Sodium oxybate (Xyrem®) in the management of narcolepsy with cataplexy

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Summary

- Sodium oxybate (Xyrem®) is an orphan drug that has been available since 2006. It is licensed for the treatment of narcolepsy with cataplexy, a rare and debilitating condition that results in frequent, uncontrolled, and short duration episodes of sleep leading to a range of other symptoms such as disturbed night-time sleep and excessive daytime sleepiness. Cataplexy is the loss of muscle tone and frequently occurs with narcolepsy. It can cause patients to collapse with resulting injuries. Patients with narcolepsy with cataplexy have poorer quality of life and experience negative social effects.

- Sodium oxybate enables patients to achieve near-normal levels of night-time sleep, resulting in reduced symptoms including cataplexy. It has demonstrated efficacy against placebo in two short term randomised studies with up to 12 month’s follow-up, and in a comparison with the stimulant modafinil. The improvements are dose-related and of uncertain practical importance. There is limited evidence that sodium oxybate therapy has a positive impact on functional aspects of quality of life.

- Sodium oxybate is associated with a relatively high frequency of adverse effects, particularly nausea, headaches, dizziness, bed-wetting, and confusion, amongst others. It also appears to have anorectic effects in a proportion of patients. However, despite these effects, the majority of patients remain on treatment. The incidence and severity of withdrawal effects appears to be small.

- Sodium oxybate is an expensive treatment. Using the mean dose from clinical studies the cost is about £12,000 per patient per annum. There are an estimated 221 diagnosed cases of narcolepsy with cataplexy within NHS North East. Treating 10% of these at the mean dose would cost about £336,000 per annum.

- Data indicates that in UK practice lower mean doses are used which will reduce the cost proportionately. Sodium oxybate is unlikely to satisfy conventional limits for cost-effectiveness if applied to all eligible patients. It may be suitable for shared-care with provision in primary care negating VAT.

- Sodium oxybate has abuse potential and is associated with a strict administration regimen. It is not licensed nor has it been robustly evaluated in paediatric (aged < 18 years) patients.
Introduction and background

The North East Treatment Advisory Group has been requested by member primary care organisations to conduct an appraisal of, and issue a subsequent recommendation for, the use of sodium oxybate (Xyrem®) within its licensed indications.

Xyrem® is an orphan drug which has been available in the UK since 2006. It is licensed for the treatment of narcolepsy with cataplexy in adult patients. The treatment of sleep disorders, including narcolepsy with cataplexy, falls under the specialised services national definition set for specialised adult respiratory services.

Narcolepsy is a disabling sleep disorder characterised by excessive daytime sleepiness and abnormal rapid-eye-movement (REM) sleep manifestations including cataplexy, sleep paralysis, and sleep-onset 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 unlocking of the knees. Cataplectic episodes may last less than one second to several minutes and may occur with frequency of less than one per annum to several per day.

Narcolepsy is often diagnosed either in adolescence or in middle age. Narcolepsy with cataplexy is estimated to affect about 35 per 100,000 of the population. Transposing this rate to the population of NHS North East yields an estimated adult (age ≥ 18 years) prevalence of 714, although a large proportion of these patients will be undiagnosed.

Narcoleptic patients generally do not spend much time asleep, even at night. Because they are unable to stay awake or asleep for long periods of time, nocturnal sleep is disrupted in a third of patients. Typically, patients fall asleep as soon as they get into bed but they wake up several times during the night.

As might be expected, 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 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 dexamfetamine (a stimulant) and
clomipramine (a noradrenergic antidepressant) being the only other drugs along with Xyrem®. 2,3 Other drugs commonly used are demonstrated in table 1. 2-4

