Clinical Commissioning Policy: Sodium oxybate for symptom control of narcolepsy with cataplexy (children)

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Clinical Commissioning Policy Proposition:
Sodium oxybate for symptom control of narcolepsy with cataplexy (children)

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Plain Language Summary

Narcolepsy is a neurological condition affecting the regulation of sleep/wake cycles. Symptoms include excessive day-time sleepiness, hallucinations, sleep paralysis and disturbed night-time sleep. It may occur with cataplexy which is a sudden, temporary muscle weakness. Symptoms of cataplexy range from jaw dropping to total collapse on the floor. It is usually triggered by an emotion and may last between a few seconds and several minutes.

Sodium oxybate (brand name Xyrem®) is a drug that is licensed for treating narcolepsy with cataplexy in adults. However, it is not licensed for use in children. It is linked to frequent side effects such as nausea, headache, bed wetting and confusion.

NHS England has concluded that there are sufficient grounds to support a proposal for the routine commissioning of sodium oxybate for children (≤18 years old) suffering from narcolepsy with cataplexy who have reached puberty and who have not responded, or are intolerant to, first and second line treatments for this condition.

1. Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission sodium oxybate for a well-defined narrow group of children (≤18 years old) suffering from narcolepsy with cataplexy who have reached puberty and who have not responded, or are intolerant to, first and second line medications.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed audit requirements.

For the purpose of consultation NHS England invites views on the updated evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether sodium oxybate for children (≤18 years old) suffering from narcolepsy with cataplexy will be routinely commissioned is planned to be made by NHS England by June 2016 following a recommendation from the Clinical Priorities Advisory Group.

2. The proposed intervention and clinical indication

Narcolepsy and cataplexy are lifelong disorders, often diagnosed in childhood, and requiring special arrangements for the transition of care from paediatric to adult neurological services. Narcolepsy with cataplexy (otherwise known as narcolepsy-cataplexy complex) is a neurological condition affecting the regulation of sleep/wake cycles characterised by excessive day-time sleepiness, cataplexy, hypnagogic hallucinations, sleep paralysis and fragmented night-time sleep. Narcolepsy may occur without cataplexy but virtually all patients with cataplexy have narcolepsy.

Sodium oxybate is derived from the neurotransmitter GABA and suppresses dopaminergic neuronal activity. It has been shown to be effective in controlling symptoms of both narcolepsy and cataplexy in adults and is licenced for such use. Sodium oxybate is known to be associated with frequent side effects (e.g. nausea, headache, bed wetting, and confusion including withdrawal effects) and may not be appropriate for all patients. One small study reported cases of suicidal ideation. Published case series evidence suggests it is also effective in children and may be appropriate for post-pubescent children (weighing >40kg) who have not responded well to first and second line treatments.

Sodium oxybate is licensed to treat adults who have narcolepsy with cataplexy by both the European Medicines Agency (EMA/359552/2014) and the U.S. Food and Drug Administration (NDA 21-19).

3. Definitions

Narcolepsy is a neurological condition affecting the brain's ability to regulate normal sleep/wake cycles. This can lead to symptoms such as disturbed night-time sleep and excessive sleepiness throughout the day.

Cataplexy is an episode of muscular weakness triggered by strong emotions such as laughter, anger and surprise. The loss of muscle tone ranges from a just-perceptible weakening of the facial muscles through weakness at the knees, to total collapse on the floor, which may cause injury.

Polysomnography is an investigation of sleep, carried out at a specialist sleep centre. The study usually involves staying overnight at the sleep centre so sleeping patterns can be analysed.

4. Aim and objectives

The policy aims to define NHS England's commissioning position for sodium oxybate for the treatment of children (≤18 years old) suffering from narcolepsy with cataplexy.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for children suffering from narcolepsy with cataplexy.

5. Epidemiology and needs assessment

Narcolepsy and cataplexy impact on all aspects of life. For this patient group problems related to tiredness e.g. poor concentration and memory; interference with life and education; daytime sleepiness and cataplexy attacks may particularly affect educational attainment (and associated future employment and economic outcomes), social/personal relationships and general well-being. Falls can occur during cataplexy attacks which may cause injury. Frequent or prolonged hallucinations occur and vivid nightmares can occur and can be frightening as patients cannot separate reality from dreams. Additionally, there is a high risk of obesity and metabolic syndrome.

The estimated incidence rate is 1.37/100,000 per year for both narcolepsy with cataplexy and narcolepsy without cataplexy and 0.74/100,000 per year for narcolepsy with cataplexy (Silber et al., 2002).

The prevalence of paediatric narcolepsy is likely to be underestimated due to misdiagnosis (Stores G, 2006) and early studies reported a median delay between symptom onset and diagnosis of more than 10 years (Morrish et al., 2004). It is thought that half the adults with narcolepsy-cataplexy will have had symptoms during childhood but not diagnosed until later (Dauvilliers et al., 2001) although this pattern is improving with increased understanding of the condition. The overall prevalence of narcolepsy (paediatric and adult) in Western countries is estimated to be 20-50 per 100,000 population (Longstreth et al., 2007).

Clinical experience suggests c. 12 paediatric patients have severe and uncontrolled narcolepsy with cataplexy in England each year, of which 2 are pre-pubertal and/or weighing below 40kg. As such, it is estimated that c. 10 paediatric patients per year are likely to be the cohort for this policy proposition.

