Shared Care Guideline

Sodium Oxybate – Narcolepsy with cataplexy

Executive Summary

- **Indication:** Narcolepsy in adult patients with cataplexy.
- Initiated by a Consultant Sleep Physician or under the direct supervision of a Consultant Sleep Physician for patients with a definitive diagnosis of narcolepsy with cataplexy in whom all other licensed or unlicensed treatment options have been tried and optimised and despite this treatment has failed to improve symptoms or in patients in whom other treatment options are not tolerated or contraindicated.
- Before initiation of Sodium Oxybate treatment, all treatment options will be discussed with patient and patient's G.P.
- **Dose:** Initially 2.25g on retiring and repeated 2.5 to 4 hours later, increased in steps of 1.5g daily in two divided doses at intervals of 2 weeks; usual maximum 9g da**ily i**n two divided doses.
- *Dose will be communicated to GP, CCG Medicine Management Team and patient by Specialist Sleep Consultant.*
- **Efficacy Monitoring:** Specific monitoring for efficacy to be carried out by tertiary care on a regular basis.
- **If a patient fails to respond to Sodium Oxybate therapy, treatment will be stopped.** This will be communicated to the patient, their G.P. and the funding CCG.

The responsibilities of the hospital specialist, GP and patient for this Shared Care Guideline can be found within this document.

Sharing of care depends on communication between the specialist, GP and the patient or their parent/carer. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. The doctor/healthcare professional who prescribes the medication has the clinical responsibility for the drug and the consequences of its use. Further information about the general responsibilities of the hospital specialist and GP can be found here

1 Scope

This guideline provides information relating to Sodium Oxybate and outlines the responsibilities of the general practitioner and the Respiratory Support and Sleep Centre at Papworth Hospital NHS Trust in the prescribing and monitoring of this medicine.

2 Aim

To provide clear and concise information to general practitioners in order that their patients with narcolepsy receive on-going safe and effective care using evidence based medicine, following evaluation by our Sleep Medicine Consultants and their team.

3 Introduction

- Narcolepsy occurs in 1 in 2500 subjects and is a chronic, debilitating, life-long neurological disease characterised initially by excessive daytime sleepiness during the second and third decades of life.

- Narcolepsy usually progresses to include cataplexy (sudden loss of muscle tone), sleep paralysis, hypnagogic hallucinations and fragmented nocturnal sleep. Excessive, uncontrollable daytime sleepiness is experienced by all patients with narcolepsy, and is usually treated with stimulants and/or modafinil during the day to help keep patients awake. Cataplexy affects approximately 75% of people with narcolepsy and is triggered by emotional stimuli such as anger, excitement or laughter.

- The severity ranges from dropping of the jaw or the head, to buckling of the legs. During an episode, speech can be slurred and eyesight impaired, but hearing and awareness remain undisturbed. Episodes can last a few seconds or for several minutes. Up until now, the only licensed therapy for cataplexy in the UK has been the tricyclic antidepressant clomipramine, which is licensed as adjunctive treatment. Other antidepressants such as imipramine and SSRIs are used, but are unlicensed for this indication.

- Sodium Oxybate (Xyrem®) is licensed for the treatment of narcolepsy in adult patients with cataplexy. At Papworth Hospital NHS Foundation Trust Sodium Oxybate will be reserved for those patients whose cataplexy fails to respond to Clomipramine (the only other licensed treatment) and other antidepressants and in whom other symptoms of narcolepsy, particularly excessive daytime sleepiness, do not respond to standard medication such as Modafinil and Dexamphetamine. The recommendation to start treatment will be made by Consultant only and the Consultant will be personally responsible for the decision to initiate Sodium Oxybate treatment.

- Sodium Oxybate is a central nervous system depressant whose precise mechanism of action is unique and differs from all other agents used in narcolepsy and probably involves systems other than central GABA systems.

- Sodium Oxybate use is associated with dose-related improvements in the symptoms of narcolepsy and reduction in the numbers of attacks of cataplexy. No withdrawal effects have been seen with Sodium Oxybate at therapeutic doses and trials demonstrated that after stabilisation on Sodium Oxybate therapy, acute withdrawal led to a gradual increase in the number of cataplexy attacks.

4 Abbreviations

- **CCG** = Clinical Commissioning Group
- **CNS** = Central Nervous System
- **GABA** = Gamma-Aminobutyric Acid
- **GHB** = Gamma Hydroxybutyrate
- **RSSC** = Respiratory Support and Sleep Centre
- **SSRI** = Selective serotonin re-uptake inhibitor

5 Dose and Administration

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

- Both doses of Sodium Oxybate should be prepared prior to bedtime. Each dose must be diluted with 60mls of water in the child resistant dosing cups provided prior to ingestion. Patients will probably need to set an alarm to awaken for the second dose. After ingesting each dose patients should then lie down and remain in bed. After dilution in the dosing cups, the preparation should be used within 24 hours.

- Absorption is delayed and decreased by a high fat meal and the patient should be told to eat at least 2 to 3 hours before going to sleep and taking the first dose of Sodium Oxybate. Patients should try to minimise variability in the timing of dosing in relation to meals.