**Table 1.** Drugs used in the treatment of narcolepsy with and without cataplexy

<table>
<thead>
<tr>
<th>Type</th>
<th>Drug examples</th>
<th>Indication or target symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathomimetic stimulant Principally adrenergic activity, also possible action on dopaminergic, GABA-ergic, and serotonergic systems.</td>
<td>Modafinil (Provigil®) Methylphenidate (Ritalin®, Equasym®, Concerta XL®). Dexamfetamine (Dexedrine®)</td>
<td>Excessive daytime sleepiness</td>
</tr>
<tr>
<td>Selective-serotonin reuptake inhibitor</td>
<td>Fluoxetine, Citalopram</td>
<td>Cataplexy and other REM-associated phenomena</td>
</tr>
<tr>
<td>Benzodiazepines and related hypnotics</td>
<td>Clonazepam, Zolpidem, Zopiclone</td>
<td>Adjuvant to aid night-time sleep</td>
</tr>
<tr>
<td>Tricyclic antidepressant acting on serotonin and noradrenaline pathways</td>
<td>Clomipramine (Anafranil®)</td>
<td>Cataplectic symptoms</td>
</tr>
<tr>
<td>Serotonin and noradrenaline reuptake inhibitor</td>
<td>Venlafaxine (Efexor®)</td>
<td>Cataplectic symptoms</td>
</tr>
<tr>
<td>Noradrenergic reuptake inhibitor</td>
<td>Reboxetine (Edronax®) Atomoxetine (Strattera®)</td>
<td>Cataplectic symptoms</td>
</tr>
</tbody>
</table>

Xyrem® 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. 2,4

The active drug in Xyrem® is sodium oxybate, the sodium salt of gamma-hydroxybutyric acid (GHB). GHB had gained notoriety as a ‘rave drug’ and a ‘date rape’ drug but has since been legislated. 5 Its mode of action has not been fully elicited but at treatment doses it is believed to act as a central nervous system depressant which promotes slow wave (deep) sleep as well as other effects on sleep patterns and reduced sleep fragmentation. 1,2

This report will review the evidence for the efficacy, safety, cost-effectiveness, and practical implications of sodium oxybate (Xyrem®) for the treatment of narcolepsy with cataplexy.
Clinical Evidence

There is evidence relating to the use of GHB in the treatment of narcolepsy with cataplexy from as early as the 1970’s. 6

Xyrem® was subject to a specific clinical evaluation programme that had at its core two placebo-controlled phase III randomised controlled trials, including some longer term follow-up data and quality of life assessments. 7-11 These two studies between them account for the largest documented reports on the use of sodium oxybate for the treatment of narcolepsy with cataplexy. 4

The US Xyrem® Multicenter Study Group conducted a four-week study with 136 patients recruited from various American centres. Patients had a mean age of 43 years (minimum 18 years), 58% were female and 92% were Caucasian. At baseline patients were experiencing a median of 21 cataplectic attacks per week (range 3 to 249). Prior to randomisation, patients had their existing medication for the control of catapletic symptoms gradually withdrawn so that by the time they were randomised to sodium oxybate or placebo they were free of these treatments. Eighty-three per cent of patients were permitted to remain on stimulant medication because their doses were stable. Relevant outcomes were recorded by patients including the primary outcome measure which was the frequency of cataplectic attacks. Patients were randomised to treatment with placebo (n = 34), sodium oxybate 3 g (n = 34), 6 g (n = 33), or 9 g (n = 35) daily. After four weeks of treatment the reduction in the number of weekly attacks (% reduction from baseline) was, respectively: 4 (28%), 7 (49%), 10 (49%), and 16 (69%). The difference between placebo and the 9 g daily group was statistically significant. Other relevant endpoints and specific symptoms demonstrated similar dose-related trends demonstrating the superiority of sodium oxybate. For example changes in the ESS (see appendix 1) from baseline were improved in the sodium oxybate groups in a dose-related manner becoming significant when compared to placebo at the 9 g dose. The change in scores was about two points in the placebo and 3 g dose groups, increasing to about three points for the 6 g group and five points in the 9 g group. 7

Longer-term data is available from this group of patients following a 12-month extension study. One-hundred and eighteen patients entered the extension phase in which all patients received sodium oxybate 6 g daily. Doses were then adjusted as required in 1.5 g increments resulting in 14% of patients being maintained on 3 g, 9% on 4.5 g, 36% on 6 g, 11% on 7.5 g, and 30% on 9 g daily. The mean reduction in the number of weekly cataplectic attacks was 58% from the preceding four-week randomised study. A further reduction was then observed down to about 90% from the baseline point of the previous study with most of the change occurring by month four. This corresponds to a mean reduction of 35 attacks per week measured from the baseline point of the preceding study. 8
Changes in ESS as observed from the preceding study also demonstrated continued, although less striking, improvement which had stabilised by month two to a median score of about 13 from a baseline score of 18.  

