

# **AUSTRALASIAN SLEEP ASSOCIATION POSITION STATEMENT AND GUIDELINES, REGARDING THE USE OF SODIUM OXYBATE IN THE TREATMENT OF NARCOLEPSY**

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## **EXECUTIVE SUMMARY**

Narcolepsy is a neurologic sleep/wake disorder characterised by excessive daytime sleepiness, sleep fragmentation and REM sleep intrusion phenomena – sleep paralysis, hypnagogic hallucinations and cataplexy. Cataplexy, a key ancillary symptom of narcolepsy, is characterised by sudden onset muscle weakness, associated with emotionally laden events.

Sodium oxybate, the sodium salt of gamma-hydroxybutyrate, is approved for use in a number of international jurisdictions for the excessive sleepiness and cataplexy associated with narcolepsy. Its use is supported by at least six randomised control trials, involving over 700 patients, where both efficacy and safety data are available. Post-marketing data from 15 countries involving approximately 26,000 patients confirm that sodium oxybate can be safely and effectively used within the confines of a strict regulatory framework. (1) Consequently, international treatment guidelines (from Europe and the United States of America) recommend the use of sodium oxybate as an important therapeutic option for patients with narcolepsy. (2,3)

Some patients with narcolepsy who are maximally treated with stimulant medication and anti-depressants remain excessively sleepy and/or have problematic cataplexy, with resultant impact on their quality of life and productivity. The Australasian Sleep Association therefore recommends and supports the registration and use of sodium oxybate in Australia as a prescriber permit-controlled Schedule 8 medication. Sodium oxybate should be used in adults or children primarily as monotherapy for excessive daytime sleepiness and/or cataplexy where inadequate benefit exists from alternative agents, or where there is intolerance to, or contraindication to the use of, these alternative agents. Significant sleep disordered breathing needs to be excluded or effectively treated prior to the commencement of sodium oxybate. Careful dose monitoring and prescribing needs to be performed by sleep medicine practitioners experienced in the management of narcolepsy.

## **BACKGROUND**

Narcolepsy is a neurologic sleep/wake disorder characterised by excessive daytime sleepiness, sleep fragmentation and so-called REM intrusion phenomena. These include hypnagogic/hypnopompic hallucinations, sleep paralysis and cataplexy. Cataplexy, sudden and often bilateral muscle weakness associated with emotionally laden events, is the classic clinical hallmark of narcolepsy, occurring in approximately 70% of patients with this disorder. (4) The population prevalence of narcolepsy is estimated at between 0.025% and 0.05%, in Western populations. (5)

Data from autopsy studies and cerebrospinal fluid analysis have shown narcolepsy with cataplexy is typically associated with marked deficiency of the orexin/hypocretin peptides in the central nervous system. (6) These peptides have been shown to influence appetite in a number of species and, in human populations, regulate the stability of night-time sleep and maintenance of wakefulness during the day. The sleep fragmentation and instability seen in patients with narcolepsy is thought to be due, at least in part, to the destabilising effect of orexin/hypocretin deficiency on sleep quality. The orexin system is seen as the critical regulator of the sleep-wake 'flip-flop' switch, that controls the stability of both sleep and wakefulness. (7)

Sodium oxybate is the sodium salt of gamma-hydroxybutyrate (GHB), an endogenous inhibitory neurotransmitter. Sodium oxybate is rapidly absorbed and excreted. Clinical effects are seen within minutes and the elimination half-life is short, typically between 30-60 minutes. (8) Food reduces the bioavailability of sodium oxybate. The effect of sodium oxybate on the symptoms of narcolepsy lasts much longer than the plasma half life of the drug. Sodium oxybate stimulates GABA-B receptors, although how this action leads to its effects on narcolepsy symptoms is poorly understood.

