

Evidence Review for NHS Surrey Area Prescribing Committee

Treatment: Sodium Oxybate (Xyrem®) for the treatment of cataplexy for patients with Narcolepsy

Prepared by: Clare Johns (Senior Technician – Pharmaceutical Commissioning, NHS Surrey)

Topic Submitted by: Linda Honey

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1. Purpose of the Review

The purpose of this document is to review the evidence supporting the clinical effectiveness of Sodium Oxybate for the treatment of narcolepsy with cataplexy

It is not within the scope of this document to provide guidance on diagnosis or the use of other available pharmacological agents in the treatment of this condition.

This review has been sent to consultant neurologists in Surrey for comment. Their opinions (Appendix 4.) have been incorporated into this document.

2. Appropriateness

2.1 The patient:

Patients that have a definitive diagnosis of narcolepsy with cataplexy, Sodium Oxybate is licensed for use in adult patients (Aged 18 years & over). Safety and effectiveness in children and adolescents has not been established, therefore use in patients under 18 years of age is not recommended.

2.2 The problem:

Definition: Cataplexy is an abrupt, reversible decrease in muscle tone caused by emotion, such as laughter, elation or anger and is reported by approximately 75% of patients with narcolepsy. The term narcolepsy is used to describe a syndrome comprising of four main characteristics symptoms: sleep attacks, cataplexy, hypnagogic hallucinations and sleep paralysis¹.

Normal sleep comprises of two separate sleep states: rapid eye movement (REM) sleep (vivid dreaming, muscle atonia, desynchronized activity on an electroencephalogram (EEG), and episodic bursts of REM) and non-REM sleep (muscle relaxation, slow/ delta wave activity on EEG, less frequent dreaming). In narcolepsy both onset and offset of REM- and non-REM sleep are impaired and narcoleptics are unable to maintain either type of sleep, leading to frequent arousals and disturbed nocturnal sleep⁴.

Effects and prognosis:

Patients with narcolepsy will have a strong almost irresistible urge to sleep recurring at intervals during the day. Sleep at inappropriate times, such as during meals are characteristic³

Complete cataplexy (sudden and severe loss of muscle tone causing collapse to the ground) is experienced by approx. 1/3 patients suffering from narcolepsy with cataplexy. The main muscles affected are the face & neck, leading to a sagging jaw, inclined head & slurred speech. Extremities can also be affected such as buckling of the knees¹. (Symptoms of narcolepsy are detailed below)

| Symptoms of Narcolepsy⁴ | |
|---|--|
| Excessive daytime sleepiness (EDS) | <ul style="list-style-type: none"> • Daytime sleep episodes occurring at inappropriate or unexpected times. • Has major social implications • First clinical symptom to emerge. |
| Cataplexy | <ul style="list-style-type: none"> • Abrupt, reversible decrease in muscle tone caused by emotion, such as laughter, elation or anger. • Reported by ~75% of narcoleptics • Mainly affect facial/neck muscles (sagging jaw, inclined head and slurred speech). Can also affect extremities (e.g. buckling of knees) • Complete cataplexy (sudden and severe loss of muscle tone causing collapse to the ground) is experienced by ~1/3 of narcoleptics with cataplexy. • Attacks are usually brief but can last up to 30 minutes. |
| Sleep paralysis | <ul style="list-style-type: none"> • Inability to move for seconds to minutes during sleep onset or offset. • Breathing is unaffected but patients are unable to move their extremities, or speak. • Up to 80% of narcoleptic patients report sleep paralysis episodes. |
| Hypnagogic hallucinations | <ul style="list-style-type: none"> • Occur during the transition between waking and sleep, and in addition to nocturnal sleep onset, may occur during daytime naps or sleep attacks. • Often bizarre or frightening visual experiences but may also have auditory or other sensory involvement. • Patients are aware they are hallucinating and remain conscious of their surroundings. • Experienced by nearly 70% of narcoleptics. |
| Automatic behaviours | <ul style="list-style-type: none"> • Experienced by ~50% of narcoleptics. • Occurs when sleep has partially overtaken the brain but body continues to perform familiar tasks with complete retrograde amnesia. • Brief lapses during conversation or routine activities, such as walking or driving. |
| Other | <ul style="list-style-type: none"> • Poor nocturnal sleep with frequent arousals • Symptoms have negative impact on the quality of life of patients. • Risk of serious motor accidents is real. • Fear of public embarrassment and injury resulting from cataplexy episodes, resulting in suppressed emotions to lessen the attacks. • May be viewed as poorly motivated or depressed. • Secondary psychological symptoms such as alienation, shame, low self esteem |

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Etiology:

Narcolepsy may have a number of etiologies and may be partially genetic. In the 1980s Japanese workers discovered that many people with narcolepsy have the tissue type human leucocyte antigen (HLA) DR2³, and 95% of people with narcolepsy and cataplexy have the HLA DQB1*0602³.