The Xyrem® International Study Group conducted an eight-week study in 228 patients recruited in North America and Europe. Patients had a mean age of 41 years (range 16 to 75), 65% were female and 86% were Caucasian. Other procedures were similar to those in the earlier American study. Patients were randomised to treatment with placebo (n = 59), or one of three sodium oxybate titration schedules with target daily doses of 4.5 g (n = 64), 6 g (n = 58), and 9 g (n = 47). The primary outcome measure was the change in ESS from baseline. After eight weeks the mean ESS score had decreased by 0.5, 1.0, 2.0 and 5.9 points respectively, demonstrating a similar dose-related response to that seen in the earlier American study. The changes in the two highest dose groups were statistically significant compared with placebo. All other reported end points demonstrated similar dose-related benefits for sodium oxybate over placebo.

A separate report provides further results from the same study focusing on the incidence of cataplexy. Prior to randomisation the whole group displayed a median of 18.5 cataplectic attacks per week. After eight weeks of treatment the median number of attacks (% median reduction compared with placebo) was, respectively: 17.4, 9.0 (57%), 8.0 (65%) and 3.0 (85%).

The same group of patients was also used to obtain quality of life data using a disease-specific measure known as the Functional Outcomes of Sleep Questionnaire (FOSQ – see appendix 2). Patients (n = 228) were administered the questionnaire on four occasions corresponding to the period prior to any changes in pre-study medication, the point immediately following withdrawal of cataplectic medication and at which treatment was commenced, and then four and eight weeks following treatment commencement. In common with other endpoints from both phase III studies the results demonstrated a dose-related response in favour of sodium oxybate. Mean changes in total FOSQ score were 1.65 with 6 g and 3.43 with 9 g (both p < 0.05 compared with within-group baseline). Not all sub-measures were independently significantly different compared with baseline with the smallest changes seen in the measures relating to ‘general productivity’ and ‘intimacy and sexual relationships’ and the greatest changes occurring in the measures relating to ‘social outcomes’ and ‘activity level’.

Another study from the Xyrem® programme is an eight-week active-comparator study of placebo (n = 55) vs. sodium oxybate (n = 50) vs. modafinil (n = 63) vs. sodium oxybate plus modafinil (n = 54). Patients had a mean age of 39 years, 52% were female, and 88% were white. Patients were required to be taking a stable dose of modafinil of between 200 to 600 mg daily and taking a stimulant drug for symptoms of excessive daytime sleepiness. It was not necessary for patients to have a diagnosis of cataplexy with their narcolepsy. The target dose
of sodium oxybate was 9 g daily by week five continued through to week eight. Placebo medication was used to double-blind the study. The primary outcome measure was the Maintenance of Wakefulness Test score (see appendix 3), which was significantly different for each active treatment arm compared with placebo. In the placebo group the mean sleep latency was 7 minutes compared with 10 minutes in the modafinil group, 12 minutes in the sodium oxybate monotherapy group and 13 minutes in the dual therapy group. The median ESS score showed a similar trend over the same period, with no change in the placebo group, an increase of 1 point in the modafinil group, and a reduction of 3 and 4 points in the sodium oxybate mono and dual therapy groups, respectively. Other outcomes demonstrated similar results with the general trend being little or no difference between placebo and modafinil, greater benefit with sodium oxybate monotherapy, and slightly greater benefit still with dual therapy. 

Results from this same study population have also been reported relating to the observed changes to sleep architecture. This found no significant changes in patients treated with placebo or modafinil. There were no significant changes to the total time spent asleep in any group however patients treated with sodium oxybate experienced a greater proportion of their sleep in deeper states with an increase of about 30 to 40 minutes in REM sleep. There were small but significant reductions in the median number of nocturnal awakenings in the dual therapy group from 27 to 19 per night, and from 27 to 21 in the sodium oxybate alone group.

Other evidence is provided by smaller studies. A 10-week dose-escalation pilot study was conducted in 25 patients who had recently been weaned from their existing anticataplectic medication. The results demonstrated three major effects: an initial induction and prolongation of REM sleep followed by a subsequent reduction of this sleep state, an increase in slow-wave sleep, and an improvement in daytime alertness despite the inability of sodium oxybate to increase total nocturnal sleep time. These changes are considered beneficial in narcolepsy and served to promote improvements in symptoms of excessive daytime sleepiness.