Sodium oxybate has been approved for use in narcolepsy by the Federal Drug Administration in the United States and the European Medicines Agency. This is an agent with a narrow therapeutic index and known toxicity, so there exists a strict regulatory framework for the prescription and dispensing of sodium oxybate, across the above jurisdictions. Post marketing data confirm the safe use of sodium oxybate within this context. (1)

## DEFINITIONS

Narcolepsy is one of a group of hypersomnias of central nervous system origin. These disorders include narcolepsy, with and without cataplexy - both primary and secondary to another medical condition - along with idiopathic hypersomnia, with and without long sleep time and recurrent hypersomnia. The diagnosis of narcolepsy is defined clinically as excessive daytime sleepiness, recurrent naps or lapses into sleep occurring almost daily for at least three months. This definition is supported by either a definite history of cataplexy or a Multiple Sleep Latency Test showing a mean sleep latency of less than or equal to eight minutes and the appearance of rapid eye movement sleep on at least two naps on multiple sleep latency testing (MSLT). (9) Hypocretin-1 levels in the cerebrospinal fluid of less than 110pg/ml are strongly supportive of the diagnosis, (6) although this test is not routinely available in Australia.

An Australian working diagnosis of narcolepsy, associated with Pharmaceutical Benefits Scheme subsidy of the wakefulness-promoting drug modafinil under the Complex Drugs Program has been further refined. This allows a mean sleep latency of less than or equal to 10 minutes on the MSLT, ensuring that a preceding overnight polysomnogram showed sleep of at least six hours and the absence of any medical/psychiatric disorder that could otherwise account for the hypersomnia. Given that sodium oxybate may be considered as a replacement for modafinil in patients with narcolepsy, then current diagnostic criteria for Complex Drugs Program support for modafinil may serve as working standards for potential Schedule 8 permits for the

prescription of sodium oxybate, by authorised medical practitioners. For the purposes of these guidelines, the authorisation would be limited to credentialed sleep medicine practitioners.

## **EFFICACY DATA – ADULT**

At least six randomised control trials exist in the medical literature, regarding the use of sodium oxybate for the treatment of narcolepsy. These studies have assessed both impact on excessive daytime sleepiness and also on frequency of cataplexy. To date, these trials have included over 700 patients with narcolepsy, for durations of between 4 and 12 weeks, with doses of sodium oxybate ranging from 3 g to 9 g per night. (10-14)

A recent meta-analysis of the six randomised control trials has been published, pooling results on subjective and objective measures of excessive daytime sleepiness. (15) At higher doses, sodium oxybate was shown to increase patients' ability to maintain wakefulness in the standardised Maintenance of Wakefulness Test protocol, with a mean difference of 5.18 minutes (95% CI 2.59 – 7.78) across 84 patients in whom the subjective measure of daytime alertness was performed. A standardised measure of situational sleepiness, the Epworth Sleepiness Scale score, was shown in one study to fall significantly in a dose-dependant manner using sodium oxybate between 4.5 g per night and 9 g per night, when compared to placebo. A subsequent study using combination therapy of sodium oxybate and modafinil showed greater reductions in Epworth Sleepiness Scale scores when compared to placebo. (14)

Subjective sleep attacks were assessed across two clinical trials, showing a small but statistically significant reduction in the frequency of sleep attacks per week. Finally, the proportion of patients that rated their symptoms as “much improved” or “very much improved” on a clinical global impression of change scale across three clinical trials was also significantly improved in patients on sodium oxybate, versus placebo. (15)

The frequency of cataplexy across the course of a week was also assessed with two clinical trials, showing statistically significant reductions in the frequency of cataplexy attacks. Mean difference per week was -8.5 attacks (95% CI -15.3, -1.6). (13,16)

## **SAFETY**

Overnight polysomnographic data in patients taking sodium oxybate in clinical trials showed dose-dependent improvements in the depth and continuity of sleep. (17,18) Onset of action is rapid and patients will usually feel sleepy within 5 minutes of administration. It is recommended in the United States product information that patients should be lying in bed at the time of dosing. Given that sodium oxybate has a dose dependent effect of respiratory depression (19), it should be not be used in conjunction with other sedative or muscle relaxant medications. This includes benzodiazepines, opioid analgesics and sedating antidepressants. Furthermore, the use

of alcohol and hypnotic medications are contraindicated in patients taking sodium oxybate. Patients with a history of depression need thorough assessment due to the danger of overdose on conscious state and respiratory drive. In actively depressed patients sodium oxybate should be avoided.

