SODIUM OXYBATE FOR NARCOLEPSY

QUESTIONS TO BE ADDRESSED:

1a. Is sodium oxybate safe and clinically effective in the reduction in number and intensity of cataplexy attack, excessive day-time sleepiness (diurnal naps), nocturnal awakenings, terrifying dream experiences, insomnia, hypnagogic hallucinations, sleep paralysis, and improvement in quality of life in adult patients with narcolepsy and cataplexy compared to no intervention, combined treatment or with only standardised treatments?

1b. Is there evidence that sodium oxybate is clinically effective in patients with narcolepsy and cataplexy who have reached puberty (and weigh >40kgs) compared with no intervention, combined treatment or with only standardised treatments?

2. Is sodium oxybate cost-effective in controlling the symptoms of narcolepsy and cataplexy in patients with narcolepsy?

SUMMARY

Background

- Narcolepsy is a sleep disorder characterised by excessive daytime sleepiness and irresistible attacks of sleep, disrupted nocturnal sleep, hypnagogic/ hypnopompic hallucinations, abnormal rapid eye movement and sleep paralysis. Cataplexy is specific to narcolepsy and is characterised by a sudden, usually bilateral, partial or complete loss of muscle tone triggered by emotional stimuli.
- The prevalence of narcolepsy with cataplexy is approximately 25 to 50 per 100,000 and the incidence is approximately 0.74 per 100,000 person-years.
- Sodium oxybate (gamma-hydroxybutyrate; Xyrem®) is a neurotransmitter product of gamma-amino butyric acid (GABA) and acts as a central nervous system depressant.

Clinical Effectiveness

- For adults, we identified two systematic reviews and meta-analyses of RCTs comparing sodium oxybate with placebo. We also identified two studies published after the search dates for the systematic reviews which provided further analysis of RCT participants.
- There is evidence from meta-analyses of RCTs for statistically significantly fewer weekly and daily cataplexy attacks with sodium oxybate compared to placebo, with a mean difference of between seven and 8.5 attacks per week (or one per day). Meta-analyses also reported statistically significantly better scores on measures of daytime sleepiness, fewer sleep attacks (of about nine attacks per week) and fewer nocturnal awakenings (of about one awakening per night) with sodium oxybate compared to placebo. In one 12-week open-label study 72% of patients receiving sodium oxybate reported reduced daily inadvertent naps and 68% reported reduced night awakenings. Results for hypnagogic hallucinations and sleep paralysis were not available in a form suitable for meta-analysis however a systematic review reported a statistically significant decrease in both outcomes in some, but not all, RCTs. In addition, a 12-week open label study found that 70% of patients reported reduced hypnagogic hallucinations and 67% reported reduced sleep paralysis episodes.

- One open-label study attempted to define clinically relevant reductions in cataplexy attacks and daytime sleepiness and found that 92% of patients maintained a ≥50% reduction in weekly cataplexy attacks from baseline and 74% of patients maintained a ≥20% reduction in daytime sleepiness from baseline after 12 months of sodium oxybate.
- The other studies did not address the clinical relevance of their results and did not present data in a way that supported an assessment of clinical relevance. It is therefore difficult to assess the clinical relevance of their statistically significant results.
- Both meta-analyses reported statistically significant increases in the proportion of patients who were rated as 'much improved' or 'very much improved' on a clinician-rated measure of impression of change. Consistent with this, 90% of patients reported their own symptoms as 'much improved' and 74% reported an improvement in their ability to concentrate in a 12-week open-label study.
- Three small uncontrolled observational studies provided limited information on the efficacy of sodium oxybate in children whose age suggests that they are likely to have reached puberty (n=23 combined).
- Two of these studies reported a statistically significant reduction in cataplexy attacks compared to baseline. The reduction in mean daily attacks was 3.7 in one study (n=13) from a mean baseline of 3.9 attacks. The reduction in median weekly attacks was 34 from a median baseline of 38.5 in the other study (n=8). Statistically significant improvements in daytime sleepiness and nocturnal sleep were also reported. One case series reported that hypnagogic hallucinations and sleep paralysis had ceased in two patients. Two studies reported improvements in outcomes related to quality of life, with an improvement in social spheres in five of eight patients in one study and an improvement in school reports in one case study.
- Because this evidence is from a very small number of patients in uncontrolled observational studies it is not possible to draw any strong conclusions about the effectiveness of sodium oxybate in patients with narcolepsy and cataplexy who have reached puberty.

Cost Effectiveness

- We did not identify any studies assessing the cost-effectiveness of sodium oxybate for narcolepsy.

Safety

- In a meta-analysis of safety outcomes in adults, rates of nausea (39 events versus 5 events), vomiting (11 events versus 0 events) and dizziness (29 events versus 6 events) were statistically significantly higher with sodium oxybate compared to placebo. Study withdrawals due to adverse events were reported, and were all less than 10%.
- Limited information on the safety of sodium oxybate in children who have reached puberty comes from two small uncontrolled studies (n=10 combined). In one study two of eight patients withdrew due to adverse effects. A further two patient's experienced terminal insomnia and individual patients experienced a range of other effects.

1 Context

1.1 Introduction

Narcolepsy is a sleep disorder characterised by excessive daytime sleepiness and irresistible attacks of sleep, disrupted nocturnal sleep, hypnagogic/ hypnopompic hallucinations, abnormal rapid eye movement and sleep paralysis [1;2]. Cataplexy is specific to narcolepsy and is

characterised by a sudden, usually bilateral, partial or complete loss of muscle tone triggered by emotional stimuli [1].