In the year 2000 it was reported that concentrations of hypocretins were markedly reduced in the cerebrospinal fluid of narcoleptic patients with cataplexy³. Hypocretin containing neurons are found in the hypothalamus and project to various parts of the brain believed to regulate sleep:⁴ their depletion explains both the rapid transition between wakefulness and rapid eye movement sleep, and the tendency for these states to fragment in narcolepsy³.

Diagnosis:

A sleep diary may be useful in the first instance. The Epworth sleepiness scale is an internationally accepted means of measuring daytime sleepiness, the major symptom of narcolepsy. If a patient's score is 10 or below this indicates a level of daytime sleepiness found in the general population. A score of 18 or more indicates that a patient has very marked daytime sleepiness that would require medical attention.

Patients would normally be referred to a specialised Sleep Centre. A history will be taken to determine the types of symptoms the patient is experiencing, the family history, the age when the first symptoms were noticed etc. Unless diagnosis is clear from presenting symptoms such as cataplexy, patients will probably stay overnight and undergo polysomnographic testing. These tests involve a measurement of the electrical activity of the brain, eye and muscle movement and breathing as the patients fall asleep and whilst asleep. How rapidly the subjects fall asleep will be measured - this is called 'sleep latency'. Several such tests are usually carried out - these are called a Multiple Sleep Latency Test (MSLT). Narcoleptic subjects usually fall asleep rapidly and thus have short sleep latency. The type of sleep they enter into from consciousness will be recorded.

Evidence that they pass rapidly into REM sleep is regarded as being positive for strong indicator for narcolepsy. Such episodes are called 'Sleep Onset Rapid Eye Movement Periods'. In some centres blood samples will be taken for analysis of tissue type. Increasingly, a sample of cerebrospinal fluid (CSF) will be taken for measurement of orexin concentration. Low CSF orexin values can be of value in the diagnostic process⁵, but is not invariably low in people with narcolepsy (especially in those without cataplexy)

2.3 The Intervention:

Sodium Oxybate is a central nervous system depressant. 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 involved².

The marketing authorisation holder for sodium oxybate, UCB Pharma, offers a patient access scheme known as the 'Xyrem® Responder Programme'. Participation can be made without a commitment to prescribe. The scheme will refund, by way of stock credit, the cost of medication prescribed within the first three months of commencing therapy for patients who discontinue treatment for any reason within the first three months. The criteria for discontinuation are not defined or judged and are instead determined entirely at

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the discretion of the responsible clinician. Claims for credit must be signed by the clinician and a representative of the dispensing pharmacy.¹⁶

Care setting: Treatment should be initiated by and remain under the guidance of a physician experienced in the treatment of sleep disorders².

Frequency:

The recommended starting dose is 4.5 g/day sodium Oxybate (Xyrem) 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 4.5g/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 dosage increments. The dose of 9g/day should not be exceeded due to the possible occurrence of severe symptoms at doses of 18 g/day or above.

A 10ml measuring syringe and two 90 ml dosing cups are provided with sodium Oxybate (Xyrem). Each dose of sodium Oxybate (Xyrem) must be diluted with 60 ml of water in the dosing cup prior to ingestion.

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

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.

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 measuring syringe and dosing cup with child resistant cap. Each measured dose of Sodium oxybate must be dispensed into the dosing cup and diluted with 60 ml of water prior to ingestion.

2.4 Alternative treatments:

Clomipramine (in combination with low dose benzodiazepines) initially 10mg daily, gradually increased until satisfactory response (range 10-75mg daily). Clomipramine is the only other drug licensed for the treatment of narcolepsy with cataplexy.

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

3. Effectiveness

3.1 Expected benefits

Sodium Oxybate would be expected to provide clinical improvement in the frequency of cataplexy attacks and reduced daytime sleepiness.