Common side effects included nausea, vomiting, dizziness, confusion and a trend towards higher rates of urinary incontinence/enuresis. The frequency of side effects follows a dose-response relationship. (15) Reported serious adverse events were infrequent in controlled trials. Long-term efficacy/safety data from clinical trials are limited. There is a published study involving a 12-month extension of the use of sodium oxybate, with high levels of reported adverse events in both placebo and sodium oxybate arms, although dizziness was the only adverse event that was seen statistically more in the sodium oxybate group. (12) There are small amounts of conflicting data available on the safety of sodium oxybate in patients with concurrent sleep apnoea (19). In one study, sodium oxybate significantly worsened oxygen desaturation in 3 patients, despite no change in overall AHI within the group. Given that sodium oxybate is an agent that can potentially cause respiratory depression, adequate assessment for sleep apnoea as part of baseline polysomnography, followed by effective treatment where appropriate, is mandatory in this setting. (3)

Concerns have been raised about the abuse potential of sodium oxybate given that illicit GHB has been used as a club drug and “date rape” drug. In the United States and Europe there is a regulatory framework for authorised and controlled prescribing and dispensing of sodium oxybate. A recent review of post-marketing safety data has been conducted on approximately 26,000 patients from 15 countries (1). Only 10 cases (0.039%) met DSM-IV abuse criteria, 4 patients (0.016%) met DSM-IV dependence criteria and 8 cases (0.031%) had withdrawal symptoms after ceasing sodium oxybate. There were only 2 confirmed cases (0.008%) of sodium oxybate facilitated sexual assault, 8 cases (0.031%) of overdose with suicidal intent. There were 21 deaths of patients on sodium oxybate, with only 1 confirmed to be related to the drug. These data show that there is a very low risk of abuse of sodium oxybate, when prescribing and dispensing of the drug is adequately regulated.

## **PAEDIATRIC NARCOLEPSY AND SODIUM OXYBATE**

Narcolepsy cases with childhood onset are often severe and have a significant impact on a child’s education and social development. Although primarily a disorder of adults, half or more of sufferers had symptoms in childhood. Pre-school age onset is unusual but well documented, with diagnosis often delayed due to a lack of awareness on the part of clinicians, but also often due to atypical or incomplete set of symptoms (20-22) . The sleep fragmentation inherent in narcolepsy is often difficult to treat. In some children additional medication to help consolidate sleep is also required. In severe cases children may be on maximum doses of several conventional medications, and still have significant symptoms which interfere with learning and social development. Sodium oxybate remains the only drug that treats all three most debilitating symptoms of narcolepsy: sleepiness, cataplexy and sleep fragmentation.

There have been four retrospective clinical studies documenting the use of sodium oxybate in children. The largest series to date described a total of 51 children from

three centres. The study set out to look at children with onset on narcolepsy before, during and after puberty, with the average age around 10 years (range 7 – 15 years). Oxybate was used in 79% of the group and was the only medication effective in treating all symptoms of narcolepsy. Overall the drug was given to 11 prepubertal children. There was no adverse effect on subsequent pubertal development. There was some weight loss and irritability, with higher rates of side effects in prepubertal children. There were no serious or irreversible side effects (20).

The second largest study was a multicentre European series, which was a retrospective study in 27 children (mean age 10.3 years, range 6 - 16 years) (21). Sodium oxybate was highly effective in controlling all symptoms of narcolepsy. The main side effects included weight loss, headache, nausea, disturbed nocturnal sleep, irritability, parasomnias (sleepwalking, sleep talking, enuresis), and/or daily episodes of sleep drunkenness. These side effects were not considered severe enough by either clinicians and patients (or parents) to stop treatment.