Results from patients who had been stabilised on sodium oxybate and received long-term treatment have also been reported. The 55 patients (female 58%, mean age 48 years) had been on sodium oxybate for a mean of 21 months (range 7 to 44) at daily doses between 3 and 9 g. Patients were then randomised to two weeks of treatment with either placebo (n = 29) or blinded treatment at their previous dose (n = 26). As might be expected, there were no changes observed in the active treatment group. The placebo group experienced a median increase of 21 cataplectic attacks during the two-week placebo period. When analysed by prior sodium oxybate daily dose, there were no significant changes in the groups receiving ≤ 4.5 g however the changes were significant in patient groups taking ≥ 6 g with a dose-related trend.
The authors note the absence of a withdrawal syndrome and rebound cataplexy as evidenced by a gradual as opposed to a sudden increase in cataplectic attacks on withdrawal. It is not clear whether this group of patients is derived from another study group as the authors are the same as those listed for one of the earlier studies.\textsuperscript{15}

Other evidence relates to smaller groups of patients with dose regimens that are slightly different to those of the licensed product, with typically lower overall doses used. However these studies do consistently report a benefit of treatment with GHB in patients with narcolepsy with and without cataplexy.\textsuperscript{16,17}

**Summary of the evidence on efficacy**

Xyrem\textsuperscript{®}, and preceding that GHB, has demonstrated clear clinical benefits in patients with narcolepsy with cataplexy in placebo controlled trials and case series reports, including some long term follow-up. Some of the most useful data is derived from only short term periods of observation. The only comparative study from the Xyrem\textsuperscript{®} development programme was also of short duration and demonstrated fairly modest improvements over modafinil with respect to cataplexy. Despite these short-comings the evidence for Xyrem\textsuperscript{®} appears to be the greatest pool of evidence for any treatment for narcolepsy with cataplexy.\textsuperscript{4}

Some criticisms have been directed at these studies: for example in the international study 83\% of patients were still taking stimulant medication\textsuperscript{9,10} suggesting that symptoms of excessive daytime sleepiness were not optimally controlled.\textsuperscript{18,19} The authors responded that this would probably reflect actual use and in that respect the trial was conducted pragmatically.\textsuperscript{20} There is a consistent dose-related trend with respect to the magnitude of effect seen on numerous outcomes, with higher doses generating greater responses than lower doses. Longer term data indicates continued gains in clinical efficacy for the first few months followed by maintenance of the effect, although this evidence is taken from open studies with smaller patient numbers.
Safety

Evidence relating to the safety of sodium oxybate is reported in the clinical studies. Adverse effects occur regularly and consistently with nausea, dizziness and headaches being the most common and occurring in 10 to 20% of patients. Other less common effects typically affecting between 1 and 10% of patients include nocturnal enuresis (bed wetting), vomiting, weight loss and anorexia, blurred vision, hypertension, non-specific gastrointestinal pain, diarrhoea, sweating, muscle cramps, arthralgia, and oedema. Common and very common effects on the central nervous system and on sleep behaviour include fatigue, a feeling of ‘alcoholic intoxication’, balance disorder, falls, abnormal dreams and nightmares, depression, anxiety, insomnia, confusion and disorientation. Not all instances of these effects are necessarily caused by Xyrem® and may be linked to the underlying condition.

In common with clinical efficacy, the incidence of adverse effects also appears to demonstrate a dose-related response with higher doses generally associated with a higher incidence.

In short term studies about 7 to 10% of patients discontinued due to study medication (including placebo). In the longer term follow-up (mean 21 months) study with 55 patients previously stabilised on Xyrem® no patients discontinued due to adverse events and no unexpected effects occurred. In the comparative study with modafinil the incidence of any adverse event was 70% with placebo, 60% with Xyrem® alone, 54% with modafinil, and 79% with combined therapy. The main differences between the Xyrem® and modafinil monotherapy groups occurred with incidences of nausea, vomiting, dizziness and somnolence. Thirteen patients withdrew from the study, with 1 from the placebo group, 2 from the modafinil group, 4 from the Xyrem® group, and 6 from the combined group.

As reported previously, the group of 55 patients with long-term follow-up were randomised to either abrupt withdrawal of Xyrem® by use of placebo for two weeks (n = 29), or continuation of Xyrem® (n = 26). A separate report assessed withdrawal symptoms following this abrupt cessation of therapy. The authors observed only five instances of symptoms in the placebo group that they considered possibly related to Xyrem® withdrawal, covering symptoms of anxiety, insomnia, dizziness, and somnolence. The authors further speculate that these symptoms were more likely to be due to the re-emergence of narcolepsy as opposed to drug withdrawal. These conclusions were later challenged and counter-challenged by other authors.