6. Evidence base

NHS England has concluded that there are sufficient grounds to support a proposal for the routine commissioning of sodium oxybate for a well-defined narrow group of children suffering from narcolepsy with cataplexy who have reached puberty and who have not responded, or are intolerant to, first and second line medications.

Evidence summary

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.

7. Proposed criteria for commissioning

Inclusion criteria:

Sodium oxybate will be prescribed for post-pubescent children (weighing >40kg and ≤18 years old) where attempts to control symptoms of narcolepsy with cataplexy have failed despite a trial of first and second line medications from each symptom group for at least three months. Specifically:

(i) Patients who present with narcolepsy with cataplexy according to International Classification of Sleep Disorders 3 (ICSD) criteria; AND

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

(iii) Show incomplete response to trial of more than one medication from each symptom group (*Narcolepsy*: methylphenidate, lisdexamphetamine, modafinil and atomexetine. *Cataplexy*: venlafaxine, clomipramine and other SSRIs. See section 8: Proposed patient pathway for more information); OR

(iv) Have significant adverse effects as a result of second line medication in each symptom group; AND

(v) Are assessed as able to benefit from sodium oxybate by a properly constituted MDT (see section 9: Proposed governance arrangements for more information).

Exclusion criteria:

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

Stopping criteria:

(i) Serious adverse effects including signs of respiratory depression; OR

(ii) Show evidence of incomplete response at three months as assessed by clinical examination according to:

a) *For cataplexy*: the severity and frequency criteria below; AND
b) *For narcolepsy*: the Epworth or Paediatric sleepiness scale below.

At least one of the cataplexy scores (either severity or frequency) should improve after 3 months of treatment.

Severity of cataplexy

1 = moderate weakness
2 = can maintain posture with external support
3 = loses posture and falls to the ground

Frequency of cataplexy

0 = <1 episode per year
1 = >1 attack per year
2 = more than one attack per month
3 = >1 attack per week
4 = >1 per day

Improvements in narcolepsy should be monitored by using either the Epworth Sleepiness Scale or the Paediatric Sleepiness Scale.

8. Proposed patient pathway

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

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

Once diagnosis is confirmed by the specialist sleep service, the patient is prescribed

one of the following first or second medications, conventionally divided into medications that improve narcolepsy and cataplexy. (Please note that which medications are 'first' and which 'second' line in the list below is based on clinical consensus. This varies across countries and there is a lack of head-to-head studies to evidence such choices).

Narcolepsy:
First line: Methylphenidate preparations (immediate and prolonged release)
Second line: Dexamphetamine, lisdexamphetamine, modafinil and atomoxetine

Cataplexy:
First line: Venlafaxine
Second line: Clomipramine and other SSRIs

If the patient shows incomplete response within three months and/or has significant associated adverse effects after trial of first and second line medications treatment options in each treatment group, sodium oxybate is proposed as third-line treatment.

Sodium oxybate should only be initiated following an MDT discussion, which should explicitly consider the psychological support arrangements that need to be put in place for the individual child, including psychological assessment where the child is deemed to be at higher risk of harm.

Dosage: Initially two doses of 2.25g per day and adjusted at one-, to two-week intervals depending on response up to a maximum daily dose of 9g (in two equally divided doses) (EMA/359552/2014). In addition, prescribing consultant will regularly monitor patients' BMI.

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

9. Proposed governance arrangements

Patients in secondary care should be referred to the designated tertiary service.

Treatment should be conducted by services with previous and ongoing experience in the diagnosis and management of young people with narcolepsy. Such services must have access to a sleep laboratory that can conduct standard polysomnography and multiple sleep latency tests to AASM standards.

MDT in such services will comprise a paediatrician and a psychologist, with the paediatrician having relevant training and experience in paediatric narcolepsy. Typically this includes paediatricians with neurodisability, neurology, and respiratory sleep training backgrounds. In some instances, the paediatrician will be supported by a consultant colleague from an adult (usually neurology) service.

Ideally such services will have access to specialised paediatric pharmacy. Psychology support might come from within the sleep services, or externally such as local child and adolescent mental health services (CAMHS). Children deemed to be

at higher risk of harm need to be registered with CAMHS services.

Sodium oxybate is a controlled drug and appropriate training and safeguards must be in place (e.g. lockable storage).

For other governance arrangements see Specialist Neurosciences Service specification.

10. Proposed mechanism for funding

The funding and commissioning will be managed through the relevant local NHS England Specialised Commissioning Team.

11. Proposed audit requirements

Sodium oxybate should only be available in experienced centres that agree to audit and publish their results using established narcolepsy outcome measures. This should include complication rates related to the use of sodium oxybate. Use of software systems (e.g. Blueteq) to track and audit use of sodium oxybate by clinicians to be mandated, in order to ensure it is administered according to the Criteria for Commissioning.

In addition, centres without an in-house database will be invited to participate in the European Narcolepsy Network (EU-NN) database to enhance the scientific understanding of this rare disease.

12. Documents which have informed this policy proposition

European Public Assessment Report, Xyrem (Sodium Oxybate) EMA/359552/2014

U.S. Food and Drug Administration, NDA 21-196

Scottish Medicine Consortium No. (246/06). March 10, 2009

13. Date of review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned (expected by June 2016).