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# Further evidence supporting the use of sodium oxybate for the treatment of cataplexy: a double-blind, placebo-controlled study in 228 patients

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**Abstract**

*Background and purpose*: To measure the effect of the nocturnal administration of sodium oxybate on cataplexy in patients with narcolepsy.
*Patients and methods*: This trial was conducted with 228 adult narcolepsy/cataplexy patients in 42 sleep clinics. Patients using anticataplectic medications were weaned from these medications, then randomized to receive 4.5, 6 or 9 g sodium oxybate nightly or placebo for 8 weeks. Patients receiving 6 and 9 g doses were titrated to their final dose in weekly 1.5 g increments. Placebo patients underwent a randomized mock dose-titration schedule. The effect of sodium oxybate on weekly cataplexy attacks was measured using patient daily diaries.
*Results*: Compared to placebo, nightly doses of 4.5, 6 and 9 g sodium oxybate for 8 weeks resulted in statistically significant median decreases in weekly cataplexy attacks of 57.0, 65.0 and 84.7%, respectively. The decrease in cataplexy at the 4.5 g dose represents a novel finding. The weekly increase in sodium oxybate dose was associated with fewer adverse events than previously reported in double-blind sodium oxybate trials using fixed doses. Some adverse events reported demonstrated a clear dose–response relationship.
*Conclusions*: In the largest study of its kind, sodium oxybate was highly effective for the treatment of cataplexy. The improvements in cataplexy are dependant on the dosage of sodium oxybate as well on the duration of treatment. Weekly dose titration appears to be well-tolerated.


*Keywords:* Cataplexy; Narcolepsy; Sodium oxybate; Gamma-hydroxybutyrate

## 1. Introduction

Sodium oxybate is currently the only medication approved in the United States for the treatment of cataplexy associated with narcolepsy (Xyrem®, Orphan Medical, Inc., Minnetonka, MN). Encouraged by promising results obtained by independent investigators [1–4], the approval of sodium oxybate for this indication was based on short-term and long-term, double-blind, placebo-controlled efficacy trials [5,6] as well as a 12-month open-label safety trial [7].

In the short-term efficacy trial, patients were randomly assigned to receive sodium oxybate at fixed doses of 3, 6 or 9 g or placebo in double-blind fashion. The nightly dose of sodium oxybate was administered in two equally divided doses. At the conclusion of the trial, sodium oxybate had significantly reduced the frequency of cataplexy attacks at the 6 and 9 g doses [5]. Subsequently, most of these patients agreed to enroll in the 12-month open-label extension trial.

In the 12-month study, all patients were started at 6 g sodium oxybate nightly in two divided doses; however, investigators titrated the dose up or down, as needed, until the optimal dose was reached. In addition, 4.5 and 7.5 g doses were introduced, enabling investigators to attain the best possible dose for each patient. By carefully titrating the dose of sodium oxybate, patients who continued on nightly sodium oxybate achieved further improvements in cataplexy symptoms which became significant after 4 weeks compared to the end of the previous trial, eventually resulting in a median decrease in cataplexy of 80–90% across all doses [7].

These results suggested that a placebo-controlled study of longer duration might provide better insight into the anticataplectic effects of sodium oxybate. The primary measure of this study was excessive daytime sleepiness, to be described in a separate report; however, the hypothesis, proposing that administration of sodium oxybate to patients with narcolepsy nightly for 8 weeks will demonstrate greater efficacy for the treatment of cataplexy compared to

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the previous 4-week study, was able to be tested. The following trial represents the largest study ever conducted with sodium oxybate for the treatment of cataplexy.

## 2. Methods

### 2.1. Subjects

Patients were included in the trial if they were 16 years of age or older and met the following criteria: a positive history of narcolepsy based on an overnight polysomnogram (PSG) and multiple sleep latency test (MSLT) performed within the previous 5 years; current symptoms of narcolepsy, including excessive daytime sleepiness, cataplexy and recurrent sleep attacks almost daily for at least 3 months; evidence of adequate support for the duration of the trial, including transportation to and from the trial site; agreement to forgo operating a car or heavy machinery if indicated by the investigator; expression of willingness to complete the entire trial as described in the protocol by signing an informed consent form. Women of child-bearing potential were required to use a medically accepted method of birth control unless surgically sterile or 2 years post-menopausal.