There does appear to be an absence of a recognised withdrawal syndrome with sodium oxybate or GHB, especially at typical Xyrem® treatment doses, despite reports of use extending back many years and at substantially higher doses. However, this aspect has not been robustly investigated.
In addition to the clinical evidence base there have been other, limited, reports relating to the safety of sodium oxybate, and Xyrem® specifically. For example a number of fatalities have been reported although each is confounded with multiple other factors and causality is not proven in any case.\textsuperscript{24-26}

There is also a single case report of restless-legs syndrome occurring \textit{de novo} in a patient recently commenced on Xyrem®. This effect has some pharmacological basis although causality in this case is not proven. The effects resolved upon cessation of Xyrem® supporting a causative hypothesis. An earlier study in 12 narcoleptic patients, six with restless legs and six without, reported that following therapy with GHB the six without did then develop restless legs.\textsuperscript{27,28}

An audit of 54 patients with narcolepsy treated with Xyrem® (female 61%, mean age 48 years), 24 of whom also had cataplexy, found that after a mean duration of therapy of 25 months at a mean daily dose of about 7 g the mean weight loss was 3.4 kg from a mean baseline weight of 78 kg. For patients who also had cataplexy the mean loss was greater and significant at 5.1 kg. The authors present this data as evidence for an additional benefit of treatment with Xyrem® as many patients with narcolepsy are clinically overweight. However the maximum weight loss is reported as over 30 kg which could be dangerous in all but the most overweight patients.\textsuperscript{29}
Cost analysis

The cost of Xyrem® is £360 (£423 including VAT) for a 180 ml bottle containing 500 mg/ml (i.e. 90 g per bottle). At the maximum licensed dose of 9 g daily one bottle would provide sufficient for 10 days treatment. Therefore the annual cost at maximum dose is about £13,000 (£15,400 including VAT).

In studies of longer term use of Xyrem® the mean daily doses were found to be 6.5 g (n = 117 with 12 months follow-up) and 6.8 g (n = 55 with 21 months follow-up, range 7 to 44 months). Median doses were found to be 6 g and 7.5 g, respectively. Therefore, it is assumed that a ‘typical’ or ‘average’ dose for cost analyses is 7 g daily although it should be noted this does not correspond to an actual licensed dose. The annual cost of treatment at this dose is about £10,000 (£12,000 incl VAT). UK sales data for Xyrem® indicates that actual mean doses used in practice are lower than this at about 5 g daily.

Figure 1. Chart showing daily doses and cost for 28 days treatment of various medications used in the treatment of narcolepsy with or without cataplexy.

It is unlikely that Xyrem® would be considered cost-effective in terms of incremental cost per quality adjusted life year when assessed against conventional limits. For example, to deliver a cost per QALY of less than £20,000 a dose of 9 g daily would have to deliver absolute improvements in quality of life of at least 65% when added to existing therapy, and at a dose of 6 g daily the improvements would need to be at least 43%. The evidence relating to quality of life indicates that benefits of this magnitude are unlikely across eligible patient populations.
The Scottish Medicines Commission reported the results of cost-effectiveness analyses submitted by UCB Pharma in support of Xyrem®. These describe a cost utility analysis which yielded a cost per QALY of £28,000. However, upon scrutiny the sponsors admitted that the analysis was flawed. The SMC crudely estimated the true figure to be in the order of £120,000. A subsequent submission estimated the ‘cost per cataplectic attack avoided’ at £10 although this outcome does not permit useful comparison with other treatments. The SMC appraisal only considered the use of Xyrem® for the treatment of cataplexy and did not consider its effects on narcolepsy, for which it is now licensed.

The estimated prevalence within NHS North East of adult patients diagnosed with narcolepsy with cataplexy is about 220. Table 2 shows the estimated patient numbers, and annual cost based on a treatment rate of 10% at a mean daily dose of 7 g, per PCT.

### Table 2. Annual cost of Xyrem® per NHS North East Primary Care Organisation if 50% of estimated diagnosed eligible patients treated.

