The East of England
Priorities Advisory Committee
Hosted by PrescQIPP

GUIDANCE STATEMENT

Sodium oxybate (Xyrem®) in the management of narcolepsy with cataplexy in adults aged 19 and older

PAC recommendations

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

- Adult patients aged 19 and older where attempts 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 three months. Specifically:
  - Patients who present with narcolepsy with cataplexy according to International Classification of Sleep Disorders 3 (ICSD) criteria; AND
  - Adequately treated co-morbid sleep disorders (such as obstructive 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 three 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 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; i.e. continuing treatment for those ≥19 years old. 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 supply of sodium oxybate should remain with the specialist centre.

4. Treatment should only be continued if patients show evidence of an adequate response to treatment as defined in section 4 of this document.

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

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

Key points

In 2013, PAC issued negative recommendations on the use of sodium oxybate for narcolepsy with cataplexy in adults due to a lack of evidence of cost effectiveness. There is limited new evidence since this time.

Historically, NHS England (NHSE) did not routinely fund for use in children (≤18 years old). However, in December 2016, NHSE issued a positive policy for use in children from puberty until 19 years of age, where they have not responded to, or are intolerant of first and second line medications.[1]

Feedback from adult clinicians in the East of England is that the use of sodium oxybate in a similar small group of adult patients that have failed on, or who are unsuitable for, other treatment options, can have life changing effects, e.g. being able to study, or return to, and remain in employment.

The number of patients eligible for treatment with sodium oxybate is expected to be low, both in terms of newly diagnosed adults and patients transitioning from paediatric services.

Although there is a lack of evidence of cost effectiveness, PAC 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.

These recommendations are in line with the Regional Medicines Optimisation Committee (RMOC) advisory statement on commissioning sodium oxybate in adult patients with narcolepsy with cataplexy.[2]

Background

Narcolepsy with cataplexy (Type 1 narcolepsy) is a disabling sleep disorder characterised by excessive daytime sleepiness and abnormal rapid-eye-movement (REM) sleep manifestations including cataplexy and disturbed night time sleep, with sleep paralysis and sleep-related hallucinations. Cataplexy frequently occurs with narcolepsy as a distinct entity. Cataplexy itself is defined as a sudden loss of muscle tone triggered by strong emotions such as laughter, excitement or fright. Cataplectic attacks are sometimes limited to facial muscles or limbs and may manifest as facial flickering, jaw tremor, head or jaw dropping, dropping of objects, or buckling of the knees. Cataplectic episodes may be as brief as a few seconds or last several minutes, and occur with a frequency of less than once a year to several a day.[3,4]

Narcolepsy without cataplexy is characterised by excessive daytime sleepiness without symptoms of cataplexy.

Narcolepsy and cataplexy are lifelong disorders, often diagnosed in childhood, although half of adults with narcolepsy-cataplexy will have had symptoms during childhood but not diagnosed until later. The overall prevalence of narcolepsy (paediatric and adult) in Western countries is estimated to be 20-50 per 100,000 population.[1]

The condition often has a negative social impact, particularly with respect to driving, accident occurrence, and work-place and professional performance, with consequent effects on employment. There is currently no cure for narcolepsy and so treatment relies upon lifestyle changes and symptomatic therapies. A range of drug treatments are used in the management of narcolepsy with cataplexy and include sympathomimetic stimulants (mostly adrenergic) for daytime sleepiness and sleep attacks, antidepressants (mostly noradrenergic) for cataplexy and other REM-associated symptoms, and hypnotics for disturbed night-time sleep (see section 5 for more details).[4]

Sodium oxybate has been used as a third line agent in patients who have inadequate response to first and second line drugs.[1] 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. In the UK it is licensed for the treatment of narcolepsy with cataplexy in adult patients.[5] In the US it is licensed for cataplexy in patients with narcolepsy and also for excessive daytime sleepiness in patients with narcolepsy.[6]

There are safety concerns around the use of sodium oxybate including its potential to cause respiratory depression, and interaction with other medications (see SPC for full details). Sodium oxybate is a sodium salt of gamma hydroxybutyrate (GHB), a CNS active substance with well known abuse potential.[5] Many patients find side effects or restrictions related to the dosage regimen, which requires getting up in the night unacceptable. Clinical experience at Royal Papworth hospital found that 40% of patients (17 out of 42) who were started on sodium oxybate subsequently discontinued treatment.[4]

Due to the small number of patients, there is a lack of conventionally robust data on cost effectiveness. Historically NHSE had a negative policy for use in children, and many Clinical Commissioning Groups (CCGs) had a negative policy for use in adults.