The Epworth sleepiness score can be used to monitor effectiveness but will only monitor sleepiness not cataplexy attacks

3.2 Side-effects/complications²

Abuse potential and dependence

The active substance in Xyrem is sodium oxybate, which is as the sodium salt of gamma hydroxybutyrate (GHB), a CNS depressant active substance with well known abuse potential.

There have been case reports of dependence after illicit use of GHB at frequent repeated doses (18 to 250 g/day) in excess of the therapeutic dose range. Whilst there is no clear evidence of emergence of dependence in patients taking sodium oxybate at therapeutic doses, this possibility cannot be excluded.

Sodium intake

Patients taking sodium oxybate will have an additional daily intake of sodium that ranges from 0.82g (for a 4.5g/day Xyrem dose) to 1.6g (for a 9g/day Xyrem dose).

Rebound effects and withdrawal syndrome

The discontinuation effects of sodium oxybate have not been systematically evaluated in controlled clinical trials. 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, events such as insomnia, headache, anxiety, dizziness, sleep disorder, somnolence, hallucination, and psychotic disorders were observed after GHB discontinuation.

Adverse events

The most commonly reported adverse drug reactions are dizziness, nausea, and headache, all occurring in 10 % to 20 % of patients.

| Very Common (≥ 1/10) | Common (≥ 1/100 to < 1/10) |
|---|---|
| <ul style="list-style-type: none"> • Dizziness, Headache • Nausea (the frequency of nausea is higher in women than men) | <ul style="list-style-type: none"> • Anorexia, Blurred Vision, Hypertension, Dyspnoea, Snoring, Vomiting, Upper abdominal pain. • Diarrhoea, Abnormal dreams, Confusion, Disorientation, Nightmares, Sleepwalking, Depression, Sleep Disorder. • Cataplexy, Anxiety, Insomnia, Middle Insomnia, Nervousness, Sleep Paralysis, Somnolence, Tremor, Balance Disorder, Disturbance in Attention, Hypoaesthesia, Paraesthesia, Sedation, Sweating. • Muscle Cramps, Arthralgia, Enuresis Nocturna, Urinary Incontinence • Asthenia, Fatigue, Feeling Drunk, Oedema Peripheral. • Fall |

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3.3 Review of evidence (See Appendix 1. for Search Strategy and Summary of Results)

(Please see appendix 2 for hierarchy of evidence quality)

A randomized, double blind, placebo controlled clinical trial⁶ was undertaken to compare three different doses of sodium oxybate with placebo. 136 narcolepsy patients with 3 to 249 (median 21) cataplexy attacks per week were randomized to receive 3g, 6g or 9g oral doses of sodium oxybate or placebo taken in equally divided doses upon going to bed and then 2.5-4 hours later for four weeks. Prior to commencing patients discontinued antiepileptic medications, however, stable doses of stimulants were permitted. The primary measure of efficacy was the change from baseline in weekly cataplexy attacks. Secondary measures included daytime sleepiness using the Epworth Sleepiness scale (ESS), inadvertent daytime naps/ sleep attacks and nighttime awakenings. Investigators assessed changes in disease severity using Clinical Global Impression of Change (CGI-c). All outcomes were found to be reduced by sodium oxybate doses of 6g and 9g compared to placebo. The 9g dose was found to be clinically significantly better than placebo for the primary outcome as well as the secondary measures. Weekly cataplexy attacks were found to be reduced by the 6g dose compared to placebo, but this was not found to be significant (p=0.529).

An extension to the above trial⁷ was carried out using 118 of the original patients. The patients were administered 6g sodium oxybate nightly, taken in equally divided doses at bedtime and then 2.5 to 4 hours later. The study protocol permitted the dose to be increased or decreased in 1.5g increments at two week intervals, but stayed within the range 3g-9g nightly. The primary efficacy measure was the change in weekly cataplexy attacks from baseline. Secondary measures were also the same as those in the original four week trial. Sodium oxybate, in doses of 3g-9g nightly produced overall improvements in narcolepsy symptoms, which were significant at four weeks and maximal after 8 weeks. Reported improvements included a significant decrease in frequency of cataplexy attacks, diminished daytime sleepiness; and patients descriptions of nocturnal sleep quality, level of alertness, and ability to concentrate (all p<0.001).