Narcolepsy and cataplexy can interfere with every aspect of life and can be extremely incapacitating [1]. Treatment focuses on symptom management and includes pharmacological management e.g. with stimulants and lifestyle changes [1;2].

The population of interest in this review is adults with narcolepsy and cataplexy and children who have reached puberty and who weigh more than 40kg [3].

1.2 Existing national policies and guidance

We did not identify any guidance from the National Institute of Health and Care Excellence on sodium oxybate for narcolepsy.

2 Epidemiology

Narcolepsy is a lifelong disorder. Narcolepsy can occur in pre-pubertal children but post-pubertal cases are more common [4]. Cataplexy is found in 75% patients with narcolepsy [5]. The prevalence of narcolepsy with cataplexy is approximately 25 to 50 per 100,000 [1]. This would equate to approximately 13,500 to 27,000 people in England with narcolepsy and cataplexy. The incidence of narcolepsy and cataplexy is approximately 0.74 per 100,000 person-years [1]. This would equate to approximately 400 new cases of narcolepsy and cataplexy in England per year.

3 The intervention

Sodium oxybate (gamma-hydroxybutyrate; Xyrem®) is a neurotransmitter product of gamma-amino butyric acid (GABA) [6] and acts as a central nervous system depressant [7]. It is licensed by the European Medicines Agency for the treatment of narcolepsy and cataplexy in adults. It is given at a dose of 4.5g to 9g per day in two equally divided doses [7].

The comparators of interest are no intervention, a combination of sodium oxybate with standard treatment, and any other standardised treatment including stimulants, antidepressants, histamine blockers and melatonin agonists.

Measurement scales used in the studies included:

- The Epworth Sleepiness Scale (ESS) is a patient-reported measure of excessive daytime sleepiness [8]. Patients rate their likelihood of falling asleep in a set of situations on a four-point scale ranging from ‘would never doze’ to high chance’. A score of ≤10 is considered ‘normal’ for a general population [2]
- The Clinical Global Impression of Change (CGIC) provides a clinician’s view of the patient’s global functioning prior to and after therapy. The seven-point scale ranges from ‘very much improved’ to ‘very much worse’ [9]
- The visual Analog Scale (VAS) for daytime sleepiness uses a scale from 0 (completely alert for the whole day) to 100 (continuous daytime sleepiness without remission during the day) [4]
- The Pediatric Daytime Sleepiness Scale (PDSS) is an eight-item scale which uses five-point Likert scales to assess daytime sleepiness. Higher scores indicated more sleepiness [10]

- The Multiple Sleep Latency Test (MSLT) assesses the time taken (minutes) to fall asleep in a quiet environment during the day [11]
- The Maintenance of Wakefulness Test (MWT) measures whether a patient is able to stay awake for a defined period of time [12]
- The Narcolepsy Symptom Assessment Questionnaire (NSAQ) is an unvalidated patient-reported outcome questionnaire assessing change in individual symptoms and overall narcolepsy status in the past week. Overall status is assessed on a five-point scale from 'much improved' to 'much worse'. Individual symptoms are rated as 'increased', 'decreased' or 'remains the same' [13].

4 Findings

A search of PubMed, Embase, Cochrane Library, TRIP and NICE Evidence Search was performed on the 15th December 2015 for studies published in English in the last 10 years. Case reports, conference papers, letters, editorials, commentary and animal studies were excluded. Details of the search strategy are provided in Section 7.

We identified two systematic reviews and meta-analyses of randomised controlled trials (RCT) comparing sodium oxybate with placebo for narcolepsy in adults (Alshaikh et al 2012 [1]; Boscolo-Berto et al 2012 [2]). We also identified two studies (Mamelak et al 2015 [13]; Bogan et al 2015 [8]) published after the search dates for the systematic reviews which provided further analysis of RCT participants. Individual RCTs included in the systematic reviews were not reviewed separately. As systematic reviews of RCTs were identified for narcolepsy and cataplexy in adults, we did not consider lower quality evidence on adults (e.g. uncontrolled observational studies) for inclusion.

We identified three uncontrolled observational studies (Huang & Guilleminault (2009) [4]; Murali & Kotagal (2006) [6]; Alshaikh et al (2011) [5]) providing information on the sub-group of interest, namely children who have reached puberty and who weigh more than 40kg. Although the studies did not report the pubertal status of the children, the age of the children suggests they were likely to have reached puberty. A further three studies (Lecendreux et al 2012 [15]; Mansukhani & Kotagal 2012 [16]; Aran et al 2010 [17]) on the effectiveness of sodium oxybate in children were not included in this review as they did not provide separate results on the effectiveness of sodium oxybate for a sub-group of children who have reached puberty. The results of these studies were reported in a recent review for NHS England on sodium oxybate for paediatric narcolepsy [14].

4.1 Evidence of effectiveness

Adults

Alshaikh et al's (2012) systematic review and meta-analysis included six RCTs comparing sodium oxybate to placebo published up to October 2010, and five companion reports (providing supplementary information on the identified RCTs). The six RCTs included a total of 741 patients with follow-up ranging from two weeks to 12 weeks [1]. Boscolo-Berto et al's (2012) systematic review and meta-analysis included nine RCTs comparing sodium oxybate to placebo published up to August 2010. The nine RCTs included a total of 1154 patients with follow-up ranging from four weeks to 12 weeks [2]. Both reviews assessed and reported on the quality of the included studies using a recognised assessment tool.

