Sodium Oxybate in Treatment-Resistant REM Sleep Behavior Disorder (RBD): A Randomized Placebo-Controlled Trial

Study Protocol

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Summary

Rapid eye movement sleep behavior disorder (RBD) is a condition resulting in violent dream-enactment during sleep which affects millions of individuals in the United States, however therapies for RBD are limited and cause significant side effects. As a result, despite using a combination of drugs, a large number of patients with RBD continue to act out violent dreams causing severe self-injuries or injuries to their bed partners. Prior studies and our own experience at Stanford have shown that sodium oxybate (SXB) can be effective in these cases of refractory RBD. This study would therefore evaluate the efficacy and tolerance of SXB in this patient population.

We propose to conduct an 8-week trial comparing SXB versus placebo randomly assigned to patients with refractory RBD, i.e. individuals who have insufficiently responded or tolerated melatonin and clonazepam. To strengthen the study design, we will use a double-blind design, and not only measure treatment efficacy based on patients, partners and clinicians report–as done in most studies; we will record RBD objective outcomes with actigraphy, a recently validated objective tool for tracking RBD activity "in vivo". In addition, our study will include the gold standard PSG-based REM activity based on video and EMG activity before and after intervention.
In summary, this study would not only address an important question from a clinical and public health perspective, it would also be the first double-blind randomized controlled study measuring a treatment response based both on clinical and physiological outcomes. We believe that this particular design should pave the way for future trials in RBD.

Scientific Basis/Rationale

Rapid eye movement (REM) sleep behavior disorder (RBD) is a neurological condition resulting in loss of muscle atonia during REM sleep (also called REM sleep without atonia, RWA) leading to violent and injurious dream-enactment behaviors[1]. The prevalence of RBD is estimated to be 0.5-1% in the general population[2,3], which represents over 2 million individuals in the United States. RBD is strongly associated with synucleinopathies, namely Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). In the remaining individuals, RBD is called "isolated", but is in most cases a prodromal symptom of neurodegenerative disease. While first episodes of dream-enactment can occur decades before neurodegenerative disease, the median time between a formal diagnosis of RBD and phenoconversion is less than 10 years[4]. Other than safety measures, the current evidence suggests melatonin (MLT) or clonazepam (CLZ) as treatment "options" due to incomplete efficacy and possible side effects[5]. The efficacy of CLZ is estimated to be about 80% in the largest case series, but this drug is often associated with limiting side effects. The data on MLT

in RBD is scarce, but suggests that although better tolerated, it may not be superior to CLZ in terms of efficacy[5,6]. As a result, a large fraction of patients with RBD continue to experience frequent breakthrough episodes despite often using a combination of CLZ and MLT. Other effective treatment options are limited and have even lower level of evidence. Off label use SXB has shown good efficacy in 3 case reports on 4 cases of refractory RBD, including one at the Stanford Sleep Medicine Center[7–9]. The first report describes a 66 year-old patient with over 2 years of frequent violent RBD episodes resulting in multiple injuries and falls in whom SXB initiated at 3g uptitrated to 4.5g nightly resulted in cessation of his episodes after 5 days at the higher dose. This effect was sustained during the 12 month follow-up period[7]. A 68 year-old man with PD (Hoehn and Yahr score 3) with 20-year history of RBD was referred to the Stanford Sleep Center after exacerbation of RBD following deep brain stimulation leading to violent dream-enactment several times weekly. Patient had failed multiple regimens including high dose MLT and could not tolerate CLZ. SXB was titrated up to 5g nightly, resulting in cessation of RBD episodes for two months. Three breakthrough episodes prompted further increase to 6g nightly dose after which RBD was controlled again[8]. Two additional non-parkinsonian patients aged 68 and 51 with refractory RBD were placed on SXB at doses of 4.5g (in a single dose) and 3g (in two doses) nightly. This lead to marked reductions in severity and frequency of RBD symptoms with elimination of most violent episodes and sustained efficacy throughout the 5 year follow-up period[9]. The mechanism by which SXB reduces RBD is unknown, but could involve reduction in sleep fragmentation, or direction modulation of sleep/wake motor control as seen in narcolepsy with cataplexy, where at higher dose it has shown to have a restorative effect on muscle atonia during REM sleep[10]. In patients with narcolepsy, with more than 16 years of postapproval use, SXB reduces symptoms of sleepiness and cataplexy with favorable long-term efficacy and safety profile[11]. SXB has been shown to be beneficial in a few other conditions such as fibromyalgia[12], binge-eating disorder[13] and symptoms of sleepiness associated with PD[14,15]. An open label study using SXB (mean nightly dose 7.8g) in 27 subjects with PD suggested subjective reduction in sleepiness, fatigue and overall improved sleep quality as compared to prior to treatment[14], while a double blind placebo-controlled crossover trial in 12 patients with PD resulted in improved sleep quality and reduced daytime sleepiness as measured by mean sleep latency test with mean SXB dose of 4.8g[15]. A drop-out rate of 10% due to side effects was reported in both studies.