The following criteria were used to exclude patients from the trial: use of sodium oxybate or any investigational therapy during the 30 days prior to trial entry; sleep apnea with an apnea/hypopnea index of $\geq$15/h or an apnea index $\geq$10 or any other cause of daytime sleepiness, e.g. restless legs syndrome; use of hypnotics, anxiolytics, antihistamines (except non-sedating antihistamines), anticonvulsants or clonidine at the start of the baseline period; the presence of any unstable disease which placed the patient at risk during the trial or compromised the study objectives; a current or recent history of a substance use disorder; clinical chemistry abnormalities including a serum creatinine greater than 2.0 mg/dl, liver function tests more than twice the upper limit of normal, or serum bilirubin more than 1.5 times the upper limit of normal, or abnormal ECG demonstrating clinically significant arrhythmias; a history of myocardial infarction within the last 6 months; an occupation that requires variable shift work or routine night shifts; a history of seizure disorder, head trauma or past invasive intracranial surgery.

Trial subjects received a modest stipend to offset travel and other personal expenses associated with participation in the study.

### 2.2. Data collection tool

Patient diaries were used to collect daily information about narcolepsy symptoms, trial medication use, concomitant medication use, and adverse experiences. Instructions on the use of daily diaries, including definitions of information being collected, were reviewed in detail with all patients during the initial visit. For example, to be considered an attack of cataplexy, the event had to be of sudden onset, precipitated by emotion, localizable to a specific muscle group(s) or part of the body, and the patient must have remained lucid and aware, i.e. not experiencing a sleep attack or micro-sleep. Patient diaries were also used to collect information on the occurrence of sleep paralysis and hypnagogic hallucinations as well as sodium oxybate-related adverse events. Patient diaries were used during the withdrawal and washout periods for patient training and habituation.

### 2.3. Dosing and administration of study drug

Trial medication was provided as a liquid solution containing sodium oxybate at a concentration of 500 mg/ml, while placebo consisted of a solution of sodium citrate which was equimolar with respect to sodium. Previous taste tests indicated the placebo is indistinguishable from sodium oxybate solution (Orphan Medical, Inc., unpublished data on file). Study drug or placebo was administered in two equally divided doses each night. Patients were instructed to prepare each dose prior to retiring to bed. The first dose was consumed immediately before going to sleep while the patient was in bed, and the second dose was taken 2.5–4 h later. Patients were encouraged to use an alarm clock to ensure they awoke for their second dose.

Patients were cautioned about the use of alcoholic beverages at any time during the trial. Similarly, patients were cautioned about the use of potentially sedating medications, such as opiate analgesics or skeletal muscle relaxants. All study subjects were encouraged to discuss with the investigator the use of over-the-counter and prescription medicines for treatment of colds, flu, allergies or headaches.

### 2.4. Study design

The overall study design is illustrated in Fig. 1. Following Visit 1, patients recorded narcolepsy symptoms and adverse events associated with current narcolepsy treatments in the daily diaries during a 14-day lead-in period. Subsequently (after Visit 2), patients were gradually tapered from tricyclic antidepressants, selective serotonin reuptake inhibitors or any other medication used for the treatment of cataplexy during a 21-day withdrawal period. The withdrawal period was followed by a washout period (following Visit 3) lasting 5 days or 5 times the half-life of the discontinued drug, whichever was longer, but not exceeding 18 days. Due to its very long elimination half-life, withdrawal was initiated at Visit 1 if the patient was using fluoxetine. If no prior anticataplectics had been used, patients still entered a 5-day period for the purpose of daily diary training.

At the end of the washout period, patients who continued to meet the inclusion criteria were randomly assigned to their eventual sodium oxybate dose group in double-blind fashion, prior to entry into the 14-day baseline period (Visit 4). During the baseline phase of the study, all patients received placebo in single-blind fashion and a baseline assessment of narcolepsy symptoms was made. This 14-day