The discrepancy in the number of included trials in the two reviews relates to whether papers were classed as an RCT or a companion report. Five RCTs were common to both systematic

reviews. However the other studies not categorised as RCTs in both reviews were included in the reference lists of both papers and there was nothing to suggest that either review had failed to identify a relevant trial. Boscolo-Berto et al, whose review included more studies and patients, stated that *'studies reporting in a mutually exclusive way different outcomes about the same cohort of patients were included if they met the remaining inclusion criteria'* [2]. Both reviews conducted separate meta-analyses for different outcomes. Again there were some discrepancies in the studies included in meta-analyses for the same outcome. Alshaikh et al stated that studies were not included in their meta-analysis when standard errors were not reported and this data was not available from the manufacturer [1]. Also, Alshaikh et al reported meta-analyses outcomes for single dosages of sodium oxybate, whereas Boscolo-Berto et al included more than one dosage of sodium oxybate in their meta-analyses. The results of these reviews are presented in Table 1.

Table 1 also includes the results of two studies published after the search dates for the systematic reviews. Bogan et al 2015 [8] reported the results of a 12-month open-label extension to an RCT (n=117). Mamelak et al 2015 [13] reported the results of a 12-week open label extension with patients who had participated in one of three RCTs (n=171).

The results are summarised below for each outcome.

Cataplexy attacks
Both meta-analyses [1;2] found statistically significantly fewer weekly cataplexy attacks with sodium oxybate compared to placebo, with a mean difference of between seven (95%CI -12.5 to -1.6) and 8.5 (95%CI -15.3 to -1.6) attacks per week. One of the meta-analyses considered daily cataplexy attacks and found statistically significantly fewer attacks with sodium oxybate compared to placebo, with a mean difference of approximately one (95%CI -1.29 to -0.9) attack per day [2]. In one 12-week open label-study [13] 85% of participants receiving sodium oxybate reported that their cataplexy attacks had reduced. In another open-label study [8] 91.5% of patients maintained a ≥50% reduction in weekly cataplexy attacks from baseline after 12 months of sodium oxybate. The median number of days taken to achieve a maximum cataplexy result (greatest reduction achieved by the patient) was 173 days (95%CI 57 to 246) and 213 days (95%CI 94 to 279) for the two RCT groups who received sodium oxybate for at least 12 months after completion of the RCT [8].

Daytime sleepiness
One meta-analyses assessed daytime sleepiness using the Maintenance of Wakefulness Test and found statistically significantly less sleepiness with sodium oxybate compared to placebo (MD 5.18 95%CI 2.59 to 7.78) [1]. One meta-analysis assessed daytime sleepiness using the Epworth Sleepiness Scale (ESS) and found statistically significantly less sleepiness with sodium oxybate compared to placebo (MD -2.81 95%CI -4.13 to -1.49) [2]. In one 12-week open-label study 71% of patients reported that the severity of their daytime sleepiness had reduced [13]. Another open-label study [8] found that 74% of patients maintained a ≥20% reduction in ESS score from baseline after 12 months of sodium oxybate. The median number of days taken to achieve a maximum ESS result (greatest reduction achieved by the patient) was 106 days (95%CI 85 to 164) and 178 days (95%CI 109 to 307) for the two RCT groups who received sodium oxybate for at least 12 months after completion of the RCT [8].

Sleep attacks
Two meta-analyses [1;2] found statistically significantly fewer weekly sleep attacks with sodium oxybate compared to placebo, with a mean difference of approximately nine attacks per week. One meta-analysis considered daily sleep attacks but did not find any significant difference between sodium oxybate and placebo [2]. In one 12-week open-label study, 72% of participants reported that their daily inadvertent naps had reduced [13].

Nocturnal awakenings
One meta-analysis [2] found statistically significantly fewer nocturnal awakenings with sodium oxybate compared to placebo (MD -1.33 95%CI -1.78 to -0.88). In one 12-week open-label study, 68% of participants reported that their number of night awakenings had reduced [13].

Hypnagogic hallucinations
Results for hypnagogic hallucinations were not available in a form suitable for meta-analysis. Results from individual RCTs found a statistically significant decrease in two RCTs and non-significant results in two RCTs (data not reported) [2]. In one 12-week open-label study, 70% of participants reported that their hypnagogic hallucinations had reduced [13].

Sleep paralysis
Results for sleep paralysis were not available in a form suitable for meta-analysis. Results from individual RCTs found a statistically significant decrease in two RCTs and non-significant results in one RCT (data not reported) [2]. In one 12-week open-label study, 67% of participants reported that their number of sleep paralysis episodes had reduced [13].

Sleep latency
One meta-analysis considered sleep latency but did not find any significant difference between sodium oxybate and placebo [2].

Quality of life
The two meta-analyses [1;2] both found a statistically significant increase in the proportion of patients who were considered ‘much improved’ or ‘very much improved’ on the clinician-rated Clinical Global Impression of Change for sodium oxybate compared to placebo. In one 12-week open-label study, 90% of patients reported some improvement in their symptoms with 60% of these describing their symptoms to be ‘much improved’ [13]. In the same study, 85% of participants reported their quality of sleep to be improved and 74% reported an improvement in their ability to concentrate [13].