Taken together, this suggests that SXB may be a viable treatment option in patients with isolated RBD or RBD associated with PD, who have failed MLT and CLZ due to lack of efficacy or intolerance.

Hypothesis

We hypothesize that nightly dose of SXB will result in reduction of RBD severity and frequency per patients report and objective polysomnographic and actigraphic (wrist-worn device) measures, over an 8-week double blind intervention comparing SXB and placebo (PBO). Additionally, we hypothesize that SXB improves sleep quality, and

reduces daytime sleepiness in subjects with RBD associated with a neurodegenerative condition.

Primary Objective

1. Reduction in RBD episodes frequency and severity (RBD log)

Secondary Objectives

1. Improvement in clinical global impression scores per patient and clinician (CGI-efficacy scale, CGI-E, and CGI-impression scale, CGI-I, respectively)
2. Reduction of RWAi by PSG
3. Reduction in movements severity and frequency during REM sleep by quantitative video-PSG analysis[16]
4. Changes in overall subjective sleepiness by Epworth sleepiness scale (ESS) and one hour after rise time by Karolinska scale
5. Tolerance and side effects to SXB and PBO

Exploratory Objectives

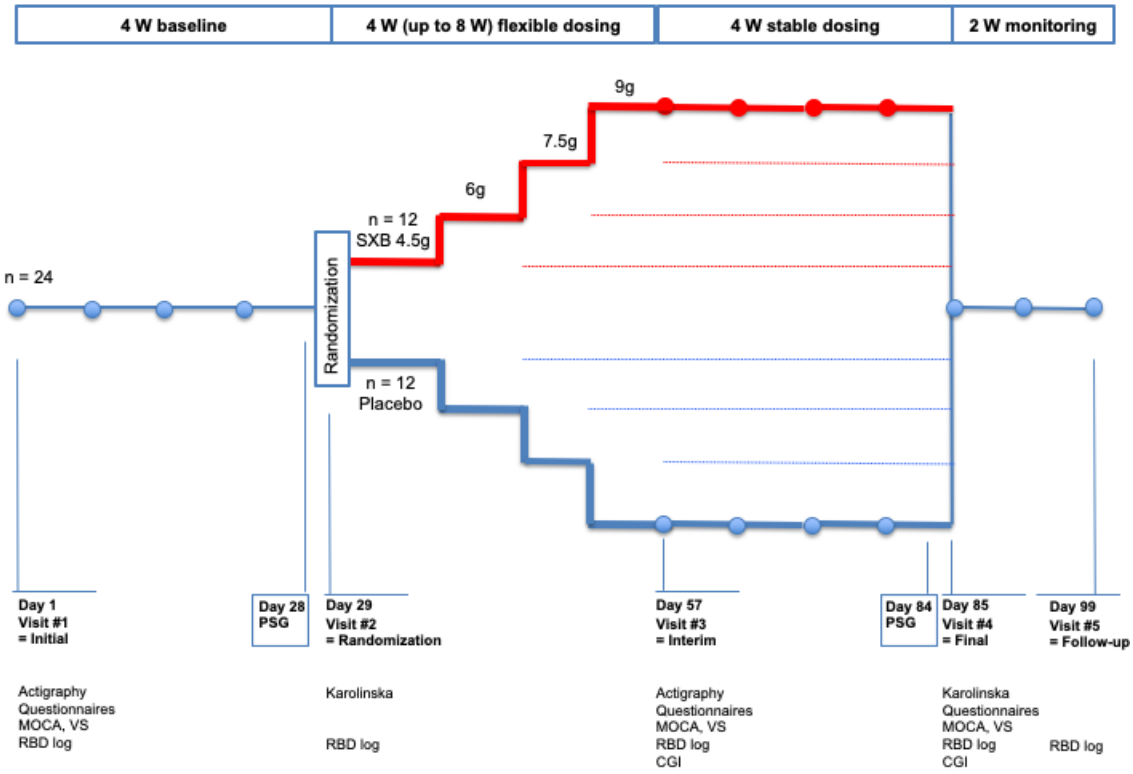
1. Reduction in "activity score" and "activity index" as measured by actigraphy[17]
2. Reduction in periodic limb movement (PLM) arousal index
3. Improved sleep quality by Pittsburgh Sleep Quality Index (PSQI)
4. Effects on mood measured by PHQ-9
5. Effects on anxiety measured by GAD-7
6. Effect on orthostatic heart rate and blood pressure (response to orthostatic maneuver)