- If the patient stops taking Sodium Oxybate for more than 14 days then titration should be restarted from the lowest dose. Each Sodium Oxybate bottle should be discarded 40 days after opening.

Dose in hepatic and renal impairment:

- Sodium Oxybate is metabolised in the liver to inactive metabolites and clearance is almost entirely by biotransformation to carbon dioxide, which is then eliminated by expiration. The doses should be halved in patients with compromised liver function and dose increments monitored closely. As less than 5% is excreted via the kidney no dosage adjustment should be necessary in patients with renal impairment. All patients with impaired renal function should consider a dietary recommendation to reduce sodium intake.

Sodium Intake:

- Daily sodium intake in patients taking Sodium Oxybate ranges from 0.5g (for a 3g dose) to 1.6g (for a 9g dose). The recommended maximum dietary intake of sodium is 2.4g per day. A dietary recommendation to reduce sodium intake should be carefully considered in patients with heart failure, hypertension or compromised renal function.

Special Populations:

- Safety and efficacy in children and adolescents has not been established therefore use in patients under 18 years of age is not recommended. Elderly patients should be monitored closely for impaired motor and/or cognitive function when taking Sodium Oxybate.

Epileptic patients

- Seizures have been observed in patients treated with Sodium Oxybate. In patients with epilepsy, the safety and efficacy of Sodium Oxybate has not been established, therefore use is not recommended.

Pregnancy and Breast Feeding:

- Not advised in pregnancy or breast feeding.

Further information can be found in the Summary of Product Characteristics http://www.medicines.org.uk/emc/medicine/17364

6 Adverse Effects

Very common (≥ 1 in 10)

- dizziness,
- headache
- nausea (the frequency of nausea is higher in women than men)

Common (≥ 1 in 100 and < 1 in 10)

- blood pressure increased
- weight decreased
- feeling drunk
- hyperhidrosis
- enuresis nocturna
- nasopharyngitis and sinusitis
- depression

Uncommon (≥ 1 in 1000 and < 1 in 100)

- hypersensitivity
- suicide attempt, psychosis, paranoia, hallucination, abnormal thinking, agitation, initial insomnia

Further information can be found in the Summary of Product Characteristics
http://www.medicines.org.uk/emc/medicine/17364

7 Cautions

- Sodium Oxybate has the potential to induce respiratory depression. Prescribers should be aware that sleep apnoea occurs in up to 50% of patients with narcolepsy. Given the possibility of increasing the risk of respiratory depression, the concomitant use of benzodiazepines and sodium oxybate should be avoided.

- Sodium Oxybate is a sodium salt of gamma hydroxybutyrate (GHB), a CNS active substance with well known abuse potential. During treatment, patients will be monitored for the risk of diversion, misuse and abuse of sodium oxybate. Patients will be evaluated for a history of drug abuse potential and monitored closely. GHB and Sodium Oxybate are Schedule 2 (CD-POM) Controlled Drugs in the UK.

- Patients must be evaluated for a history of drug abuse and such patients monitored closely.

- The combined use of alcohol with Sodium Oxybate may result in potentiation of the central nervous system-depressant effects of Sodium Oxybate and alcohol. Therefore, patients should be warned strongly against the use of any alcoholic beverages in conjunction with Sodium Oxybate. Sodium Oxybate should not be used in combination with sedative or other CNS depressants.

- Patients may become confused while being on Sodium Oxybate. If this occurs, they should be evaluated fully, and an appropriate intervention considered on an individual basis. Other neuropsychiatric events include psychosis, paranoia, hallucinations and agitation. The emergence of depression when patients are treated with Sodium Oxybate requires careful and immediate action.

- Sodium Oxybate has a major influence on the ability to drive and use machines.

- For at least 6 hours after taking Sodium Oxybate, patients must not undertake activities requiring complete mental alertness or motor co-ordination, such as operating machinery or driving.

- When patients first start taking Sodium Oxybate, until they know whether this medicinal product will still have some carryover effect on them the next day, they should use extreme care while driving a car, operating heavy machines, or performing any other task that could be dangerous or require full mental alertness.

- If a patient experiences urinary or faecal incontinence during Sodium Oxybate therapy, the prescriber should consider pursuing investigations to rule out underlying aetiologies.

- Sleepwalking has been reported in patients treated in clinical trials with Sodium Oxybate. The risk of self-harm should be borne in mind in any sleepwalking patient. Therefore, episodes of sleepwalking should be fully evaluated and a referral made to the patient RSSC consultant for this evaluation in order that appropriate interventions are considered.

- Sodium Oxybate is considered unsafe in patients with porphyria.

Rebound effects and withdrawal syndrome

- The discontinuation effects of sodium oxybate have not been systematically evaluated in controlled clinical trials. In some patients, cataplexy may return at a higher frequency on cessation of sodium oxybate therapy, however this may be due to the normal variability of the disease.

- Although the clinical trial experience with sodium oxybate in narcolepsy/cataplexy patients at therapeutic doses does not show clear evidence of a withdrawal syndrome, in rare cases, events such as insomnia, headache, anxiety, dizziness, sleep disorder, somnolence, hallucination, and psychotic disorders were observed after GHB discontinuation.