There is evidence from RCTs and open-label extension studies for statistically significant improvements in cataplexy attacks, daytime sleepiness, sleep attacks, nocturnal awakenings and symptom improvement with sodium oxybate in adults compared to placebo. A systematic review reported mixed results for sleep paralysis and hypnogogic hallucinations with statistically significant results reported in some RCTs but non-significant results in others. In one 12-week open-label study approximately two-thirds of patients reported reductions in sleep paralysis and hypnagogic hallucinations. One study (Brogan et al 2015) [8] defined clinically relevant outcomes as a ≥20% reduction in ESS score from baseline or a ≥50% reduction in weekly cataplexy attacks from baseline. The other study authors did not address the clinical relevance of their results and did not present data in a way that supported an assessment of clinical relevance, for example baseline scores were not provided.

We did not identify any studies comparing the effectiveness of sodium oxybate to a combination of sodium oxybate with standard treatment or any other standardised treatment including stimulants, antidepressants, histamine blockers and melatonin agonists. However, the included studies generally allowed participants to take concurrent medication alongside the sodium oxybate.

Table 1: Summary of evidence for adults

Study	Population	Group 1	Group 2	Results	Comments
Alshaikh et al (2012) [1] Systematic review and meta-analysis of 6 RCTs Multiple counties	Patients with narcolepsy N=741 Mean age ranged from 36 years to 47.7 years Trial duration ranged from 2 weeks to 8 weeks Follow-up ranged from 2 weeks to 12 weeks	Sodium oxybate (SO) N not reported	Placebo N not reported	**Meta-analyses results** Weekly cataplexy attacks (2 studies; n=124): • Statistically significantly fewer with 4.5g/ night SO compared to placebo (MD -8.5 95%CI -15.3 to -1.6) (I^2=0%) Excessive daytime sleepiness assessed by MWT (2 studies; n=192): • Statistically significantly less with 9g/ night SO compared to placebo (MD 5.18 95%CI 2.59 to 7.78) (I^2=0%) Weekly sleep attacks (2 studies; n=203): • Statistically significantly less with 9g/ night SO compared to placebo (MD -9.65 95%CI -17.72 to -1.59) (I^2=13%) Impression of change assessed by CGIC (3 studies; n=190): • Proportion of patients 'much improved' or 'very much improved' statistically significantly increased with 9g/ night SO compared to placebo (RR 2.42 95%CI 1.77 to 3.32) (I^2=0%)	Different efficacy outcomes were assessed in separate meta-analysis. The dosage of sodium oxybate varied. Heterogeneity scores were low In one RCT (not suitable for meta-analysis) median ESS score was reduced by 20% with sodium oxybate. Baseline scores or improvement from baseline were not reported for other studies or outcomes The authors stated that all 6 RCTs had adequate blinding of participants and addressed incomplete outcome data. All 6 RCTs were rated unclear on other biases due to private-industry funding
Boscolo-Berto et al (2012) [2] Systematic review and meta-analysis of 9 RCTs	Patients with narcolepsy N=1154 Age of participants not reported	Sodium oxybate N=771	Placebo N=383	**Meta-analyses results** Weekly cataplexy attacks (3 studies; n=204): • Statistically significantly fewer with 3 to 9g/ night SO compared to placebo (MD -7.04 95%CI -12.45 to -1.63) (I^2=93%) Daily cataplexy attacks (2 studies; n=82): • Statistically significantly fewer with 4g/ night SO compared to placebo (MD -1.10 95%CI -1.29 to -0.9) (I^2=0%)	Different efficacy outcomes were assessed in separate meta-analysis. The dosage of sodium oxybate varied. Heterogeneity scores ranged from low to high The authors commented

Multiple countries	Trial duration ranged from 2 weeks to 8 weeks Follow-up ranged from 4 weeks to 8 weeks			Subjective daytime sleepiness assessed by ESS (6 studies; n=527): • Statistically significantly less with 3 to 9g/ night SO compared to placebo (MD -2.81 95%CI -4.13 to -1.49) (I^2=94%) Weekly sleep attacks (2 studies; n=206): • Statistically significantly fewer with 6 to 9g/ night SO compared to placebo (MD -9.30 95%CI -15.92 to -2.68) (I^2=15%) Daily sleep attacks (2 studies; n=82): • No significant difference between groups Impression of change assessed by CGIC (7 studies; n=655): • Proportion of patients 'much improved' or 'very much improved' statistically significantly increased with 3 to 9g/ night SO compared to placebo (OR 3.45 95%CI 2.47 to 4.80) (I^2=0%) Subjective nocturnal awakenings (2 studies; n=86) • Statistically significant fewer with 4g/ night SO compared to placebo (MD -1.33 95%CI -1.78 to -0.88) (I^2=0%) Sleep latency (minutes) and total sleep time • No significant difference between groups Results for hypnagogic hallucinations and sleep paralysis were not available in a form suitable for meta-analysis. Results from individual RCTs found: • A statistically significant decrease in hypnagogic hallucinations in two RCTs and non-significant results in two RCTs • A statistically significant decrease in sleep paralysis in two RCTs and non-significant results in one RCT	that the reduction in cataplexy attacks was up to 69% from baseline in one of the included trials. Baseline scores or improvement from baseline were not reported for other studies or outcomes The authors judged all of the included RCTs to be of good quality and all were double-blinded