Fifty five narcolepsy patients with cataplexy who had received continuous treatment with sodium oxybate for 7-44 months (mean; 21 months) were enrolled in a double blind treatment withdrawal paradigm⁸ During the 2 week double blind phase, the abrupt withdrawal of sodium oxybate therapy in the placebo group resulted in a significant increase in the number of cataplexies (p<0.001) compared to the patients who remained on the sodium oxybate therapy. All 55 enrolled patients completed the trial.

Another study⁹, with 228 patients was a double blind placebo controlled study looking at the effect of nocturnal administration of sodium oxybate on cataplexy in patients with narcolepsy. Three doses of sodium oxybate (4.5g, 6g and 9g) and placebo were compared for eight weeks. The number of cataplexy attacks were recorded via patient diaries. At the end of the first 4 weeks of treatment, the frequency of cataplexy significantly decreased by a median of 44.3% (p=0.006), 51.9% (p<0.001) and 61.8% (p<0.001) in the 4.5g, 6g and 9g respectively, compared to placebo. The frequency of cataplexy was significantly decreased even further during the subsequent 4 week treatment period, resulting in final median decreases of 57% (p=0.003), 65% (p=0.002) and 84.7% (p<0.001), compared to placebo.

AWMSG www.wales.nhs.uk (October 2008)
Appraisal notice to NHS Wales

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Sodium oxybate (Xyrem®) has not been endorsed for use within NHS Wales for the treatment of cataplexy associated with narcolepsy.

The holder of the marketing authorisation has not made a submission to AWMSG for the appraisal of sodium oxybate (Xyrem®) for the above indication. As a result, AWMSG cannot advise the Minister for Health and Social Services whether this medicine should be available for use within NHS Wales.

www.scottishmedicines.org.uk (August 2007)

Link to SMC discussion document

[http://www.scottishmedicines.org.uk/files/sodium%20oxybate%20500mg%20ml%20oral%20solution%20\(Xyrem\)%20Resubmission%20FINAL%20August%202007%20for%20website.pdf](http://www.scottishmedicines.org.uk/files/sodium%20oxybate%20500mg%20ml%20oral%20solution%20(Xyrem)%20Resubmission%20FINAL%20August%202007%20for%20website.pdf)

ADVICE: following a resubmission

Sodium oxybate (Xyrem®) is not recommended for use within NHS Scotland for the treatment of cataplexy in adult patients with narcolepsy.

The manufacturer's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC.

www.nice.org.uk Not being considered currently

Thames valley priorities committee (June 2007)

Sodium oxybate for cataplexy and excessive daytime sleepiness in narcolepsy

The Thames Valley Priorities Committees have reviewed the evidence for Sodium Oxybate for the treatment of cataplexy in adult patients with narcolepsy and considered its use to be a LOW PRIORITY due to limited evidence of clinical and cost effectiveness when compared to existing treatments available.

Summary

Sodium oxybate is the sodium salt of gamma hydroxybutyrate (GHB). It is licensed as a liquid for oral administration in the treatment of cataplexy in adult patients with narcolepsy. In two short term (4 to 8 weeks) randomised placebo controlled studies, sodium oxybate, at the licensed dose range, produced a median percent reduction in weekly cataplexy attacks ranging from 49% to 85%, compared with only 14% to 22% in the placebo groups. Long term open follow up studies (up to 12 months), showed that its effects are sustained, and sudden withdrawal does not produce an acute increase in the frequency of cataplexy attacks. There are however, no clinical studies directly comparing sodium oxybate with the other treatment options (for example, tricyclic antidepressants and selective serotonin reuptake inhibitors, SSRI) commonly used in cataplexy.

In January 2010 the North East Treatment advisory Group concluded that:

The group was satisfied that the relative efficacy and safety of sodium oxybate (Xyrem®) in the management of narcolepsy with cataplexy had been adequately demonstrated. However, the treatment is unlikely to meet conventional cost effectiveness criteria if applied to all eligible patients and in the absence of evidence to indicate cost effectiveness if the treatment is targeted at the most severe cases, the group did not recommend sodium oxybate. Patients may still access treatment via individual funding requests if exceptionality can be demonstrated.