Trial Design

The total duration of this randomized, double-blind, placebo-controlled trial will be 2 years. For each participant the total duration of the study will be 14 weeks, including 8 weeks of intervention with SXB or PBO, preceded by a 4-week period of collection of baseline data, and followed by a 2-week period of data collection post-intervention. Subjects taking MLT or any other medication capable of affecting RBD other than clonazepam (CLZ) will maintain their regimen at fixed dose throughout the 14-week duration of the study. Those taking CLZ will proceed to reduction and discontinuation of CLZ, followed by a 2-week washout period prior to receiving study drug. If unable to discontinue CLZ prior to study drug, they will reduce CLZ to lowest acceptable dose by the end of the 4-week baseline period followed by cross-taper with SXB during the first 2 weeks of flexible dosing.
In each arm, dosage of SXB and PBO will be titrated up weekly (this weekly titration will occur via phone calls by the PI on days 2-6 after each new dose change) by up to 1.5g nightly dose increments from an initial 4.5g total nightly dose (which could be given

in two unequal doses if needed, or one single dose no greater than 4.5g) to an optimal individual dose based on clinical response on RBD symptoms and tolerability, to a maximum nightly dose of 9g ("flexible dose" period lasting up to 8 weeks). The optimal dose for each participant will then be continued for at least 4 weeks ("stable dose").

Flowchart



MOCA: Montreal Cognitive Assessment

PSG: Polysomnography
CGI: Clinical Global Impression questionnaires

- **Day 1 (Visit #1 = Initial visit with research coordinator):**
  - Verification of inclusion and exclusion criteria
  - Enrollment (if not performed prior)
  - Physical Exam (MoCA,
  - PSQI, PHQ-9, GAD-7, SCOPA-AUT, Epworth sleepiness scale
  - provide RBD logs and sleep diary for the 14 following weeks, 2 blank Karolinska scales, and two actigraphy devices (Philips Actiwatch2) to be worn on dominant wrist and ankle for one month

- instructions on when to complete Karolinska scale #1 (Day 21-27, one hour after waking up the day prior to sleep study) from home
- Instructions on clonazepam taper, when applies
- pregnancy testing for female subjects of childbearing age, when applicable
- collection of adverse events (AEs)
- MD (PI, coPI) will be available as needed via telephone or remote video conference system

- **Day 1-28 (phone calls, weekly, when applicable):** guidance on downtitration of CLZ

- **Day 28 ± 7 days**: 1st video-PSG wearing home actigraphy device (Philips Actiwatch2) and additional wrist and ankle high-frequency actigraphy device (Xiaomi Amazfit Arc)

- **Day 29 (One day after Day 28 ± 7 days, Visit #2 = Randomization visit with research coordinator):**
  - Collection of 1-month RBD log and sleep diary
  - Collection of Karolinska scale #1
  - Collection of all actigraphy devices
  - Epworth sleepiness scale
  - Randomization
  - Subjects receive SXB or PBO and instructions on titration schedule
  - pregnancy testing for female subjects of childbearing age, when applicable
  - collection of adverse events (AEs)
  - MD (PI, coPI) will be available as needed via telephone or remote video conference system

Day 30-84 ± 7 days (phone calls): Every week after each new dose the subject will be called (including when the dose will remain stable), these phone calls will be made between day 2-6 to discuss response, record adverse events, and determine the next weeks titration dose.

