy.," Journal of Clinical Sleep Medicine, vol. 1, no. 4, pp. 391 - 397, 2005.

[22] Xyrem International Study Group, "Further evidence supporting the use of sodium oxybate for the treatment of cataplexy: a double-blind, placebo controlled trial in 228 patients," Sleep Medicine, vol. 6, pp. 415-421, 2005.

[23] Black et al, "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.," Journal of Clinical Sleep Medicine , vol. 6, no. 6, pp. 596 - 602, 2010.

[24] Black et al, "Sodium Oxybate Improves Excessive Daytime Sleepiness in Narcolepsy," Sleep, vol. 29, no. 7, pp. 939 - 946, 2006.

[25] Black et al, "The nightly administration of sodium oxybate results in significant reduction in the nocturnal sleep disruption of patients with narcolepsy," vol. 10, pp. 829 - 835, 2009.

[26] Alshaikh et al, "Sodium Oxybate for Narcolepsy with Cataplexy: Systematice Review and Meta-Analysis," Journal of Clinical Sleep Medicine, vol. 8, no. 4, pp. 451 - 458, 2012

[27] University of York, "Critical Abstract: Alshaikh et al. Sodium oxybate for narcolepsy with cataplexy: systmatic review and meta analysis, Journal of Clinical Sleep Medicine 2012; 8(4): 451 - 458," Centre for Reviews and Dissemination, 2015.

[28] University of York, "Critical Abstract: Boscolo-Berto et al. Narcolepsy and effectiveness of gamma-hydroxybutyrate (GHB): a systematic review and meta-analysis of randomised controlled trials. Sleep Medicine Reviews 2012; 16(5): 431 - 443," Centre for Reviews and Dissemination, 2015.

[29] Boscolo-Berto et al, "Narcolepsy and effectiveness of gamma-hydroxybutyrate (GHB): a systematic review and meta-analysis of randomised controlled trials," Sleep Medicine Reviews, vol. 16, no. 5, pp. 431-443, 2012

[30] LMMG new medicine review sodium oxybate 2016. https://www.lancsmmg.nhs.uk/medicines-library/sodium-oxybate/

[31] Lehert P et al; Multiple treatment comparison in narcolepsy: a network meta-analysis. SleepJ, 2018, Vol 41, No.12, 1-13 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6289237/

[32] Abad V C; An evaluation of sodium oxybate as a treatment option for narcolepsy. Expert Opinion on Pharmacotherapy,Volume 20, 2019 - Issue 10. https://www.tandfonline.com/doi/abs/10.1080/14656566.2019.1617273?journalCode=ieop20

[33] Bogan R K et al; Efficacy and safety of calcium, magnesium, potassium, and sodium oxybates (lower-sodium oxybate [LXB]; JZP-258) in a placebo-controlled, double-blind, randomized withdrawal study in adults with narcolepsy with cataplexy. Sleep, Volume 44, Issue 3, March 2021 1-13 https://academic.oup.com/sleep/article/44/3/zsaa206/5923328

[34] NHS, Lancashire and South Cumbria. https://www.england.nhs.uk/lancashire-and-south-cumbria-ics/#:~:text=The%20system%20covers%20a%20population,are%20higher%20levels%20of%20deprivation.

[35] Narcolepsy with or without cataplexy in adults: pitolisant. Evidence summary [ES8]Published: 14 March 2017 https://www.nice.org.uk/advice/es8/chapter/Key-points

[36] Office for national statistics. Overview of the UK population January 2021. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/articles/overviewoftheukpopulation/january2021