4. Summary of Key Points for Consideration

4.1 National guidance: There is no national guidance available or in development.

4.2 Efficacy

The evidence above shows clinical benefit over placebo. Higher doses of sodium Oxybate appear to show greater responses than lower doses

4.3 Potential Benefits over existing therapy

There is currently no cure for narcolepsy and so treatment relies upon lifestyle changes and symptomatic therapies. A range of drug treatments is 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. Few drugs are actually licensed for narcolepsy with cataplexy, with clomipramine (a noradrenergic antidepressant) being the only other drug along with Xyrem®.^{13 14} Other drugs commonly used are demonstrated in table 1.^{13 15}

Table 1. Drugs used in the treatment of narcolepsy with cataplexy

| Type | Drug Examples | Indication of target symptoms |
|---|---|--|
| Selective-serotonin reuptake inhibitor | Fluoxetine, Citalopram | Cataplexy and other REM associated phenomena |
| Benzodiazepines and related hypnotics | Clonazepam, Zolpidem, Zopiclone | Adjuvant to aid night-time sleep |
| Tricyclic antidepressant acting on serotonin and noradrenaline pathways | Clomipramine (Anafranil®) | Cataplectic symptoms |
| Serotonin and noradrenaline reuptake inhibitor | Venlafaxine (Efexor®) | Cataplectic symptoms |
| Noradrenergic reuptake inhibitor | Reboxetine (Edronax®) Atomoxetine (Strattera®) | Cataplectic symptoms |

Sodium Oxybate is distinguished from other drugs used in the treatment of narcolepsy with cataplexy as it is considered to be effective in controlling daytime sleepiness, cataplexy, and disturbed night-time sleep; i.e. it is used to control multiple symptoms whereas other drug treatments are usually targeted at a single symptomatic aspect^{13 15}.

4.4 Potential disadvantages

Sodium Oxybate presents a significant burden of adverse effects to a large proportion of patients with the most common being headache, nausea, vomiting, dizziness and confusion. The effects usually become apparent soon after initiation of treatment which should facilitate identification of patients who will not be able to tolerate treatment.

Sodium Oxybate has potential for misdirection and abuse and patients should be evaluated for a history of drug abuse.

Sodium Oxybate is associated with specific administration instructions that mean it might not be suitable for some patients. For example, it should be taken at least two hours after the consumption of any food, the daily dose must be divided in two with the first dose taken immediately prior to night-time sleep and the second dose taken 2½ to 4 hours later, it contains a high sodium load that could be significant in some patients, and each dose must be diluted with 60 ml of water prior to consumption.

4.5 Budgetary Impact

4.5.1 Cost: (licensed preparations only)

| Drug | Dose regimen | Cost per year (£) VAT no included |
|-----------------------|--------------------------|-----------------------------------|
| Sodium Oxybate | 4.5-9g/day orally | £6480 - £12,960 |
| Anafranil SR® | 75mg/day orally | £115 |
| clomipramine | 10-75mg/day orally | £35- £92 |

4.5.2 Precedent setting:

Narcolepsy is often diagnosed either in adolescence or in middle age. Narcolepsy with cataplexy is estimated to affect about 3 5/10,000 of the population. Transposing this into the population of NHS Surrey there would be an estimated prevalence of 360 & 600 patients.

However, information supplied a clinician at a tertiary centre estimates that most patients, seen at the tertiary centre, (95%) are adequately controlled with other medications. Therefore, there is a potential for between 18 & 30 patients not being controlled on other medications who may require Sodium Oxybate.

NHS Surrey has received 1 funding application for this treatment to date (2007 to date) from a tertiary centre. Sodium Oxybate became a payment by results excluded drug in 2009/10.

Epact data shows that 1 GP Practice in Surrey has prescribed Sodium Oxybate liquid in December 2009.

Sodium Oxybate for narcolepsy with cataplexy is not commissioned by PCTs contacted in South West London currently.

5. Conclusions and Recommendations

Sodium Oxybate & Clomipramine are the only licensed preparations for narcolepsy with cataplexy.

The annual incidence for NHS Surrey for patients that are not adequately controlled on standard interventions would be approximately 18 to 30 patients in Surrey. NHS Surrey has received 1 application to date (2007 to date).

There have been several fully published trials evaluating the use of Sodium Oxybate for the treatment of narcolepsy with cataplexy in adult patients conducted by the Xyrem® multicenter study group. There is a summary of trials above showing clinical benefit over placebo. There are no studies available showing comparisons between other treatment options.

The marketing authorisation holder for sodium oxybate, UCB Pharma, offers a patient access scheme known as the 'Xyrem® Responder Programme'. Participation can be made without a commitment to prescribe. The scheme will refund, by way of stock credit,

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the cost of medication prescribed within the first three months of commencing therapy for patients who discontinue treatment for any reason within the first three months.