- **Day 57-85 ± 7 days (Visit #3 = Interim visit with research coordinator):**
  - Collection of 1-month RBD log and sleep diary
  - Epworth sleepiness scale
  - PSQI, PHQ-9, GAD-7
  - Completion of CGI-E by participants
  - Completion of CGI-I by clinician
  - Physical Exam (including MoCA, orthostatic vital signs)
  - instructions on when to complete Karolinska scale #2 (Day 78-84, one hour after waking up the day prior to sleep study) from home
  - Participants provided with two actigraphy devices (Philips Actiwatch2) to be worn on dominant wrist and ankle for one month
  - pregnancy testing for female subjects of childbearing age, when applicable

- Collection of AEs, side effects
- MD (PI, coPI) will be available as needed via telephone or remote video conference system

- **Day 84-112 ± 7 days:** 2nd video-PSG wearing home actigraphy device (Philips Actiwatch2) and additional wrist and ankle high-frequency actigraphy device (Xiaomi Amazfit Arc)

- **Day 85-113 (One day after Day 84-112 ± 7 days, Visit #4 = Final Visit with research coordinator):**
  - Collection of high-frequency actigraphy device (Xiaomi Amazfit Arc)
  - Collection of 1-month RBD log and sleep diary
  - Collection of AEs, side effects
  - Collection of Karolinska scale #2
  - Epworth sleepiness scale
  - PSQI, PHQ-9, GAD-7, SCOPA-AUT
  - Completion of CGI-E by participants
  - Completion of CGI-I by clinician
  - Physical Exam (including MoCA,
  - Verification of any protocol deviation (e.g., change in drug regimen that could affect RBD outcome)
  - Discontinuation of treatment
  - MD (PI, coPI) will be available as needed via telephone or remote video conference system

- **Day 99-127 ± 7 days (Visit #5 = Follow-up Visit with research coordinator):**
  - Collection of AEs
  - Collection of actigraphy devices
  - Collection of 2-week RBD log and sleep diary
  - Compensation
  - End of study
  - MD (PI, coPI) will be available as needed via telephone or remote video conference system

Treatment Regimen

Being diagnosed with "refractory RBD", all participants will have received and failed prior treatments with CLZ and MLT prior to being eligible for the study. Treatment failure is defined as insufficient efficacy, or intolerance to treatment limiting the possibility of uptitration or leading to discontinuation, resulting in persistent of RBD episodes averaging 2 per week or 8 per month or greater.

At study entry, we expect most participants to currently being treated with CLZ and/or MLT. Subjects taking MLT or any other medication capable of affecting RBD other than CLZ will maintain their regimen at fixed dose throughout the 14-week duration of the study. In subjects treated with CLZ, CLZ will be titrated down and discontinued 2 weeks prior to start of study drug, or when unable to be discontinued, cross-tapered during the first 2 weeks of receiving study drug until reaching the lowest possible CLZ dose, which will then be continued until the end of the stable dosing period

Participants will be randomized in a double-blind manner to either SXB or PBO. The duration of the intervention in both conditions will be no longer than 12 weeks, including up to 8 weeks of flexible dosing and 4 weeks of stable dosing. Treatment will be initiated with 4.5g dose of SXB or PBO, given nightly in two doses 2.5-4h apart according to the standard protocol used in narcolepsy. PBO will be similar in appearance, smell and flavor to the subjects, so that the investigators and participants will be unable to distinguish it from SXB. The dose will be increased or decreased by 0.5 - 1.5g weekly increments until reaching the optimal dose based on clinical response and tolerance, not exceeding 9g nightly. Evidence has shown that patients with RBD treated with sodium oxybate respond to nightly doses ranging from 3-6 g. Among these subjects, some have benefited from a 5 gram nightly dose. This flexibility in dosage is determined on an individual basis, in which the final dose must be both effective and tolerated. Dosage flexibility is essential as this older population with prodromal or overt signs of neurodegeneration may not require or tolerate the higher dosages used in patients with narcolepsy. Although the "default" regimen will be two equally divided doses 2.5-4hours apart, if required, the drug will be given in two unequal doses, or in one single dose, with no single dose allowed to be greater than 4.5g. Once optimal dose reached, fixed dose will be continued for at least 4 weeks and discontinued over one night. During the two weeks following discontinuation, data will continue to be collected. Patients will be allowed to resume usual treatment, including CLZ.