Further information can be found in the Summary of Product Characteristics
http://www.medicines.org.uk/emc/medicine/17364.

8 Contraindications

- Hypersensitivity to Sodium Oxybate or to any of the excipients.
- Patients with major depression.
- Patients with epilepsy.
- Sodium Oxybate is contra-indicated in patients being treated with sedative hypnotic agents, opioids and barbiturates as it has the potential to induce respiratory depression.
- Sodium Oxybate is contra-indicated in patients with succinic semialdehyde dehydrogenase deficiency. This rare disorder is an inborn error of metabolism variably characterised by mental retardation, hypotonia, and ataxia.

Further information can be found in the Summary of Product Characteristics
http://www.medicines.org.uk/emc/medicine/17364
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9 Interactions

- No pharmacokinetic interactions have been demonstrated with drugs commonly used in patients with narcolepsy. Sodium Oxybate should not be used in combination with sedative hypnotics or other CNS depressants. Antidepressants have been used in the treatment of narcolepsy. A possible additive effect of antidepressants and Sodium Oxybate cannot be excluded. The rate of adverse reactions is increased when Sodium Oxybate is co-administered with tricyclic antidepressants.
- The combined use of alcohol with sodium oxybate may result in potentiation of the central nervous system-depressant effects of sodium oxybate. Patients should be warned against the use of any alcoholic beverages in conjunction with sodium oxybate.

Further information can be found in the Summary of Product Characteristics
http://www.medicines.org.uk/emc/medicine/17364

10 Monitoring Standards & Actions to take in the event of abnormal test results/symptoms

- Laboratory tests are not required to monitor patient response to Sodium Oxybate administration.

11 Shared Care Responsibilities

a. Hospital specialist:

The patients will be assessed by one of the consultants (Dr I E Smith, Dr T Quinnell, Dr M Davies, Dr N Oscroft and Dr Mason). If the patient is in agreement with the treatment plan then the hospital will undertake to:

- Ensure that an agreement to accept prescribing responsibility has been obtained from the general practitioner before treatment is initiated.
- Evaluate patients for a history of drug abuse and account for any additional risks in these patients
- Provide information to the patient regarding the medicine
- Provide an initial supply of Sodium Oxybate (costs to be reimbursed from the CCG).
- Recommend an initial dose and how this may be titrated according to the response to treatment.
- Inform the GP after each clinic attendance if there is any change to treatment or monitoring.
- Inform GP of patients who do not attend clinic appointments and discuss patient's on-going treatment plan.
- Review the patient's progress on treatment. If the patient has failed to respond to treatment after an eight week period then Sodium Oxybate therapy will be discontinued.
- Be available for advice to the general practitioner.
- Answer patient enquiries on any aspect of this therapy.
- Review all treatment responders at an out-patient clinic 4 months after initiation of therapy and then again at an out-patient clinic 4 to 6 months later. Patients will then be seen every six months or annually as clinically indicated.
- Communicate all relevant information regarding treatment to the general practitioner and to the Chief Pharmacist, C&P CCG.

b. General Practitioner:

- Continue to prescribe Sodium Oxybate once this has been initiated by the Respiratory Support and Sleep Centre consultant specialists.
- Communicate any adverse events or other problems with the medicine to the supervising consultant at Papworth Hospital.
- Request advice from the hospital specialist when necessary.
- Monitor blood pressure on a regular basis.

c. Patient or parent/carer:

- Report to the Consultant or GP if they do not have a clear understanding of their treatment.
- Patients must not exceed the recommended dose.
- Patients must attend their scheduled clinic appointments.
- Must inform other clinical staff that they are receiving treatment.
- Report any adverse effects to their Consultant or GP whilst taking Sodium Oxybate.
- Share any concerns they have in relation to treatment with Sodium Oxybate.
- Obtain their prescription from the same dedicated pharmacy of their own choice.

12 Contact numbers for advice and support

Papworth Hospital NHS Foundation Trust		
Specialist	**Post**	**Telephone** (direct lines)
Dr Ian E Smith	Director of RSSC and Consultant Sleep Physician	01480 364164
Dr Tim Quinnell	Consultant Sleep Physician	01480 364174
Dr Mike Davies	Consultant Sleep Physician	01480 364542
Dr Nick Oscroft	Consultant Sleep Physician	01480 364551
Dr Martina Mason	Consultant Sleep Physician	01480 364165
Mrs Netta Tyler	RSSC Directorate Pharmacist	01480 364762
Pharmacy Medicines Information Service		01480 364179
Pharmacy Medicines Helpline		01480 364739 (answerphone)

13 Equality and Diversity Statement

This document complies with the Papworth Hospital NHS Foundation Trust service Equality and Diversity statement.

14 Disclaimer

It is your responsibility to check that this printed out copy is the most recent issue of this document.

15 Document Management

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The information contained in this guideline is issued on the understanding that it is accurate based on the resources at the time of issue. For further information please refer to the most recent Summary of Product Characteristics
http://www.medicines.org.uk/emc/medicine/17364.