Potential disadvantages to treatment include significant adverse effects which become apparent soon after initiation.

Sodium Oxybate has potential for misdirection and abuse and patients should be evaluated for a history of drug abuse.

Sodium Oxybate is associated with specific administration instructions that mean it might not be suitable for some patients.

Options:

- NHS Surrey do not routinely fund this intervention due to limited evidence of clinical and cost effectiveness.
- NHS Surrey will fund patients within specific prescribing criteria
 - One clinician restricts consideration of use to those who have proved resistant to two antiepileptic agents, one of which is Clomipramine, the only other licensed preparation.

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Appendix 1: Evidence search

Search terms used:

| Resource | Used in this review? |
|--|------------------------|
| <p>National Library for Health (NHL) http://www.library.nhs.uk/Default.aspx</p> <p>A gateway site with access to other resources such as Reviews (Bandolier, Cochrane, CRD etc), Guidelines (e.g. NICE), Clinical Knowledge Summaries (CKS) and Journals including AMED, British Nursing Index, CINAHL, E-books, EMBASE, HMIC, MEDLINE, My Journals, PsycINFO, PubMed, Databases from Dialog.</p> | <p>✓</p> |
| <p>National Institute of Health and Clinical Excellence (NICE) http://www.nice.org.uk/</p> <p>NICE produces national guidance in three areas of health:</p> <ol style="list-style-type: none"> 1. Public health - guidance on the promotion of good health and the prevention of ill health 2. Health technologies - guidance on the use of new and existing medicines, treatments and procedures within the NHS 3. Clinical practice - guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS. | <p>✓ (through NHL)</p> |
| <p>Bandolier http://www.medicine.ox.ac.uk/bandolier/index.html</p> <p>Bandolier is a website about the use of evidence in health, healthcare, and medicine. Information comes from systematic reviews, meta-analyses, randomised trials, and from high quality observational studies.</p> | <p>✓ (through NHL)</p> |
| <p>Centre for Reviews and Dissemination http://www.york.ac.uk/inst/crd/</p> <p>CRD undertakes high quality systematic reviews that evaluate the effects of health and social care interventions and the delivery and organisation of health care. Databases maintained by CRD include Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) Database</p> | <p>✓ (through NHL)</p> |
| <p>Scottish Intercollegiate Guidelines Network (SIGN) http://www.sign.ac.uk/</p> <p>Scottish equivalent of NICE</p> | <p>✓</p> |
| <p>Medical Services Advisory Committee (Australia) http://www.msac.gov.au/internet/msac/publishing.nsf/Content/home-</p> | <p>✓</p> |

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| The principal role of the Medical Services Advisory Committee (MSAC) is to advise the Australian Minister for Health and Ageing on evidence relating to the safety, effectiveness and cost-effectiveness of new medical technologies and procedures. | |
| Canadian Agency for Drugs and Technologies in Health (CADTH) http://www.cadth.ca/index.php/en/home The Canadian Agency for Drugs and Technologies in Health (CADTH) is a national body that provides Canada's federal, provincial and territorial health care decision makers with credible, impartial advice and evidence-based information about the effectiveness and efficiency of drugs and other health technologies. | ✓ |

Appendix 2: Grading of evidence

- Ia: systematic review or meta-analysis of randomised controlled trials
- Ib: at least one randomised controlled trial
- IIa: at least one well-designed controlled study without randomisation
- IIb: at least one well-designed quasi-experimental study, such as a cohort study
- III: well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, case-control studies and case series
- IV: expert committee reports, opinions and/or clinical experience of respected authorities

Appendix 3: References

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2. Summary of product characteristics Sodium Oxybate (Xyrem). Accessed on 13th May at 2.30pm. www.medicines.org.uk
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11. East Sussex Hospitals NHS Trust Medicines Information, New Product Information (August 2007)
12. Mamelak M, Black J, et al. A pilot study on the effects of sodium oxybate on sleep architecture and daytime alertness in narcolepsy. *Sleep* 2004; 27 (7):1327-1334.
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16. 'Xyrem responder programme' information from UCB Pharma Ltd.
17. North East Treatment Advisory Group Sodium oxybate (Xyrem®) in the management of narcolepsy with cataplexy (December 2009)