Bogan et al (2015) [8] Post-hoc analysis of data from an RCT and 12-month open-label extension US	Adults with narcolepsy and cataplexy N=117 Mean age not reported for these patients Follow-up 12 months	Patients who received sodium oxybate in the 4-week RCT and 12-month extension (SO) N=86	Patients who received placebo in the 4-week RCT and sodium oxybate in the 12-month extension (PSO) N=31	**All patients** • ESS response: 74.0% • Cataplexy response: 91.5% **Group 1 (SO)** • First ESS response: median 37 days (95%CI 31 to 50) • Maximum ESS response: median 106 days (95% CI 85 to 164) • First cataplexy response: median 25 days (95%CI 17 to 29) • Maximum cataplexy response: median 213 days (95%CI 94 to 279) **Group 2 (PSO)** • First ESS response: median 60 days (95%CI 30 to 305) • Maximum ESS response: median 178 days (95% CI 109 to 307) • First cataplexy response: median 17 days (95%CI 15 to 29) • Maximum cataplexy response: median 173 days (95%CI 57 to 246)	136 patients enrolled in the original RCT. Results are presented for patients who completed the open-label extension ESS first response defined as ≥20% reduction in ESS score from baseline Cataplexy first response defined as ≥50% reduction in weekly cataplexy attacks from baseline Maximum response defined as greatest reduction achieved by the patient
Mamelak et al (2015) [13] Multi-centre open-label study Multiple countries	Adults with narcolepsy and cataplexy N=171 Mean age 41.9±14.9 Follow-up 12 weeks	Sodium oxybate	N/a	**Patient-reported NASQ outcomes (i.e. patient's assessment of the change in their symptoms in the past week):** **Reported reduction in number of cataplexy attacks** At 6 weeks: 87% At 12 weeks: 85% **Reported reduction in number of daily inadvertent naps** At 6 weeks: 69% At 12 weeks: 72% **Reported reduction in severity of daytime sleepiness** At 6 weeks: 73% At 12 weeks: 71% **Reported reduction in number of awakenings at night** At 6 weeks: 65%	This study included patients who participated in one of three RCTs but had not been titrated to adequate response The efficacy results are from 171 (of 202) patients who completed treatment The NASQ reports patient's subjective assessment of change (e.g. percentage reporting that their cataplexy attacks had reduced)

				At 12 weeks: 68% **Reported reduction in number of hypnagogic hallucinations** At 6 weeks: 66% At 12 weeks: 70% **Reported reduction in number of sleep paralysis episodes** At 6 weeks: 61% At 12 weeks: 67% **Reported symptoms 'much improved' or 'somewhat improved'** At 6 weeks: 92% At 12 weeks: 90% **Reported symptoms 'much improved'** At 6 weeks: 54% At 12 weeks: 60% **Reported quality of sleep 'much improved' or 'somewhat improved'** At 6 weeks: 87% At 12 weeks: 85% **Reported ability to concentrate 'much improved' or 'somewhat improved'** At 6 weeks: 70% At 12 weeks: 74%	

CGIC – clinical global impression of change; ESS – Epworth Sleepiness Scale; MD – mean difference; MWT – maintenance of wakefulness test; NASQ – Narcolepsy Symptom Assessment Questionnaire; OR – odds ratio; RR – risk ratio; SO – sodium oxybate

Children who have reached puberty

Table 2 presents the results of three small uncontrolled observational studies on the effectiveness of sodium oxybate in children who have reached puberty. Huang & Guilleminault (2009) [4] is a prospective review of 13 patients; Murali & Kotagal (2006) [6] is a retrospective review of eight patients; and Alshaikh et al (2011) [5] presents the results of two case studies.

Cataplexy attacks

Two studies reported a statistically significant reduction in cataplexy attacks compared to baseline. The reduction in mean daily attacks was 3.7 in one study from a mean baseline of 3.9 attacks [4]. The reduction in median weekly attacks was 34 from a median baseline of 38.5 in the other study [6]. A third study reported that cataplexy attacks had ceased in two patients but did not provide data on this [5].

Daytime sleepiness

One study reported a statistically significant reduction in mean scores on two measures of daytime sleepiness (PDSS and VAS sleepiness) [4] compared to baseline. One study reported a statistically significant reduction in median ESS score from baseline (from median 19 to 12.5[1]) [6]. There was no difference in the baseline and follow-up ESS scores in a case study of two patients [5].

Nocturnal sleep

One study reported a statistically significant increase in nocturnal total sleep from 496 minutes at baseline to 521 minutes at three month follow-up [4]. One study reported an improvement in sleep efficiency in one patient from 51% at baseline to 78% at follow-up. The other patient in this study showed a small improvement in sleep efficiency (76% to 79%) [5].

Hypnagogic hallucinations and sleep paralysis

One case study reported that hypnagogic hallucinations and sleep paralysis had ceased in two patients however data were not provided [5].

Sleep latency

Two studies reported an increase in sleep latency from baseline to follow-up [4; 5].

Quality of life

One study stated that five of eight patients reported an improvement in social spheres after a mean duration of 11.4 months of sodium oxybate therapy [6]. One patient reported an improvement in monthly school reports [5].

Statistically significant improvements were observed for cataplexy attacks, daytime sleepiness and nocturnal sleep. The clinical significance of the results is unclear and data on impacts on quality of life was limited. We did not identify any comparative studies in children who have reached puberty. The evidence for this sub-group comes from three small uncontrolled observational studies which represent a lower quality of evidence with a high likelihood of bias.