The third series from the Mayo Clinic described the use of oxybate in 15 patients (mean age 11 years, range 3-17 years) (22). Sodium oxybate improved sleepiness in 13/15 patients (Epworth Sleepiness Scale (ESS) fell from a median of 18 to 12 (n = 10, p = 0.01). Cataplexy frequency decreased from a median of 38/week pre-treatment to <1/week post treatment (n = 14, p < 0.001). Cataplexy severity changed from severe to mild in all 15 subjects (p < 0.001). Two of the 15 patients (13%) discontinued sodium oxybate, one for insurance reasons and the other due to constipation and dissociative feelings. Overall, side effects occurred in 6/15 (40%) individuals. Improvement in social/academic spheres was noted in 11/15 (73%) subjects after starting sodium oxybate. The median BMI before and after treatment remained unchanged at 23 (n = 14, p = 0.99). Median values of height and weight before and after treatment also did not change significantly. The mean dose of sodium oxybate was 5 ± 2 g. Dose escalation owing to development of tolerance was not encountered.

## **AUSTRALIAN TREATMENT GUIDELINES FOR THE MANAGEMENT OF NARCOLEPSY WITH SODIUM OXYBATE**

Sodium oxybate is a drug with great promise in the treatment of patients with narcolepsy, with or without cataplexy. Given the above evidence, it should be available to Australian patients under appropriate sleep physician supervision. Currently, excessive daytime sleepiness in patients with narcolepsy is managed with psychostimulant medications - dexamphetamine, methylphenidate - or modafinil. Non-drug strategies include appropriate sleep/wake scheduling and programmed naps. (3) For cataplexy, along with the above recommendations on sleep and nap scheduling, antidepressant agents such as tricyclic antidepressants, selective serotonin reuptake inhibitors and serotonin - noradrenaline reuptake inhibitors have been used effectively in the management of cataplexy in Australian patients. However, the current treatment armamentarium is at times inadequate to control either the sleepiness, the cataplexy or both groups of symptoms. Sleep fragmentation in narcolepsy is also a common feature and is not influenced by the first-line medications. Furthermore, the above agents have a range of potential side effects, which at times make specific therapy intolerable with existing agents.

**INDICATION FOR THE USE OF SODIUM OXYBATE IN NARCOLEPSY:**

Therapy for excessive daytime sleepiness and/or cataplexy where there has been inadequate clinical benefit from maximal doses of alternative wakefulness promoting medications, antidepressants and non-pharmacological strategies; and/or where there have been unacceptable side effects, or contraindication to the use of these alternative agents.

**DOSING AND ADMINISTRATION:**

Recommendations for the administration of sodium oxybate are based on product information and usage in Europe and the USA (23). Recommended adult doses are between 2.25g and 9g per night, usually given in two divided doses due to the short duration of action on sleep continuity. The second dose is taken between 2.5 and 4 hours after the first dose. Doses higher than 9g have not been studied and therefore should not generally be used. The following information refers to adult patients.

- Prepare both doses before bedtime
- Take the first dose at least 2 hours after eating food
- Take sodium oxybate while in bed and lie down immediately after dosing. Remain in bed
- Commence on 4.5g in divided doses. Take 2.25g each dose, the second approximately 2.5 – 4 hours after the first.
- Increase the dose by 1.5g per night (0.75g each dose) at weekly intervals depending on clinical effectiveness and side effects, with a maximal dose of 9g per night.
- Patients with hepatic impairment should commence at half the initial dose – 2.25g in divided doses.

**SUMMARY**

There is sufficient evidence from clinical trials and international clinical practice justifying the use of sodium oxybate in the management of narcolepsy, with and without cataplexy. Sodium oxybate is effective at improving symptoms of excessive daytime sleepiness, cataplexy and sleep fragmentation. These benefits need to be balanced against the known side effect profile of this agent and comorbidities need to be considered in each individual patient, including the presence and control of coexistent sleep-disordered breathing. Sodium oxybate should therefore be used as second-line therapy for patients in whom other treatments are ineffective or not tolerated. Its use should be limited to sleep physicians who actively manage patients with narcolepsy and close clinical follow up is required. The Australasian Sleep Association supports the inclusion of sodium oxybate in Schedule 8 of the Poisons Standard, to allow its use for adult and paediatric patients with narcolepsy, only on the prescription from an authorised medical practitioner. This would be subject to agreed clinical definitions and close monitoring of both prescription and dispensing of

this agent. Its use should therefore be limited to sleep physicians who actively manage patients with narcolepsy.

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