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Journals

| Study | Number of participants | Duration | Results for primary endpoint | Other outcomes | Safety info |
|---|------------------------|------------------|---|--|---|
| <p>Xyrem® multicenter study group. A randomized, double blind, placebo-controlled trial comparing sodium oxybate nightly doses of 3g, 6g and 9g to placebo.</p> | <p>136</p> | <p>4 weeks</p> | <p>Compared to placebo, weekly cataplexy attacks were decreased by sodium oxybate at the 6g dose (p=0.0529) and significantly at the 9g dose (p=0.0008).</p> <p>Median % change from baseline for cataplexy attacks per week: 3g: 49% 6g: 49% 9g : 69% Placebo: 28%</p> | <p>Compared to placebo; Daytime sleepiness using the ESS scale was reduced at all doses, but only significantly at 9g dose (p=0.0001). Disease severity using Clinical Global Impression of Change (CGI-c) was significantly improved at the 9g dose (p=0.0002). The frequency of inadvertent naps/ sleep attacks and night time awakenings showed similar dose-response trends, but were significantly reduced at the 9g dose (p=0.0122 and p=0.0035, respectively).</p> | <p>Sodium oxybate was well tolerated at all three doses. Nausea, headache, dizziness and enuresis were the most commonly reported adverse events. 16 patients did not complete trial- 10 withdrew due to an adverse event. All but one was considered to be mild or moderate in severity.</p> |
| <p>Xyrem® multicenter study group. A 12 month, open-label, trial with patients receiving nightly 6g sodium oxybate doses which could be increased or decreased in 1.5g increments at two week intervals, but staying within 3-9g nightly.</p> | <p>118</p> | <p>12 months</p> | <p>Sodium oxybate doses of 3g to 9g nightly produced a significant decrease in the frequency of cataplexy attacks (p<0.001) compared to baseline.</p> <p>Number of cataplexy attacks decreased after 1 month by an average of 23.65 per week from baseline</p> | <p>Daytime sleepiness, patient descriptions of nocturnal sleep quality, level of alertness and ability to concentrate were reported as improvements (p<0.001 for each)</p> | <p>11 (9.4%) patients withdrew from the study due to an adverse event. The most commonly reported adverse events were headache, nausea, viral infection, dizziness, pain, enuresis and somnolence. Of these events only dizziness occurred at a significant level (p<0.05).</p> |

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| | | | (p<0.001)and by 35.48 per week at the end of the study period | | | | | | | | | | | |
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| Xyrem® multicenter study group. A long term double blind treatment withdrawal paradigm study in patients with narcolepsy. Patients chosen were those who had undergone continuous sodium oxybate therapy for a minimum of 6 months(mean 21months). | 55 | 2 weeks double blind after long term Tx | The abrupt withdrawal of sodium oxybate in the placebo group resulted in a significant (p<0.001) increase in the number of cataplexies reported compared to the group of patients who remained on their sodium oxybate. | <p>Primary efficacy variable was the change in the number of weekly cataplexy attacks from the baseline to the double-blind phase. Study was divided into 2 phases.</p> <p>Phase 1: Initial 2 weeks during which patients continued to take sodium Oxybate in a single blind manner. Daily diaries were used to record cataplexy attacks and adverse events</p> <p>Phase 2: 2 week period. Half of the patients were assigned to continue active treatment (n=26) and half assigned to placebo (n=29) in a double blind fashion. Daily diary use continued.</p> <p>In the sodium Oxybate group there was no mean change in the number of cataplexy attacks between phases 1 and 2. However, in the placebo group the number of cataplexy attacks increased significantly more during the same period (p<0.001).</p> <p>:</p> <table border="1"> <thead> <tr> <th>Frequency of cataplexy attacks mean (range)</th> <th>Sodium Oxybate</th> <th>Placebo</th> </tr> </thead> <tbody> <tr> <td>Beginning of period 1</td> <td>9.9± 21.4 (0-93)</td> <td>15.8±39.9 (0-197)</td> </tr> <tr> <td>End of period 2</td> <td>12.8± 33.5 (0-158)</td> <td>46.5± 73.8 (0-250)</td> </tr> </tbody> </table> | Frequency of cataplexy attacks mean (range) | Sodium Oxybate | Placebo | Beginning of period 1 | 9.9± 21.4 (0-93) | 15.8±39.9 (0-197) | End of period 2 | 12.8± 33.5 (0-158) | 46.5± 73.8 (0-250) | All 55 patients remained in the study. During the double blind treatment period 12 (22%) patients reported an adverse event., including 3 patients in the sodium oxybate group and 9 in the placebo group. |
| Frequency of cataplexy attacks mean (range) | Sodium Oxybate | Placebo | | | | | | | | | | | | |
| Beginning of period 1 | 9.9± 21.4 (0-93) | 15.8±39.9 (0-197) | | | | | | | | | | | | |
| End of period 2 | 12.8± 33.5 (0-158) | 46.5± 73.8 (0-250) | | | | | | | | | | | | |