In this study, the choice of flexible dosing for patients receiving SXB is based on a few factors. From the 4 case reports summarized above, effective doses of SXB in patients with refractory RBD ranged from 3g to 6g nightly, one patient requiring uptitration of his initial 5g dose to 6g. No adverse events or side effects were reported by the authors. In patients with narcolepsy, the efficacy of SXB is dose-dependent, showing superior efficacy with 9g nightly dose compared to 6g. Taken together, this data suggests that higher SXB doses will be more likely to control RBD symptoms, however with a higher risk of side effects. In the two studies evaluating SXB efficacy and tolerance in patients with PD using flexible dosing, final mean doses were 7.8g and 4.8g[14,15].
Our study will include a mixed group of participants, some with a neurological diagnosis of PD and some otherwise healthy individuals. We identify risk of dizziness and falls as the most concerning risk in patients with a diagnosis of synucleinopathy, as this could be aggravated by SXB. We will therefore carefully exclude from this study any participant who already suffers from balance impairment resulting in falls or requiring an ambulating device, as well as any patient with symptomatic orthostatic hypotension. Taken all these considerations into account, and given the expected interindividual variability regarding

optimal dose of SXB, we chose flexible dosing for highest clinical benefit while minimizing the risk of side effects.

The total amount of SXB for the 12 participants randomized to active drug is: 5,292g.
The total amount of PBO for the 12 participants randomized to placebo drug is: 5,292g.

Option for “Rescue” Open Label Extension Period

All participants, should they decide to drop out of the study, may become eligible for a “Rescue” open label extension period, during which they will receive open label active drug sodium oxybate in an unblinded fashion. This will provide patients the opportunity of experiencing benefit from the study drug. Such participants would then receive ascending doses of sodium oxybate, according to the protocol, and will also be asked to present for visits and second polysomnography starting at visit 2, otherwise required by the protocol until the end of the study.

Inclusion Criteria

- Adult patients aged 40 to 85 years
- Women may be included only if they have a negative β-HCG test at screen; are sterile (documented hysterectomy, bilateral oophorectomy, or bilateral salpingectomy, or congenitally sterile) or postmenopausal (no menses for 12 months without alternative medical cause).
- Women with childbearing potential whose male partners are potentially fertile must use one of the following highly effective birth control methods for the duration of the study (ie, starting at screening) and for 30 days after last dose of study drug
    - estrogen-progestin oral contraceptive pills, patches, or vaginal ring
    - progestogen pills, implant or injection
    - intrauterine device (IUD)
    - intrauterine hormone-releasing system (IUS)
    - bilateral tubal occlusion
    - vasectomised partner (the sole sexual partner who has received medical assessment of the surgical success)or
    - abstain from heterosexual intercourse
- In individuals without a diagnosis of Parkinson's disease (PD), PSG-confirmed “definite RBD” per the International Classification of Sleep Disorders, 3rd edition (ICSD-3)
- In individuals with a diagnosis of PD, either PSG-confirmed diagnosis of RBD ("definite RBD") or history of dream-enactment ("probable RBD")
- RBD episodes ≥ 2/week or ≥ 8/month (defined as vocalization and/or limb or body movements attributed to dream-enactment)
- Reliable reporting by bed witness in the absence of patient awareness

