



Original Article

Safety and efficacy of long-term use of sodium oxybate for narcolepsy with cataplexy in routine clinical practice



Panagis Drakatos^a, Dimosthenis Lykouras^{a,b}, Grainne D'Ancona^a, Sean Higgins^a,
Nadia Gildeh^a, Raluca Macavei^a, Ivana Rosenzweig^{a,c}, Joerg Steier^{a,d},
Adrian J. Williams^a, Rexford Muza^a, Brian D. Kent^a, Guy Leschziner^{a,e,*}

^a Sleep Disorders Centre, Guy's Hospital, Great Maze Pond, London, SE1 9RT, United Kingdom

^b Department of Pulmonary Medicine, University Hospital of Patras, Rio Patras 26500, Greece

^c Sleep and Brain Plasticity Centre, Department of Neuroimaging, IoPPN, King's College London, United Kingdom

^d Faculty of Life Sciences and Medicine, King's College London, United Kingdom

^e Department of Basic and Clinical Neuroscience, King's College London, United Kingdom

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ABSTRACT

Background: Sodium oxybate is licensed in Europe for the treatment of narcolepsy with cataplexy in adults. The aim of this study was to assess the efficacy and safety of sodium oxybate in clinical practice in patients with narcolepsy and cataplexy refractory to other treatments.

Materials and methods: This was a retrospective single centre study including patients with severe narcolepsy with cataplexy refractory to other treatments, who were initiated on sodium oxybate between 2009 and 2015. Patients were allowed to be on other stimulants or/and anti-cataplectic agents. Epworth sleepiness scale (ESS) and weekly cataplexy events were recorded. Side effects (SEs) were recorded at every follow-up visit.

Results: 90 patients were prescribed sodium oxybate, with a total of 3116 patient-months of drug exposure. ESS and weekly cataplexy events were significantly reduced by sodium oxybate for all patients ($\Delta\text{ESS} = 4.3 \pm 4.4$ and $\Delta\text{cataplexy} = 21.8 \pm 18.5$ events/week; $p < 0.0001$, respectively). The required maintenance dose could not be predicted based upon gender, body mass index, or clinical factors. 60% of patients were able to reduce or come off other medications. Half of the patients experienced at least one SE, and 26.6% had to stop treatment due to limiting SEs. Nausea, mood swings and enuresis were the most commonly reported SEs. SEs that led to drug discontinuation, particularly psychosis, were associated with increasing age and were observed early after the initiation of the drug.

Conclusions: Sodium oxybate provides a good clinical efficacy and acceptable safety profile in routine clinical practice for the treatment of patients suffering from narcolepsy with cataplexy. A quarter of patients experience SEs requiring withdrawal of the drug with older patients being more vulnerable to the more serious SEs.

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1. Introduction

Narcolepsy is a chronic neurological disorder causing dysregulation of sleep and wakefulness, with a prevalence of approximately 1 in 3000 [1]. It is characterised by excessive daytime sleepiness (EDS), cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis and disturbed sleep [2].

There is no cure for narcolepsy at present, and current treatment focuses on symptom control. A reduction in daytime sleepiness is achievable with medications that increase wakefulness, including wake promoters such as modafinil, amphetamines, and methylphenidate, while cataplexy is typically controlled through the use of antidepressant drugs which suppress Rapid Eye Movement sleep [3–6].

Sodium oxybate, the sodium salt of gamma-hydroxybutyrate (GHB), an endogenous metabolite of gamma-aminobutyric acid (GABA), is a central nervous system depressant. It is indicated for the treatment of both cataplexy and EDS associated with narcolepsy [7]. Its mode of action is uncertain, but it may involve stimulation of

* Corresponding author. Sleep Disorders Centre, Guy's Hospital, Great Maze Pond, London, SE1 9RT, United Kingdom.

E-mail address: guy.leschziner@gstt.nhs.uk (G. Leschziner).

GABA-B receptors [8]. Sodium oxybate is rapidly absorbed and metabolised, having a mean elimination half-life of 90–120 min. It is currently authorized by the European Medicines Agency to treat narcolepsy with cataplexy in adults, and by the US Food and Drug Administration (FDA) to treat cataplexy in patients with narcolepsy, with an “expanded indication” for the treatment of EDS [3,9].

Existing data regarding the tolerability and efficacy of sodium oxybate in narcolepsy originate from prospective drug trials [10–13]. We aimed to analyse the use of sodium oxybate in routine European clinical practice, where sodium oxybate is reserved for a sub-group of patients with narcolepsy with cataplexy, patients more likely to be on multiple other therapies with a more severe phenotype.

2. Materials and methods

We performed a retrospective study assessing patients attending a tertiary referral sleep disorders centre. All patients diagnosed with narcolepsy with cataplexy and initiated on sodium oxybate between 2009 and 2015 were included. A full medical history, sleep history, sleep study results and demographics were recorded for all patients. The reduction of Epworth Sleepiness Scale (ESS) score (Δ ESS) and of cataplexy events expressed in events/week (Δ cataplexy) were recorded from patients' notes and relevant diaries, as the differences between ESS and cataplexy events before sodium oxybate initiation (baseline) and after a dose of sodium oxybate providing optimal clinical effect was achieved (final).