The revised NHSE policy for use in children acknowledges the lack of cost effectiveness data but supports use in a small cohort of patients that have not responded to or cannot have current treatments.[1] Feedback from East of England clinicians based on clinical experience is that sodium oxybate can have life changing effects when used in a similar small group of adult patients in whom all other treatments have failed.

Current commissioning positions vary across the country. The Scottish Medicines Consortium (SMC) and the All Wales Medicines Strategy Group (AWMSG) currently do not recommend the use of sodium oxybate in adults. The Northern Treatment Advisory Group (NTAG) recommend for continuation of treatment only if the patient has benefited as a child.[7-10]

Some CCGs in London, Merseyside, and Cambridge and Peterborough, have taken a pragmatic approach and fund for adult patients who have failed to respond adequately to first line treatments, in line with with clear starting and stopping criteria.

As the small group of adult patients who may benefit from sodium oxybate treatment form a cohort, Individual Funding Requests (IFRs) for these patients would not be approved.

In October 2019, the RMOC published an advisory statement on commissioning sodium oxybate in adult patients with narcolepsy with cataplexy, and set out criteria for patients who should be considered for funding. The recommendations in this document are in line with those in the RMOC guidance statement.[2]

1. Dose and administration

Sodium oxybate (Xyrem®) is required to be taken at bedtime while in bed and again 2.5 to 4 hours later. The recommended starting dose is 4.5g/day divided in two equal doses of 2.25g. The starting dosage can then be increased to a maximum of 9g/day in increments of 1.5g/day (i.e. 0.75g per dose). A minimum of one to two weeks is recommended between dosage increases to evaluate clinical response and minimize adverse effects. The dose of 9g/day should not be exceeded due to the potential for severe side effects at doses of 18g/day or above. Single doses of 4.5g should not be given unless the patient has been titrated previously to that dose level.[5]

Treatment duration: For some patients this will be a life-long treatment.

Sodium oxybate is a controlled drug and is classified as a Schedule 2 (CD-POM).[9]

2. Clinical effectiveness

A report commissioned by the Northern Therapeutic Advisory Group (NTAG) in 2017 summarises the available data on the clinical effectiveness of sodium oxybate.[9]

The North East Therapeutic Advisory Group (now part of NTAG) appraisal conducted in 2009 summarised the evidence from two randomised controlled trials (RCTs) and several smaller studies.[11] It concluded that sodium oxybate has clear clinical benefits and there is a clear dose-response relationship for both efficacy and adverse effects. Longer term data indicated continued gains in clinical efficacy for the first few months followed by maintenance of the effect, although this evidence was taken from open studies with smaller patient numbers.

A systematic review and meta-analysis, which considered all of the trial reports discussed in the 2009 NETAG appraisal, was published in 2012.[12] Articles were identified for inclusion via searches of databases including Medline, Embase, CINHAL, the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov. Included studies were randomised controlled trials of sodium oxybate in people diagnosed with narcolepsy and cataplexy. Two reviewers independently screened the search results, assessed study quality and extracted data using a standardised extraction form. When assessed for bias, none of the included studies had adequate sequence generation or concealment of treatment allocation. Blinding, accounting for incomplete data and freedom from selective reporting were generally good. Pooled estimates of treatment effects were derived using a random effects model. Further detail on the study characteristics can be found in table 2 of the NTAG report on sodium oxybate.[9,10] Patients with other sleep disorders other than narcolepsy were excluded.