Exclusion Criteria

- History of falls during ambulation in the last 6 months despite adequate neurologic treatment
- Requirement of an ambulatory device at home
- Inadequately treated symptomatic orthostatic hypotension (syncopal episode in the last 6 months)
- BMI > 35
- Untreated or uncontrolled OSA (4% desaturation AHI>15)
- Liver impairment
- Renal impairment
- Congestive heart failure
- Uncontrolled hypertension
- Treatment with valproic acid
- Current history of NREM parasomnias or parasomnia overlap syndrome (at least 2 episodes in the last 6 months)
- Diagnosis of narcolepsy
- Cognitive impairment resulting in inability to comply with treatment instructions
- Diagnosis of any dementia including dementia with Lewy bodies
- Diagnosis of multiple system atrophy
- RBD attributed to a CNS lesion
- PD Hoehn and Yahr stage 4 and 5
- Any change of PD regimen during the study period
- Current alcoholism or prior history of drug abuse
- Pregnancy
- Epilepsy currently treated with sedating antiepileptic drugs;
- Concomitant use of other CNS depressants, including but not limited to opioid analgesics, benzodiazepines other than clonazepam, muscle relaxants, and/or illicit CNS depressants
- Current depression (at least PHQ-9 score = 10), history of psychosis
- Any change of antidepressant regimen during the study period
- Chronic severe RLS (iRLS>20) (at least 3 days per week)
- Succinic semi-aldehyde dehydrogenase deficiency (SSADH)

Primary Endpoint

- Number of RBD episodes in one month (RBD log), last month of treatment compared to 1-month baseline

Secondary Endpoints

- Severity of RBD episodes in one month (RBD log), last month of treatment compared to 1-month baseline. Severity is scored from 1 to 3 (1: least severe, 3 most severe):
    1. non injurious behaviors: facial expressions, non-aggressive vocalizations (mumbling, gentle talking, casual conversation, singing, laughing...), twitches, gentle shaking, non-aggressive movements of fingers, arms or legs...;

2. potentially injurious: punching, kicking, arm flailing or thrashing around, at least one limb or head out of bed, sitting up in bed, crawling, attempting to stand up or leave bed, near falls, cursing, screaming, shouting, yelling, or any behavior requiring bed partner to wake up participant;
3. injurious: any contact with bed partner (hitting or grabbing), wall or furniture, any fall or leaving bed (doving out, walking, jumping).

- CGI efficacy scale (CGE-E): 4-point therapeutic effect scale and 4-point side effect scale, jointly filled by patient and partner on last day of treatment
- CGI improvement scale (CGI-I): 7-point improvement scale filled by clinician on last day of treatment
- RWAi according SINBAR criteria comparing PSG pre-intervention to PSG post-intervention
- video-PSG analysis of REM related vocalizations and movements ("simple" versus "complex") as per Sixel-Döring and colleagues[16]
- Sleep outcomes: EDS, Karolinska 1 h after awakening

Exploratory Endpoints

- "Activity index" as recorded by actigraphy[17] (percentage of 30-second epochs with an activity score above zero) last month of treatment compared to 1-month baseline
- Sleep outcomes: PSQI
- Cognitive outcome: MoCA
- Mood and Anxiety: PHQ-9 and GAD-7
- Orthostatic vital signs

Sample Size Justification/Statistical Analysis

Sample size calculation was made for the outcome of number of RBD episodes per month. Based on the data published by Brunetti et al.[18], the number of RBD episodes decreased from 11.2 +-5.2 at baseline to 10.3 +-3.7 per month in the placebo arm. To detect an effect size of 50% reduction in the number of RBD episodes per month ([placebo-active]/placebo) with a power of 80% and alpha of 5%, the number of participants would need to be 10 per arm. Based on prior studies using SXB in subjects with PD, a conservative drop out rate of 15-20% could be anticipated[14,15], which would require to enroll at least 24 participants, i.e. 12 participants per arm.

Reporting to Jazz Pharmaceuticals

The Investigator/Sponsor will comply with all relevant regulatory safety reporting responsibilities. Additionally, the Investigator/Sponsor will report to Jazz Pharmaceuticals all Serious Adverse Events (SAEs) (initial and follow up) experienced by any patient who has received a Jazz Pharmaceuticals Inc (JP) medicinal product,

regardless of the suspected causal relationship between the event and the Jazz Pharmaceuticals medicinal product. All SAEs must be submitted in English within one (1) business day of initial receipt via email or fax to [redacted].

Any pregnancy occurring in a female subject or in a male subjects female partner will be reported to Jazz Pharmaceuticals, Inc within one (1) business day of initial receipt via email or fax to [redacted].

In addition, all other AEs will be reported to the JP Pharmacovigilance Department in summary or line-item form upon JP's request and/or at the conclusion of the study.

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