Due to the nature of the study and the limitations that apply in the UK for sodium oxybate treatment eligibility, patients could already be on other drugs for narcolepsy (stimulants or/and anti-cataplectic agents). According to policies in place for prescribing of sodium oxybate within the UK National Health Service (NHS), patients were only eligible for this drug if they had tried at least two stimulants and/or two anti-cataplectic agents, and remained symptomatic with an ESS ≥ 17 or with an average 21 cataplectic events per week.

All the patients in this study were initially treated with oral sodium oxybate 4.5 g/night, given as two equally divided doses 2.5–4 h apart and titrated, according to response, up to a maximum dose of up to 9 g/night in two doses of 4.5 g each, with dose adjustments every two weeks, as stipulated in the approved prescribing protocol. Any subsequent reduction or elimination of other drugs for narcolepsy was recorded. Appropriate approval from the institutional review board on human research was obtained (project number 4641).

3. Diagnosis

The diagnosis of narcolepsy with cataplexy was made according to the International Classification of Sleep Disorders-2 (ICSD-2) criteria of the American Academy of Sleep Medicine (AASM), due to the retrospective nature of the study [14].

4. Outcomes analysis

Safety and tolerability were evaluated based on reported side effects (SEs), without a pre-established list of SEs, during every follow-up visit after initiation of sodium oxybate. SEs were categorized into groups: namely infections, psychiatric, neurological, gastrointestinal, general, sleep disorders and cardiological SEs, in keeping with those listed in the summary of product characteristics [15]. Reports from patients' notes of mood changes throughout the day, which could vary from elevated mood to anger to sadness within a few hours, and changes in mood clearly out of proportion to circumstances which could also cause impairment in

functioning, were grouped under the term mood swings. Psychotic symptoms were confirmed by formal psychiatric assessment and were made according to the Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-V) criteria [16].

5. Statistics

Results are reported as mean \pm SD if not otherwise indicated. Following testing for normality, comparison between groups was performed using independent-samples Mann–Whitney *U* test. Spearman product correlation coefficient was used for correlations between continuous and nominal variables and Chi Square with Cramer's *V* product for correlations between nominal variables. Comparison of baseline and final ESS and cataplexy events within patients was calculated using related-samples Wilcoxon Signed-Ranks Test. A multiple stepwise linear regression analysis was performed to identify which variables most satisfactorily explained Δ ESS and Δ cataplexy in our patients. Binary regression analysis with forward stepwise method was applied in three prediction models: 1) to predict which patients exhibited a reduction of other drugs (wake promoters, stimulants or/and anti-cataplectic agents) due to sodium oxybate initiation, 2) which experienced any SEs secondary to sodium oxybate, and 3) which patients had to discontinue the drug due to SEs. Statistical significance was defined as $p < 0.05$. IBM SPSS Statistics V24.0 (SPSS, Chicago, IL/USA) was used for all statistical analysis.

6. Results

6.1. Efficacy

A total of 90 patients with narcolepsy with cataplexy, aged 42.5 ± 14.9 years, were prescribed sodium oxybate during the study period, with a total of 3116 patient-months of drug exposure, and a median 35.5 months (interquartile range 11.0–54.0) of follow up time (FU) (Table 1).

Sodium oxybate significantly reduced the ESS (Δ ESS = 4.3 ± 4.4 , $p < 0.0001$). The most common optimal dose of sodium oxybate was 9 g/night (31/90, 33.3%), but many patients were treated with lower doses (22.2% required 4.5 g/night, 22% 6 g/night, and 18% 7.5 g/night).

The improvement in ESS (Δ ESS) correlated with higher final dose of the drug ($r = 0.389$, $p < 0.001$), but no correlation was found with age and BMI. A stepwise regression analysis was performed for predictors of Δ ESS in the group of patients that did not discontinue sodium oxybate due to side effects or lack of efficacy. Age,

Table 1
Demographics, baseline characteristics and treatment of the studied cohort.

Parameters (n = 90)	Mean \pm SD
Age (years)	42.5 \pm 14.9
Gender (M/F)	38/52
BMI (kg/m ²)	30.1 \pm 7.8
*ESS baseline	18.9 \pm 3.4
*ESS final	14.5 \pm 5.1
*Cataplexy events/week baseline	26.2 \pm 22.7
*Cataplexy events/week final	4.4 \pm 10.8
Patients on stimulants or wake promoters, n (%)	36 (40)
Patients on anticataplectic agents, n (%)	7 (7.8)
Patients on combination treatment, n (%)	44 (48.9)
Patients on no treatment, n (%)	3 (3.3)
FU time (months)	35.5 (IQR 11.0–54.0)

BMI, Body Mass Index; ESS, Epworth Sleepiness Scale score. *: Baseline and final term uses as reference points the status before sodium oxybate initiation and after optimum dose of sodium oxybate had been achieved, respectively. FU, follow-up is reported as median; IQR, interquartile range. The term combination treatment refers to stimulants or wake promoters and anti-cataplectic agents.

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