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| | | | | Attacks at week 3 | No change | 4.2 | |
|--|-----|---------|---|--|-----------|---|--|
| | | | | Attacks at week 4 | No change | 11.7 | |
| Xyrem International study group. A randomized, double blind, placebo-controlled study. Patients were weaned off from any previous antiepileptic medications, then randomized to receive either 4.5g, 6g or 9g sodium oxybate nightly or placebo for 8 weeks. | 228 | 8 weeks | Compared with placebo, doses of 4.5g, 6g and 9g sodium oxybate for 8 weeks resulted in statistically significant median decreases in weekly cataplexy attacks of 57%(p=0.003), 65% (p=0.002) and 84.7% (p<0.001), respectively. | Significant improvements of other REM-related narcolepsy symptoms in these patients were difficult to achieve due to the low baseline frequency of these symptoms. Although there was a suggestion of improvement in these narcolepsy symptoms, they did not achieve significance except for the reduction in sleep paralysis at the 6g dose | | 21 patients discontinued the trial due to an adverse event in the placebo (1), 4.5g(1), 6g (4) and 9g (15) dose groups. Adverse events with greater than 5% incidence included nausea, and dizziness, which appeared to be dose related. Although >5% patients reported enuresis, this was not significantly different than placebo patients. | |

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| <p>Mamelak and Black et al. An open label study where patients were weaned from previous antiepileptic medications and administered increasing doses of sodium oxybate over a ten week period. The effect of sodium oxybate was measured using nocturnal polysomnograms, the Epworth Sleepiness scale, the maintenance of wakefulness test and a narcolepsy symptoms questionnaire.</p> | <p>25</p> | <p>10 weeks</p> | <p>Dose related increases from baseline in slow-wave sleep duration ($p < 0.05$) and delta power (accumulated EEG 0.5-4Hz signal power; $p < 0.005$), as well as increases in sleep latency ($p < 0.05$) and nocturnal awakenings ($p < 0.01$). REM sleep duration increased initially at lower doses, but as doses increased REM-sleep duration declined in a dose related manner ($p < 0.05$).</p> | <p>Administration of sodium oxybate was associated with a progressive dose-related improvement in ESS scores, becoming significant after the initial 4 weeks of treatment. Patients were observed for periodic leg movements (PLM) during the study; the administration of sodium oxybate at doses of 4.5g to 9g nightly did not cause a significant increase in PLM nor was there any evidence of a dose response or any differences between the first and second half of the night.</p> | <p>Two patients discontinued the study due to adverse events, specifically a respiratory disorder and depression at the 4.5g and 7.5g doses, respectively. The most commonly reported events were; nausea, back pain, anorexia, vomiting, oedema, sleep disorder and somnolence.</p> |
| <p>Weaver and Cuellar. A multicentre, double blind, placebo controlled study to compare Sodium oxybate with placebo in improving quality of life in patients with narcolepsy. Patients were allocated to receive either 4.5g,</p> | <p>228</p> | <p>8 weeks</p> | <p>All sodium oxybate treatment groups had significant ($p < 0.001$) within- group changes in the median FOSQ total score from baseline. When compared with placebo, the group treated with 9g per day of sodium oxybate had</p> | | <p>Twenty participants who were treated with sodium oxybate discontinued trial medication as a result of treatment-emergent adverse events or serious adverse events. The AE's which most commonly led to discontinuing treatment included nausea, dizziness, hypoesthesia,</p> |

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| <p>6g, or 9g sodium oxybate or placebo. The change in quality of life was measured with the Functional Outcomes of Sleep Questionnaire (FOSQ).</p> | | | <p>statistically significant improvement ($p < 0.001$) in all components of the FOSQ except for the intimacy and sexual relationships subscale.</p> | | <p>somnolence, chest pain and dyspnoea.</p> |
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ATTACHMENT 5: