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Is Sodium Oxybate a Safe and Effective Treatment for Patients with Fibromyalgia

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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Abstract

Objective: The objective of this systematic review is to determine whether or not Sodium Oxybate is a safe and effective treatment of pain and sleep-related symptoms of fibromyalgia.

Study design: Review of three English language primary randomized controlled trials published between 2003-2010.

Data Sources: Randomized, controlled clinical trials comparing Sodium Oxybate to a placebo group were found using PubMed and Cochrane database.

Outcome Measured: Disease improvement and adverse effects (nausea). Disease improvement was measure using Disease the Tender point index (TPI) (rated 0-4), subjective daily assessments of pain /fatigue, PVAS score (0= no pain, 100= worst possible pain), FVAS score (0= no fatigue, 100= worst possible fatigue), Fibromyalgia Impact Questionnaire (FIQ) (rated 1-100), The Jenkins Scale for sleep (JSS) (rated 1-20), a quality-of-life questionnaire (SF-36) (rated 1-100), Patient Global Impression of Change (PGI-C), Tender Point Count (TPC) (rated: 0-18), Clinical Global Impression of Change (CGI-S), Epworth Sleepiness Scale (ESS) (rated: 1-24), and Functional Outcome of Sleep Questionnaire (FOSQ) (rated: 5-20). Adverse effects (nausea) were measured using incidence of cases reported.

Results: Three randomized controlled trials were included in this review. The higher dose of Soidum Oxybate (6.0g/day) was shown to be more effective than the lower dose (4.5g/day) at relieving fibromyalgia symptoms. Although the higher dose of Sodium Oxybate was more effective, nausea was more commonly experiences in this group than the group given the lower daily dose.

Conclusion: The results of the randomized controlled trials reviewed demonstrated that Sodium Oxybate 6.0 g/day was more effective than the 4.5g/day dosage at improving fibromyalgia symptoms. However due the adverse effect of nausea 4.5g/day is a safe starting dose for patients. The relatively low incidence of nausea encourages its use in fibromyalgia. Further studies should be done regarding the titration from doses 4.5g/day to 6.0g/day to see if the adverse effect of nausea has a lower incidence.

Key Words: fibromyalgia, Sodium Oxybate, sleep, pain, fatigue, quality of sleep

Introduction

Fibromyalgia syndrome (FMS) is a long-term chronic pain syndrome affecting an estimated 5% of Americans.[1] The syndrome is characterized by widespread pain affecting joints, muscles, tendons, bones, and various soft tissues.[1] Other features common to FMS include insomnia, fatigue, stiffness, headaches, cognitive changes, affective symptoms, and IBS symptoms.[2] FMS is a common disorder, affecting about 3-6 million people in the US population.[2] The syndrome is seen most commonly in adult females between the ages of 20-50.[3] Patients seek care in efforts to determine the source of such widespread deep chronic pain and to palliate the pain. Practitioners then order various expensive diagnostic studies such as lab work and multiple imaging studies, all of which will be negative in FMS, working towards a diagnosis of exclusion. As a result, total healthcare costs over a 12 month period were about three times higher in FMS patients than the mean (SD) at about $9573 vs. $3291.[4] It was determined that patients with FMS are seen in an out-patient setting about 10 times a year and about 25 times in the year preceding their diagnosis with FMS.[4]

FMS is a diagnosis of exclusion; however, the American College of Rheumatology has designated 18 sites on the body as possible tender points to aid in the diagnosis of fibromyalgia. There is no cure for this painful syndrome. The etiology is unclear but researchers have noted that symptoms tend to begin after an infection, physical trauma, or due to psychological stress.[2] More commonly, FMS symptoms are seen as a gradual onset of widespread pain that continues to worsen with no single event attributable. The pathogenesis is also not well understood. However, it is believes that there is a genetic predisposition for FMS causing an imbalance and disregulation of various neurotransmitter functioning.[3] FMS is thought to be a central sensitization problem, where the patient with FMS has an amplified perception of pain due

improper processing of pain signals in the brain. Because there is no clear etiology there is controversy regarding the best way to treat the symptoms of FMS.[3]

Various medication have been tried to treat this central pain disorder. Medications include, tricyclic antidepressants, cyclobenzaprine, tizanidine, SSRIs, SNRIs, gabapentin, NSAIDs, oral corticosteroids, and tramadol. Currently, the only pharmacologic therapy specifically indicated for FMS is Lyrica (pregabalin).[2] Non-pharmacologic therapy includes cardiovascular exercise, cognitive behavioral therapy, and patient education.[2] Management goals are aimed towards pain relief, increase in the quality of sleep, and increase in physical functioning.

The treatment options that have been listed above are all efficacious means of treating FMS. However, as with all treatment options there are different effects on various populations of patients. Sodium Oxybate is a metabolite of the inhibitory neurotransmitter, GABA.[1] It is currently approved to treat narcoleptics with symptoms of cataplexy and excessive daytime sleepiness.[3] This treatment method was shown to be effective in patients with such symptoms because it works to consolidate fragmented sleep and decrease the number of night time awakenings.[3] Researchers noted in the studies regarding the efficacy of Sodium Oxybate in those with narcolepsy, that patients with the comorbiditiy of FMS had improvement of their pain and sleep related complaints as well.[3] Thus, it was proposed that Sodium Oxybate may be effective in patients with FMS.

Objective

The objective of this selective EBM review is to determine whether or not Sodium Oxybate is a safe and effective treatment for patients with fibromyalgia. The use of Sodium

Oxybate has been shown to be effective in the treatment of the symptoms of fatigue, quality of sleep, and pain in patients with FMS.

Methods

All three trials used met the following criteria. Participants had to be over the age of 18 with a diagnosis of FMS, determined by the American College of Rheumatology criteria. The intervention used was Sodium Oxybate of either a dose of 4.5 g/day or 6.0 g/day. The treatment groups receiving Sodium Oxybate were compared to those receiving a control treatment. Outcomes measured were the reduction in symptoms associated with FMS, including fatigue, pain, quality of sleep, and adverse effects (nausea); which are patient oriented evidence that matters (POEM). The types of studies used were randomized controlled trials, all of which are compared to a placebo comparison group.

In both the Moldofsky et al and Russel et al primary literature, studies were designed in similar fashion. Eligibility was determined and participants completed a 39 day "washout period" from prescription medications that need to be discontinued. Participants then began a two week period where their PVAS scores submitted three times daily to determine FMS participants baseline. Both studies randomized participants into three group of either placebo, 4.5g/day, or 6.0g/day doses administered at bedtime for a period of 8 weeks.[1,2] During the study there were three treatment visits to assess efficacy. In the Scharf et al study, patients we randomized to one of two groups and received either 6.0 g/day sodium oxybate or placebo for one month, with an intervening two week washout period.[3] Participants were then switched to the opposite group and tested for another month. The efficacy was assessed at the end of both month periods.

Key words used in literature search were fibromyalgia, Sodium Oxybate, sleep, pain, fatigue, and quality of sleep. All articles were published in the English language in peer reviewed journals after the year of 2003. Literature searches occurred via PubMed and Medline using Cochrane databases. Articles were selected based on the relevance of the outcomes in the patients with FMS (POEMs). Studies that were included were those that were double blind, randomized, and placebo controlled, and based on the outcome that was important to the patient. Those excluded were studies that included patients under the age of 18 years. Statistics reported in these studies were relative benefit increase (RBI), absolute benefit increase (ABI), numbers needed to treat (NNT), numbers needed to harm (NNH), p-values, and change from baseline.

Outcomes measured were those of patient oriented evidence that matters. Disease improvement was measured using the Tender Point Index (TPI) (rated 0-4), subjective daily assessments of pain /fatigue, PVAS score (0= no pain, 100= worst possible pain), FVAS score (0= no fatigue, 100= worst possible fatigue), Fibromyalgia Impact Questionnaire (FIQ) (rated 1-100), The Jenkins Scale for sleep (JSS) (rated 1-20), a quality-of-life questionnaire (SF-36) (rated 1-100), Patient Global Impression of Change (PGI-C), Tender Point Count (TPC) (rated: 0-18), Clinical Global Impression of Change (CGI-S), Epworth Sleepiness Scale (ESS) (rated: 1-24), and Functional Outcome of Sleep Questionnaire (FOSQ) (rated: 5-20). Adverse effects (nausea) were measured based on the incidence reported per patient. Table 1 demonstrates the demographics included in the studies.

Table 1: Characteristics of Studies Included for Analysis of Sodium Oxybate in the Treatment of FMS

Study/ type	#Pts/age	Inclusion criteria	Exclusion criteria	W/D	Interventions
Moldofsky; 2010 (1) RCT	151 pts 18+	PVAS greater than 4 (scale of 1-10) Discontinued used of opiates, antidepressants, cyclobenzaprine, tramadol.	Presence of inflammatory rheumatic disease, thyroid disease, seizures; Apnea hypopnea index of >15/hour on screening polysomnogram; History of head trauma resulting in LOC, migraines, intracranial surgery, substance abuse, succinic semialdehyde dehydrogenase deficiency ; Use of specific drugs within 30 prior to screening; Serum creatine of >2.0 mg/dl, abnormal LFTs/EKG , pregnancy; Occupations that required night shift work	44	Sodium Oxybate 4.5g/day and 6.0g/day
Russell; 2009 (2) RCT	188 pts 18+	Mean score PVAS >40 (on a 0-100 VAS scale) for up to 2 weeks before randomization Required discontinuation of opiates, antidepressants, cyclobenzaprine, tramadol.	Presence of inflammatory rheumatic disease, thyroid disease, seizures; Apnea hypopnea index of >15/hour on screening polysomnogram; History of head trauma resulting in LOC, migraines, intracranial surgery, substance abuse, succinic semialdehyde dehydrogenase deficiency ; Use of specific drugs within 30 prior to screening; Serum creatine of >2.0 mg/dl, abnormal LFTs/EKG , pregnancy; Occupations that required night shift work	42	Sodium Oxybate: (in oral solution) 4.5 gm/night 6.0 gm/night

Scharf MB; 2003 (3) RCT	24 pts 18+	Confirmed diagnosis of FMS History of widespread pain/tiredness and pain at 11/18 tender point sites Alpha intrusion in a mean of at least 30% of non REM epochs on 2 of 3 nights of the pre-Treatment PSG evaluations Patients who have never taken sodium oxybate	N/A	3	Sodium Oxybate 6.0g/day

Results

The results were presented in dichotomous form for studies done by Russel et al and Scharf et al, while Results for Moldofsky et al were reported in continuous form. Russel et al demonstrated 34.5% in the Sodium Oxybate group and a 12.5% in the placebo group achieved a 20% criteria improvement of primary outcome variable (POV) being pain.[2] The test was seen to be statistically significant ($P < 0.05$). The relative benefit increase (RBI) was calculated to be 182% and the absolute benefit increase was 20%. This study determines that the number needed to treat (NNT) was 5 for the treatment of Sodium Oxybate being 4.5g/day compared to placebo (Table 2).

Scharf et al showed that the testing was statistically significant ($P<0.05$). In regards to "morning alertness" the absolute benefit increase was shown to be 6% and the relative benefit increase was 800%. Numbers needed to treat was determined to be 17 for those receiving 6.0g/day. In regards to "sleep quality" the absolute benefit increase was shown to be 23% and the

relative benefit increase was 230%. Numbers needed to treat was determined to be 5 for those receiving 6.0g/day compared to placebo (Table 2).

Moldofsky et al analyzed both daytime sleepiness and sleep quality at both 4.5g/day and 6.0g/day doses. The data was reported in dichotomous data. The mean baseline for daytime sleepiness was 11.2 and placebo improved from baseline by -1.0 while the 4.5g/day treatment group improved by -3.1 and the 6.0g/day treatment group improved by -4.7 from baseline.[1] The mean baseline for sleep quality was 16.6.[1] The placebo group improved from baseline by -3.8 and the 4.5g/day treatment group improved by -7.1 and the 6.0g/day treatment group improved by -8.4 from baseline (Table 2).[1]

Table 2: Efficacy of Sodium Oxybate on Improving FMS symptoms

Study	Symptoms	Therapy dosage	Statistical data			
			P-value	RBI	ABI	NNT
Russel	Reduction of pain	4.5g/d	0.007	182%	20%	5
Scharf	Morning alertness	6.0g/d	0.0033	800%	6%	17
	Sleep quality	6.0 g/d	0.0003	230%	23%	5
			Baseline mean	Placebo: change in baseline	Tx: Improvement from baseline	
Moldofsky	Daytime sleepiness	4.5g/d	11.2	-1.0	-3.1	
	Daytime sleepiness	6.0g/d	11.2	-1.0	-4.7	
	Sleep quality	4.5g/d	16.6	-3.8	-7.1	
	Sleep qualiry	6.0g/d	16.6	-3.8	-8.4	

RBI= Relative Benefit Increase ABI= Absolute Benefit Increase NNT= Numbers Needed to treat

One of the most common treatment emergent adverse effects experienced in two of the trials was that of nausea. There was an incident of 16.7% in both the Russel et al and Moldofsky et al treatment groups, and only a 9.23% incidence in the placebo groups.[1,2] The symptom of nausea was describes as mild and tolerable. Nausea was more common in the Sodium Oxybate treatment group than in the placebo group. There was no data notation regarding adverse events in the Scharf et al study (Table 3).

Table 3: Incidences of Nausea in Sodium Oxybate vs. Placebo Group

Study	Incidences of nausea in treatment group	Incidences of nausea in control group	p-value	RRI	ARI	NNH
Russel	10/60 (16.7%)	6/65 (9.23%)	0.02	88	8	13
Moldofsky	10/60 (16.7%)	6/65 (9.23%)	0.02	88	8	13
Scharf	-	-	-	-	-	-

RRI= Relative Risk Increase ARI= Absolute Risk Increase NNH= Numbers Needed to Harm

Discussion

The randomized controlled trials on the study of the efficacy and safety of Sodium Oxybate on the treatment of FMS demonstrated that 6.0g/day was shown to be more effective in relieving symptoms of pain and sleep related symptoms than 4.5g/day. However the concern

with the higher dosing of Sodium Oxybate would be the intolerable adverse reaction of nausea which caused a significant amount of participants in the 6.0 g/day treatment group to withdrawal. Therefore**,** despite the greater efficacy of 6.0g/day, the 4.5g/day seemed to outweigh the greater efficacy with the safer adverse reaction profile. However, patients from both groups stated the efficacy of Sodium Oxybate therapy at either dosage was superior to any other previous pharmacological therapy they had tried previously.[3] The treatment of 4.5g/day is an effective starting dose in the treatment of symptoms related to FMS. However, the therapy can be increased to 6.0g/day if adverse effects are tolerable. Both therapies are safe and effective forms of treatment of FMS.

Conclusion

Sodium Oxybate was shown to be effective and safe in the treatment of fibromyalgia. Results were able to show significant improvement in participants' complaints of pain and sleep related symptoms. It was demonstrated that 4.5g/day is a safe and effective starting dose, and that 6.0g/day is a more efficacious therapy, but with a greater side effect profile. Overall, Sodium Oxybate demonstrated low number of treatment emergent adverse effects, especially with the 4.5g/day therapy, indicating the therapy to be a safe and tolerable therapy. Examining the methods used, limitation of the studies suggest a possible higher response rate could have been seen with stricter monitoring of patient compliance. Patients were expected to administer their therapy in the evening and then another dose 2-4 hours after the initial dose. It is possible if the administration timeframe was more standard there would be more consistent results. However, the studies did not comment on the non-compliance of the medication administration and results

demonstrated a high response rate, regardless. Further studies could be performed to determine how a titration effect from a lower dose of Sodium Oxybate up to 6.0g/day would change the side effect profile, if at all. This would possibly decrease the amount of patients needing to withdrawal from the study and result in data demonstrating a more effective and tolerable therapy.

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