<table>
<thead>
<tr>
<th>PCO</th>
<th>PCT</th>
<th>Estimated prevalence diagnosed adult cases</th>
<th>Estimated patient population if 10% treated with Xyrem®</th>
<th>Annual cost* if 10% treated with Xyrem® mean dose 7 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHS Durham &amp; Darlington</td>
<td>County Durham</td>
<td>43</td>
<td>5</td>
<td>£60,043</td>
</tr>
<tr>
<td></td>
<td>Darlington</td>
<td>9</td>
<td>1</td>
<td>£12,009</td>
</tr>
<tr>
<td>NHS North of Tyne</td>
<td>Newcastle</td>
<td>23</td>
<td>3</td>
<td>£36,026</td>
</tr>
<tr>
<td></td>
<td>North Tyneside</td>
<td>18</td>
<td>2</td>
<td>£24,017</td>
</tr>
<tr>
<td></td>
<td>Northumberland Care Trust</td>
<td>27</td>
<td>3</td>
<td>£36,026</td>
</tr>
<tr>
<td>NHS South of Tyne</td>
<td>Gateshead</td>
<td>17</td>
<td>2</td>
<td>£24,017</td>
</tr>
<tr>
<td></td>
<td>South Tyneside</td>
<td>13</td>
<td>2</td>
<td>£24,017</td>
</tr>
<tr>
<td></td>
<td>Sunderland Teaching</td>
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<td>3</td>
<td>£36,026</td>
</tr>
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<td>NHS Tees</td>
<td>Hartlepool</td>
<td>8</td>
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<td>£12,009</td>
</tr>
<tr>
<td></td>
<td>Middlesbrough</td>
<td>12</td>
<td>2</td>
<td>£24,017</td>
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<tr>
<td></td>
<td>North Tees</td>
<td>16</td>
<td>2</td>
<td>£24,017</td>
</tr>
<tr>
<td></td>
<td>Redcar and Cleveland</td>
<td>11</td>
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<td>SHA: NHS North East</td>
<td></td>
<td>221</td>
<td>28</td>
<td>£336,238</td>
</tr>
</tbody>
</table>

* Including VAT at 17.5%

The estimated patient population in table 2 has been selected as 10% of diagnosed adult cases based on expert opinion. The true figure may vary from this estimate by an unknown proportion. Across the UK 147 patients have been prescribed Xyrem® which has been available for nearly 4 years. Of these patients, 22 are known to have discontinued treatment with eight discontinuing for clinical reasons such as a lack of efficacy or adverse effects, and several others discontinuing due to funding issues (precise data not available). Current estimates indicate that there are about 20 patients within NHS North East maintained on Xyrem®. There are also anecdotal reports that treatment...
requests for at least ten patients have not been accepted. This indicates a current prospective or actual treatment pool of about 30 patients, which is similar to that estimated in table 2.

The marketing authorisation holder for Xyrem®, 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 the discretion of the responsible clinician. Claims for credit must be signed by the clinician and a representative of the dispensing pharmacy. Unverified reports indicate that few claims have been made under the scheme, with most treatment discontinuations occurring after more than three months.

VAT applies to medication provided by acute trusts but not to medication dispensed via independent dispensing contractors such as community pharmacies. Currently, where Xyrem® is prescribed, this is usually via acute trusts although alternative arrangements for supply are possible which could reduce the cost. For example shared-care arrangements are utilised elsewhere in the NHS, which will also remove VAT from the cost of treatment.

Other costs that might be associated with the use of Xyrem® include medical appointments with an appropriate specialist. For example, the dose of Xyrem® should only be titrated in 1.5 g daily dose intervals and no more frequently than fortnightly. Therefore, a number of separate appointments may be required early on in treatment to establish a suitable dose. Current arrangements within NHS North East for a follow-up neurology outpatient appointment fall in the bracket. It is likely that patients diagnosed with narcolepsy with cataplexy will already be under the care of a specialist.

No evidence was identified relating to health outcome sequelae and healthcare utilisation for patients on Xyrem® compared with those not on Xyrem®.

Decisions made by other bodies

In March 2006 the Scottish Medicines Commission assessed Xyrem® for cataplexy only and did not recommend it on the basis of cost-effectiveness.

The All Wales Medicines Strategy Group did not endorse the use of Xyrem® following non-submission by the marketing authorisation holder.

The North of Tyne Area Prescribing Committee has previously issued a negative recommendation regarding Xyrem®. This recommendation remained unchanged following an appeal.