[1] An ESS score of 10 is considered a healthy level of daytime sleepiness compared to the general population. A score of between 10 and 18 is considered an excessive level of daytime sleepiness compared to the general population. A score of 18 or above is considered a very high level of excessive daytime sleepiness [18]

Table 2: Summary of evidence for sub-group of children who have reached puberty

Study	Population	Intervention	Results	Comments
Huang & Guilleminault (2009) [4] Prospective review Taiwan	Teenagers with narcolepsy and cataplexy N=13 Mean age 15.27±1.72 Follow-up 3 months	Sodium oxybate	Statistically significant improvements at 3 months compared to baseline were found for: **Number of cataplexy attacks per day (Mean± SD)** Baseline: 3.9±1.3 At 3 months: 0.2±0.8 (p=0.001) **PDSS (Mean± SD)** Baseline: 20.95±3.50 At 3 months: 14.90±4.0 (p=0.001) **VAS sleepiness (Mean± SD)** Baseline: 79.25±14.70 At 3 months: 48.0±10.7 (p=0.001) **Nocturnal total sleep (minutes) (Mean± SD)** Baseline: 496±33 At 3 months: 521±31 (p=0.002) **Sleep latency (minutes) assessed by MSLT (Mean± SD)** Baseline: 2.8±3.10 At 3 months: 4.6±3.7 (p=0.05)	This study also included a second group of teenagers who received baclofen. Only the results for sodium oxybate are included The pubertal status of the patients was not reported. This study is included as the age of the participants suggests that they are likely to have reached puberty
Murali & Kotagal (2006) [6] Retrospective review US	Children with narcolepsy and cataplexy N=8 Median age 15.5 (range 11 to 17) Mean(SD) duration of therapy with	Sodium oxybate	Statistically significant improvements compared to baseline were found for: **Number of cataplexy attacks per week** Baseline: Median 38.5 (range 3 to 700) At follow-up: Median 4.5 (range <1 to35) (p=0.008)[2] The mean severity of cataplexy attacks decreased, but this difference was not statistically significant **ESS score** Baseline: Median 19 (range 13 to 23)	The pubertal status of the patients was not reported. This study is included as the age of the participants suggests that they are likely to have reached puberty

[2] After the removal of one outlier patient with extremely frequent cataplexy attacks the reduction in median number of cataplexy attacks was still statistically significant (35 vs 2, p=0.016)

	sodium oxybate: 11.4(8.6) months (range 3 to 28 months)		At follow-up: Median 12.5 (range 9 to 22) (p=0.02) 5 patients reported an improvement in social spheres and 1 patient reported no improvement. The 2 other patients response was 'don't know'	
Alshaikh et al (2011) [5] Case series Saudi Arabia	Children with narcolepsy and cataplexy N=2 Case A Age: 11 years Weight: 47.1kg Follow-up: 31 months Case B Age: 17 years Weight: not reported Follow-up: 18 months	Sodium oxybate	Cataplexy, sleep paralysis and hypnagogic hallucination reported to have ceased after treatment for both patients (data not provided) **ESS score** • Case A: Pre-treatment=9; final follow-up=9 • Case B: Pre-treatment=21; final follow-up=22 **Sleep efficiency** • Case A: Pre-treatment=51%; final follow-up=78% • Case B: Pre-treatment=76%; final follow-up=79% **Sleep latency (minutes) assessed by MSLT** • Case A: Pre-treatment=2.0; final follow-up=4.36 • Case B: Pre-treatment=0.72; final follow-up=6.37 Case A school performance improved in monthly school reports	This case series also included two adults. We have only reported the results for the two children The pubertal status of the patients was not reported. This study is included as the age of the participants suggests that they are likely to have reached puberty

ESS – Epworth Sleepiness Scale; MSLT – Multiple Sleep Latency Test; PDSS – Pediatric Daytime Sleepiness Scale; SD – standard deviation; VAS – Visual Analog Scale

4.2 Trials in progress

We searched clinicaltrials.gov on the 19th January 2016. We identified one phase III RCT in progress assessing the efficacy of safety of sodium oxybate in children aged 7 to 17 years compared to placebo (NCT02221869). This multi-centre double-blind RCT aims to recruit 100 patients with narcolepsy and cataplexy and has an estimated completion date of August 2017. We also identified a phase IV observational cohort study on the long-term safety of sodium oxybate for narcolepsy (NCT00244465). This multi-centre study aims to recruit 750 patients with follow-up for a maximum of 18 months. No age range for participants was reported and the estimated completion date is August 2017.

4.3 Evidence of cost-effectiveness

We did not identify any studies assessing the cost-effectiveness of sodium oxybate for narcolepsy.

4.4 Safety

Alshaikh et al (2012) [1] conducted a meta-analysis of safety outcomes from six RCTs. One open-label study on adults [13] and two uncontrolled observational studies [5;6] on children who are likely to have reached puberty also provided data on safety outcomes. The results are summarised in Table 3.

Table 3: Safety outcomes for sodium oxybate

Study	Safety outcomes	Comments
Alshaikh et al (2012) [1] Systematic review and meta-analysis of 6 RCTs	**Meta-analyses results** • Nausea (3 studies; n=295): Statistically significantly higher with SO compared to placebo (39 events vs. 5 events) (RR 7.74 95%CI 3.15 to 19.05) • Vomiting (2 studies; n=178): Statistically significantly higher with SO (11 events vs. 0 events) (RR 11.83 95%CI 1.56 to 89.43) • Dizziness (3 studies; n=295): Statistically significantly higher with SO (29 events vs. 6 events) (RR 4.32 95%CI 1.14 to 16.41) • Enuresis (2 studies; n=184): No significant difference between SO and placebo groups Other adverse events mentioned but not subject to meta-analysis included urinary incontinence and acute confusion **Study withdrawals due to adverse events** • 21 patients (9.2%) (1 study) • 10 patients (7.4%) (1 study) • 1 patient receiving placebo and 4 receiving SO (1 study)	The meta-analysis compared a dosage of 9g/ night of SO with placebo Heterogenity between studies was low with the exception of the dizziness meta-analysis which was moderate (52%)
Mamelak et al (2015) [13] Open-label 12-week study with 202 adults	114 (56%) patients reported an adverse event, including: • Nausea (10%) • Headache (7%) • Dizziness (5%) • Viral infection (5%) • Sinusitis (4%) • Enuresis (2%) • Pain (2%) • Anxiety (2%) • Vomiting (1%) • Appetite loss (1%) • Impaired concentration (1%)	All patients receiving at least one dose of sodium oxybate were included in the safety analysis

	• Urinary tract infection (1%) • Sedation excessive (1%) • Bloating (<1%) • Unresponsive (<1%) • Otitis media (<1%) 5 patients (2%) had serious adverse events, 2 of which were considered treatment related Study withdrawals due to adverse events: 9 patients (4%)	
Murali & Kotagal (2006) [6] Review of 8 children aged 11 to 17	Discontinuation of SO due to adverse events: 2 patients (25%) Reasons for discontinuation included increased nightmares and suicidal ideation and dissociated feelings Other adverse events included: • Terminal insomnia (2 patients) • Tremors (1 patient) • Constipation (1 patient)	
Alshaikh et al (2011) [5] Case study of 2 patients	Case A experienced nausea, vomiting, snoring and enuresis. Case A also experienced convulsions during titration which disappeared when the dose was reduced Case B experienced nightmares and body jerks during sleep which disappeared after one month of treatment	

RR – relative risk; SO – sodium oxybate

4.5 Summary of section 4

For adults, we included two systematic reviews and meta-analyses of RCTs comparing sodium oxybate with placebo. We also identified two studies published after the search dates for the systematic reviews which provided further analysis of RCT participants. We included three studies that provided results on the efficacy of sodium oxybate in children whose age suggests that they are likely to have reached puberty. These were small uncontrolled observational studies including a total of 23 patients.

Clinical effectiveness in adults

There is evidence from meta-analyses of RCTs for statistically significantly fewer weekly and daily cataplexy attacks with sodium oxybate compared to placebo, with a mean difference of between seven and 8.5 attacks per week (or one per day). Meta-analyses also reported statistically significantly better scores on measures of daytime sleepiness, fewer sleep attacks (of about nine attacks per week) and fewer nocturnal awakenings (of about one awakening per night) with sodium oxybate compared to placebo. In one 12-week open-label study 72% of patients reported reduced daily inadvertent naps and 68% reported reduced night awakenings with sodium oxybate. Results for hypnagogic hallucinations and sleep paralysis were not available in a form suitable for meta-analysis however a systematic review reported a statistically significant decrease in both outcomes in some, but not all, RCTs. In addition, a 12-week open label study found that 70% of patients reported reduced hypnagogic hallucinations and 67% reported reduced sleep paralysis episodes. Two meta-analyses reported statistically significant increases in the proportion of patients who were rated as 'much improved' or 'very much improved' on a clinician-rated measure of impression of change. In a 12-week open-label study, 90% of patients reported their symptoms as 'much improved' and 74% reported an improvement in their ability to concentrate. One open-label study attempted to define clinically relevant reductions in cataplexy attacks and daytime sleepiness and found that 92% of patients maintained a ≥50% reduction in weekly cataplexy

attacks from baseline and 74% of patients maintained a ≥20% reduction in daytime sleepiness from baseline after 12 months of sodium oxybate. The other studies did not address the clinical relevance of their statistically significant results and did not report baseline scores or improvement from baseline. It is therefore difficult to assess the clinical relevance of the results.

Clinical effectiveness in children who have reached puberty
There is evidence from uncontrolled observational studies for statistically significant reductions from baseline for cataplexy attacks. In one study (n=13) the reduction in mean daily attacks was 3.7 (from a baseline of 3.9) and in another study (n=8) the reduction in median weekly attacks was 34 (from a baseline of 38.5). Statistically significant improvements in daytime sleepiness and nocturnal sleep were also reported. One case study reported that hypnagogic hallucinations and sleep paralysis had ceased in two patients but did not provide data. Two studies reported improvements in some quality of life outcomes, with an improvement in social spheres in five of eight patients in one study and an improvement in school reports in one case study. The evidence for this sub-group is from a small number of patients in uncontrolled observational studies which represent a lower quality of evidence.

We did not identify any studies assessing the cost-effectiveness of sodium oxybate for narcolepsy.

In a meta-analysis of safety outcomes in adults, rates of nausea (39 events versus 5 events), vomiting (11 events versus 0 events) and dizziness (29 events versus 6 events) were statistically significantly higher with sodium oxybate compared to placebo. In a 12-week open-label study, 56% adults reported an adverse event, of which 2% were considered serious. Study withdrawals due to adverse events were reported, however these were all less than 10% of participants.

Limited information on the safety of sodium oxybate in children who have reached puberty comes from two small studies (n=10 combined). In one study, two of eight patients withdrew due to adverse effects, namely nightmares, suicidal ideation and dissociated feelings. In addition, two patients from this study experienced terminal insomnia and individual patients from both studies experienced a range of other effects.

We identified a phase III RCT in progress comparing sodium oxybate to placebo in children aged seven to 17 and a phase IV study looking at the long term safety of sodium oxybate. The estimated completion date for both trials is August 2017.