All of the efficacy outcomes reported favoured sodium oxybate and all were statistically significant, with the exception of the proportion of REM sleep occurring (of uncertain clinical relevance). However, sample sizes for some comparisons were very small, and confidence intervals were wide in several cases, limiting the precision of these estimates of treatment effect. Further detail on the efficacy outcomes can be found in table 2 of the NTAG report on sodium oxybate.[9] All outcomes except percentage of REM sleep favour sodium oxybate.

No other new trials of sodium oxybate were found. However, several new post-hoc analyses of older trials have been published. The four week trial (n=136) published in 2002 compared sodium oxybate to placebo for the primary outcome of change from baseline in the number of weekly cataplexy attacks.[13] The trial had a 12 month open-label extension, which found extended treatment led to further reduction in cataplexy attacks and improvement in quality of life.[14] In the new analysis, Bogan et al examined data from the trial and extension to determine the mean time to treatment response.[15] A total of 86 patients were treated with sodium oxybate in both the original trial and the extension. Of these, 78% were considered responders using the Epworth Sleepiness Scale (ESS) and 91% were cataplexy responders. The median time to first response was 37 days (95% CI 31-50) for excessive daytime sleepiness (EDS) and maximum response was achieved in 106 days (95% CI 85-164 days). The first cataplexy response was observed at 25 days (95% CI 17-29 days) and maximum response was achieved at 213 days (95% CI 94-279 days).

An eight week trial (n=228) published in 2005 compared several doses of sodium oxybate to placebo for the primary outcome of change in sleepiness, as measured using ESS.[16] Bogan et al published a further analysis in 2016 which assessed the impact on quality of life, as measured using the Medical Outcomes Survey short form 36 (SF-36) questionnaire. The questionnaire was administered at baseline, and at weeks 4 and 8 and a change of 5 points was considered to represent the minimum clinically important difference. The analysis found that all doses of sodium oxybate (4.5g, 6g or 9g daily) were associated with significant improvements in the physical components of quality of life ($p<0.05$). However, only the 9g dose exceeded the minimum clinically important difference, with a change from baseline of 6.3 ±9.1 points. In contrast, only the 6g dose was associated with a significant improvement in the mental components of quality of life (3.8 points, $p<0.05$ vs. baseline).[9]

A 4 week trial (n=278) published in 2006 recruited patients already taking modafinil.[17] Participants were then randomised to receive sodium oxybate monotherapy, modafinil monotherapy, sodium oxybate + modafinil combination therapy or placebo. Black et al published a further analysis of this trial in 2016 which examined the outcomes in patients with and without cataplexy.[18] Cataplexy was not an inclusion criterion, but 95 participants with a diagnosis of narcolepsy with cataplexy were retrospectively identified. Results in patients with and without cataplexy were compared using the ESS, maintenance of wakefulness test, and clinician's global impression of change. Patients were taking modafinil prior to the trial starting, so patients in the modafinil arm generally did not see any significant change in symptoms. Sodium oxybate was generally associated with improvements regardless of presence of cataplexy, as was the combination of sodium oxybate with modafinil. Further detail of the change from baseline in patients with and without cataplexy (post-hoc analysis) can be found in table 4 of the NTAG report on sodium oxybate published in May 2017.[9]

3. Cost effectiveness and cost impact

Cost effectiveness

Cost-effectiveness has not been demonstrated for the use of sodium oxybate for the management of narcolepsy with cataplexy in any patient group (children or adults).[1] Due to the small number of patients, it is unlikely that conventionally robust data on cost effectiveness will be available in the short to medium term.

Cost impact

Initially sodium oxybate (Xyrem®) was registered with the European Medicines Agency (EMA) as an orphan medicine due to the rarity of the condition and low patient numbers. However, Xyrem® has now been removed from the community register of orphan medicinal products, at the request of the marketing authorisation holder.[19]

Sodium oxybate is excluded from the National Tariff payment system.[20]

The cost of sodium oxybate varies with the dose, which ranges from 4.5g to 9g daily. Mean doses used in practice are likely to be in the middle of that range.[10]

Comparative costs of supplying sodium oxybate in primary and secondary care settings are shown in table 1.

Table 1: Comparative costs of supplying sodium oxybate in primary and secondary care[21]

Drug	Annual cost per patient	
	Supplied in secondary care (inc. VAT)	Supplied in primary care (exc. VAT)
Sodium oxybate Oral solution 500mg/ml x 180ml = £360 Dose range: 4.5g to 9g per day	£7,884 - £15,768	£6,570 - £13,140

The number of patients eligible for treatment with sodium oxybate is expected to be low. NHS England estimates that there are currently ten children treated with sodium oxybate nationally, with an additional ten children per year being eligible for treatment.[1] Two children resident in the East of England are currently being treated at the Evelina Children's Centre under the NHSE policy.[22]

Numbers of adult patients eligible for treatment are low. Papworth Hospital currently have 25 adult patients on sodium oxybate treatment out of a caseload of approximately 350. It is estimated that a maximum of eight additional patients in the East of England currently fulfil the criteria specified in section 4 of this document and would be eligible for a trial of sodium oxybate at their next review appointment.[4]

Cambridge and Peterborough CCG have an agreement in place to fund treatment for adults in line with this policy. They currently have seven patients who are prescribed sodium oxybate out of a total population of 884,000, which suggests an approximate prevalence of one patient requiring sodium oxybate treatment per 126,000 population.[23]

4. Criteria for commissioning

Inclusion criteria

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

- Adult patients aged 19 and older where attempts 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 three months. Specifically:

- Patients who present with narcolepsy with cataplexy according to International Classification of Sleep Disorders 3 (ICSD) criteria; AND
- Adequately treated co-morbid sleep disorders (such as obstructive sleep apnoea and restless legs syndrome) as assessed clinically and by polysomnogram (PSG) where appropriate*; AND
- Failure to respond to non-pharmacological treatments consisting of behavioural and environmental adaptations, for example planned naps AND
- Inadequate response (within three 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.

* Restless legs syndrome is an awake phenomenon and does not generally need a PSG, although patient with periodic limb movement may do.

- Continuation treatment for children transitioning to adult services where sodium oxybate has been commissioned by NHS England; i.e. continuing treatment for those ≥19 years old. Children transitioning to adult services should be reviewed by a Consultant Sleep Physician and assessed for suitability for continued treatment.

Exclusion criteria

- Patients who do not fit the above criteria and for whom this treatment is contraindicated, including exclusion as advised by manufacturer.

Review and stopping criteria

- Serious adverse effects including signs of respiratory depression; OR
- Evidence of inadequate response at three months as assessed by clinical review according to:
  - For cataplexy: the severity and frequency criteria below (table 2); AND
  - For narcolepsy: the Epworth Sleepiness Scale.

At least one of the cataplexy scores (either severity or frequency) should improve after three months of treatment.

NB. There is no validated tool for assessing the severity and frequency of cataplexy in adults. However, feedback from adult sleep specialists is that the scoring system used in the NHSE policy for children could be pragmatically applied to adult patients.

Table 2: Scoring system for severity and frequency of cataplexy[1]

Severity of cataplexy	Score	Frequency of cataplexy	Score
Mild weakness	0	<1 attack per year	0
Moderate weakness	1	≥1 attack per year	1
Can maintain posture with external support	2	>1 attack per month	2
Loses posture and falls to the ground	3	>1 attack per week	3
		>1 attack per day	4

- 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.

5. Patient pathway

First line treatment consists of behavioural and environmental adaptations and wakefulness promoting medication for daytime sleepiness. Failure to respond to these interventions will progress to second line therapies.

Referrals to specialist sleep services can be made from primary or secondary care.

Once diagnosis is confirmed by the specialist sleep service, the patient is prescribed one of the following first or second line medications, conventionally divided into medications that improve excessive daytime sleepiness and those that treat cataplexy. (Note that medications that are classed as 'first' and 'second' line in the list below are based on clinical consensus. This varies between countries, and there is a lack of head-to-head studies to evidence such choices).

	First line	Second line	Third line
Excessive daytime sleepiness	Modafinil	Dexamphetamine Methylphenidate (immediate or prolonged release)	
Cataplexy	Clomipramine	Venlafaxine SSRIs	Sodium oxybate

NB. Pitolisant is considered a third line agent for treating excessive daytime sleepiness and may also be used as an alternative third line agent for patients with refractory cataplexy symptoms, however it is not currently commissioned by most CCGs in the East of England.[4]

6. Prescribing considerations

Sodium oxybate should be initiated and titrated to effect in secondary or tertiary care by a specialist sleep centre with expertise in treating narcolepsy, including experience in use of sodium oxybate.

The specialist sleep centre must have access to a sleep laboratory that can conduct standard polysomnography and multiple sleep latency tests to American Academy of Sleep Medicine (AASM) standards. The specialist sleep centre should involve a multi-disciplinary team, including consultants and access to a range of other specialities which may include psychology, psychiatry, specialist pharmacists, and sleep technologists.[2]

Considerations should include whether psychological support arrangements need to be put in place for the individual patient, including psychological assessment where the patient is deemed to be at higher risk of harm.

Prescribing and supply of sodium oxybate should remain with the specialist centre, e.g. via the Homecare route.

The RMOC recommends that adult patients currently receiving sodium oxybate should be reviewed to ensure that the treatment remains effective and that there is an ongoing need.[2]

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Document history

PAC approval date	2nd March 2020	**Version**	2.0
Consultation process	Dr. Tim Quinnell, Consultant Respiratory and Sleep Disorders Physician, Respiratory Support and Sleep Centre, Royal Papworth Hospital. Professor Paul Gringras, Professor of Children's Sleep Medicine and Neurodisability, Evelina Centre, Guys and St Thomas Hospital		
QA process	Katie Smith, Director of Clinical Quality, PrescQIPP, 18th March 2020.		

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Appendix 1: Assessment against ethical and commissioning principles

Treatment assessed

Sodium oxybate for the management of narcolepsy with cataplexy in adults.

East of England Priorities Advisory Committee recommendation

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

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  - Adequately treated co-morbid sleep disorders (such as obstructive 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 three 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 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; i.e. continuing treatment for those ≥19 years old. 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 supply of sodium oxybate should remain with the specialist centre.

Clinical effectiveness

Clinical efficacy was assessed in a meta-analysis and systematic review which demonstrates significant improvements in number of cataplexy attacks, wakefulness, number of sleep attacks and global clinician global impression of change associated with sodium oxybate.

Cost effectiveness

Cost-effectiveness has not been demonstrated for the use of sodium oxybate for the management of narcolepsy with cataplexy in any patient group (children or adults). However, due to the small number of patients, it is unlikely that conventionally robust data on cost effectiveness will be available in the short to medium term.

Narcolepsy with cataplexy is a condition that often has a negative social impact, particularly with respect to driving, accident occurrence, and work-place and professional performance, with consequent effects on education and employment. The costs associated with supporting patients with refectory narcolepsy with cataplexy have not been quantified but need to be considered.

Equity

Currently children and young people under the age of 19 are able to access sodium oxybate treatment under NHS England commissioning policy. These recommendations ensure equity in access to treatment for adult patients aged 19 and over.

Needs of the community

Sodium oxybate is a high cost treatment however the number of eligible patients is likely to be small. There is a lack of data on cost-effectiveness, however clinical experience has shown that treatment in the small group of eligible patients may have life changing effects e.g. allowing patients to be able to study or return to and remain in employment. The unquantified social costs of providing support for these patients have been considered when making these recommendations.

Need for healthcare (incorporates patient choice and exceptional need)

A small group of patients who do not respond to first and second line therapies would benefit from this treatment. This group of patients are often unable to remain in education or employment and have significant social needs.

Policy drivers

NHSE Clinical Commissioning Policy: Sodium oxybate for symptom control of narcolepsy with cataplexy (children) December 2016 Reference: NHS England: 16065/P https://www.england.nhs.uk/publication/clinical-commissioning-policy-sodium-oxybate-for-symptom-control-of-narcolepsy-with-cataplexy-children/

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Disinvestment

None