No other NHS body within NHS North East is known to have issued a treatment recommendation regarding Xyrem®.
Points to consider

- Sodium oxybate has a long history of clinical benefit in narcolepsy with cataplexy. The Xyrem® clinical evidence base constitutes the greatest source of evidence of any treatment for this indication and consistently shows benefit over placebo. In addition, Xyrem® has demonstrated benefit in parameters specific to cataplexy compared with standard treatment doses of modafinil. The drug appears to elicit its therapeutic effects by enabling a deeper and better quality of sleep at night resulting in reduced daytime symptoms. Concomitant stimulant, and sometimes anticataplectic, medication is usually still required.

- Xyrem® 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.

- Xyrem® has potential for misdirection and abuse and patients should be evaluated for a history of drug abuse.

- Xyrem® 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.

- Xyrem® is designated as an orphan drug for its licensed indication. It is a costly product that is unlikely to fulfil established criteria for cost-effectiveness across all eligible patients. It has not been recommended for use in Scotland or Wales. Clinical evidence indicates that the mean annual cost of treatment is about £10,000 per patient (range £4,400 to £13,100) although data indicates that in practice lower doses are used and hence lower costs incurred. This cost does not include VAT which is payable on drugs supplied via acute trusts. The corresponding cost including VAT is about £12,000 (range £5,100 to £15,400). Other treatments used for this indication range in cost from less than £100 to nearly £4,000 per annum. Xyrem® is often used in addition to existing treatments but may present some cost-saving opportunities if existing therapies are reduced or withdrawn.

- Xyrem® may be suitable for shared care, which has already been implemented within the NHS.
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Author’s declaration
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Appendix 1: The Epworth Sleepiness Scale (ESS)

The ESS is a self-administered questionnaire with eight items each with a score from 0 to 3, so that the range for overall scale is 0 to 24. Each of the eight item-scores of the ESS provides a measure of one situational sleep propensity: the habitual tendency to doze or stay awake in that situation as part of daily life. The ESS relies on subjective and retrospective reports of dozing behaviour such as a nodding head and lapses of attention, and measures sleep propensity. Having a high sleep propensity (i.e. excessive daytime sleepiness) means having a history of dozing in situations that have a relatively low soporific nature in which normal subjects seldom doze. A normal score is considered to be between 0 and 10 points.

Sample of the ESS

Score: 0 = would never doze; 1 = slight chance of dozing; 2 = moderate chance of dozing; 3 = high chance of dozing.

Situation:
1. Sitting and reading
2. Watching TV
3. Sitting, inactive in a public place (e.g. a theatre or a meeting)
4. As a passenger in a car for an hour without a break
5. Lying down to rest in the afternoon when circumstance permit
6. Sitting and talking to someone
7. Sitting quietly after a lunch without alcohol
8. In a car, while stopped for a few minutes in the traffic


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Appendix 2: The Functional Outcomes of Sleep Questionnaire (FOSQ)

The FOSQ is a patient-reported measure designed to assess the impact of disorders of excessive sleepiness on multiple activities of everyday living. It is divided into five factors covering the following aspects: activity level, vigilance, intimacy and sexual relationships, general productivity, and social outcome. It is further broken down into 30 specific questions or items varying between two and nine for each factor. The total score is generated from the mean item scores for each factor. With factor scores ranging from 1 to 4 the total score ranges form 5 to 20. The FOSQ assesses only functional status which is itself only a component of ‘quality of life’.


Appendix 3: The Maintenance of Wakefulness Test (MWT)

The MWT measures a subject’s ability to stay awake in a quiet, nonstimulating situation for a given period time. It may be used to evaluate the response to therapy for individuals in whom conditions causing daytime sleepiness have been diagnosed. The test is conducted using an assortment of quantitative instruments that can objectively detect sleep, including the type/stage/depth of sleep. The duration of the MWT can vary but it is recommended that 40 minutes duration is used. Four 20-minute tests, each two hours apart, were used in the study of sodium oxybate and modafinil. Patients are required to sit or lie still and remain in a dark and silent room for the duration of the test. They are not permitted to use any physical technique to assist in staying awake (e.g. pinching themselves). The test is repeated, usually four times, with the mean sleep latency time in minutes taken as the result.

Mean sleep latency of less than eight minutes is taken to be abnormal, whereas staying awake for all four trials of a 40 minute test provides the strongest support of an individual’s ability to stay awake. Values between 8 and 40 minutes are of uncertain significance. There are no established cut-off values for a change in mean sleep latency when used to evaluate a response to treatment.