5 Discussion and conclusions

1a. Is sodium oxybate safe and clinically effective in the reduction in number and intensity of cataplexy attack, excessive day-time sleepiness (diurnal naps), nocturnal awakenings, terrifying dream experiences, insomnia, hypnagogic hallucinations, sleep paralysis, and improvement in quality of life in adult patients with narcolepsy and cataplexy compared to no intervention, combined treatment or with only standardised treatments?

There is evidence from meta-analyses of RCTs and open-label extension studies for statistically significantly better results for sodium oxybate compared to placebo for cataplexy attacks, daytime sleepiness, sleep attacks, nocturnal awakenings and symptom improvement. There is evidence of a reduction in sleep paralysis and hypnagogic hallucinations in some RCTS, and approximately two-thirds of patients in one 12-week open-label study reported a reduction in sleep paralysis and hypnagogic hallucinations. We did not identify any studies comparing sodium oxybate to

combined treatment or standardised treatments. One open-label study attempted to define a clinically relevant reduction for cataplexy attacks and daytime sleepiness and this criteria was achieved by a high proportion of patients in that study. The other study authors did not address the clinical relevance of their results and did not present data in a way that supported an assessment of clinical relevance. It is therefore difficult to assess the clinical relevance of the results.

In a meta-analysis of safety outcomes in adults, rates of nausea, vomiting and dizziness were statistically significantly higher with sodium oxybate compared to placebo. In one open-label study, 56% adults reported an adverse event of which 2% were considered serious. Study withdrawals due to adverse events were reported and were all less than 10% of participants.

1b. Is there evidence that sodium oxybate is clinically effective in patients with narcolepsy and cataplexy who have reached puberty (and weigh >40kgs) compared with no intervention, combined treatment or with only standardised treatments?

We did not identify any studies comparing sodium oxybate with no intervention, combined treatment or standardised treatments in children who have reached puberty. There is limited evidence from three, small uncontrolled observational studies (n=23 combined) whose populations are of an age which suggests they have reached puberty, for statistically significant reductions from baseline for cataplexy attacks. In one study (n=13) the reduction in mean daily attacks was 3.7 (from a baseline of 3.9) and in another study (n=8) the reduction in median weekly attacks was 34 (from a baseline of 38.5). There was also some evidence for statistically significant improvements from baseline in daytime sleepiness and nocturnal sleep. There were reported improvements (statistical tests not performed) for some patients in hypnogogic hallucinations, sleep paralysis and quality of life related outcomes. Limited information on the safety of sodium oxybate in children who have reached puberty comes from two small studies (n=10 combined). In one study, two of the eight patients withdrew due to adverse effects (nightmares, suicidal ideation and dissociated feelings) and another two patients experienced terminal insomnia. Individual patients from both studies experienced a range of other effects.

Because this evidence is from a very small number of patients in uncontrolled observational studies it is not possible to draw any strong conclusions about the effectiveness of sodium oxybate in patients with narcolepsy and cataplexy who have reached puberty and the results should be treated with caution.

2. Is sodium oxybate cost-effective in controlling the symptoms of narcolepsy and cataplexy in patients with narcolepsy?

We did not identify any studies assessing the cost-effectiveness of sodium oxybate for narcolepsy.

Competing Interest

All SPH authors have completed the ICMJE uniform disclosure form (www.icmje.org/coi_disclosure.pdf) and declare: grants from NHS England to SPH to undertake the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work

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7 Search Strategy

Table 4: Population, Intervention, Comparator and Outcomes (PICO)

P- Patients/ population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Adults with narcolepsy and cataplexy Subgroup for consideration: Children who have reached puberty and who weigh more than 40kg
I - Intervention Which intervention, treatment or approach should be used?	Sodium oxybate
C - Comparison What is/ are the main alternative/s to compare with the intervention being considered?	**Any treatment option below over and in relation to time:** • No intervention • Combination of sodium oxybate with standard treatment • Any other standardised treatment including: <u>Stimulants</u> • Including Modafinil, Methyphenidate (immediate and prolonged release) • Dextroamphetamines, Atomoxetine <u>Antidepressants</u> • Including Velafaxine, Clomipramine, Citalopram and Fluoxetine <u>Histamine blockers</u> • Pitolisant <u>Melatonin agonists</u> • Melatonin, Ramelteon, Tasimelteon • Clonidine
O - Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	Any, including: • Reduction in number and intensity of cataplexy attack • Reduction in excessive day-time sleepiness (diurnal naps) • Reduction in nocturnal awakenings • Reduction in terrifying dream experiences • Reduction in insomnia • Reduction in hypnagogic hallucinations • Reduction in sleep paralysis • Quality of life • Adverse events • Cost-effectiveness
Assumptions/ limits applied to search	Study types: • Meta-analysis • Systematic reviews • Randomised controlled trials • Prospective non-randomised clinical study • Other clinical study • Health economic studies

Search date: 15th December
Databases searched: PubMed, Embase, Cochrane Library, TRIP and NICE Evidence Search
Limited to studies published in English and last 10 years
Conference papers, letters, commentary, editorials and case reports excluded. Animal studies excluded

PubMed search:

("Narcolepsy"[Mesh:NoExp] OR narcolep*[Title/Abstract] OR "daytime sleepiness"[Title/Abstract] OR "day-time sleepiness"[Title/Abstract])

AND

("sodium oxybate"[Title/Abstract] OR xyrem[Title/Abstract] OR "gamma hydroxybutyrate"[Title/Abstract] OR "Sodium Oxybate"[Mesh])