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Sodium oxybate: a potential new pharmacological option for the treatment of fibromyalgia syndrome

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***Abstract*:** Fibromyalgia syndrome (FMS) is a common disorder, characterized by diffuse pain and tenderness, stiffness, fatigue, affective disorders and significant sleep pathology. A new set of diagnostic criteria have been developed which should make it easier for a busy clinician to diagnose the condition. US Food and Drug Administration (FDA) approved medications for the treatment of FMS have, for the most part, been geared to modulate the pain pathways to give the patient some degree of relief. A different kind of pharmacological agent, sodium oxybate (SXB), is described that is currently approved for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. SXB, an endogenous metabolite of the inhibitory neurotransmitter gamma-hydroxybutyrate, is thought to act independently as a neurotransmitter with a presumed ability to modulate numerous other central nervous system neurotransmitters. In addition SXB has been shown to robustly increase slow wave sleep and decrease sleep fragmentation. Several large clinical trials have demonstrated SXB's ability to statistically improve pain, fatigue and a wide array of quality of life measurements of patients with fibromyalgia. SXB is not FDA approved to treat fibromyalgia.

***Keywords*:** fatigue, fibromyalgia, pain, polysomnography, sleep, sleep fragmentation, sodium oxybate

Introduction

Fibromyalgia syndrome (FMS) is estimated to affect 2–4% of the general population [Wolfe *et al.* 1995]. It is characterized by widespread pain with generalized areas of tenderness that is associated with global constitutional symptoms including sleep disturbances, fatigue, stiffness, headaches, cognitive impairment, affective symptoms and irritable bowel syndrome [Aaron *et al.* 2001, 2000]. To date, treatment has concentrated primarily on modifying nociceptive input and central nervous system (CNS) signaling. A different modality of treatment has been proposed that is postulated not only to reduce CNS nociceptive input but also to directly improve the quantity and quality of the patient's nocturnal sleep. This in turn has been shown to reduce subjective pain levels and improve measures of quality of life scales.

In 1990, the American College of Rheumatology (ACR) set forth criteria for the research diagnosis of FMS, which requires at least 11 of 18 tender points (tender point count or TPC) to be identified at predesignated specific sites and the presence of widespread pain. Widespread pain is defined as axial pain, left- and right-sided pain and upper and lower segment pain [Wolfe *et al.* 1990].

In May 2010 the ACR gave provisional approval to a newer set of criteria that removed the necessity of doing a TPC. Instead a widespread pain index (WPI) was introduced, a measure of the number of painful body regions, and a symptom severity (SS) scale that takes into account the temporal, and quantitative aspects of the spectrum of fibromyalgia symptoms, including pain, fatigue, trouble with sleep, trouble with anxiety or depression, and problems awakening unrefreshed [Goldenberg *et al.* 2010].

This newer set of diagnostic criteria has been designed to enable physicians who have not been trained to conduct the 'formal' TPCs or have clinical time constraints (precluding the

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detailed TPC examination to be performed) make an accurate diagnosis and to start pharmacological therapy when appropriate.

FMS is more common in adult women and frequently occurs in combination with other conditions, including rheumatoid arthritis, lupus, and Sjögren's syndrome. It has been estimated that up to 25% of patients with FMS have a major depressive and/or anxiety disorder, in some cases attributable to a higher number of reports of a history of physical, sexual or emotional abuse in childhood.

The history of the study of FMS is punctuated by conflicting ideas about the characterization of the syndrome, the origin and extent of the myriad symptoms and ultimately the appropriate therapy for the condition. In 1904 the term 'fibrositis' was coined for a group of painful disorders that did not meet the more formal criteria for such conditions as rheumatoid arthritis or osteoarthritis. There were schools of thought suggesting the pain was of psychopathological origin because there was no obvious physiological evidence for muscle and/or articular pathology.

In 1975 Moldofsky and colleagues reported a possible biological marker for FMS describing a 'non-REM [rapid eye movement] sleep disturbance' in patients with 'fibrositis syndrome' (see the section on 'Fibromyalgia and sleep') [Moldofsky *et al.* 1975]. Shortly thereafter, the term fibrositis was replaced by the current appellation: fibromyalgia.

Pathophysiology of fibromyalgia syndrome

It is currently thought that the pathophysiology of FMS relates to dysfunctional regulation of the major pain-modulating neurotransmitters in the CNS leading to altered sensory processing. In a study using functional magnetic resonance imaging (fMRI), patients with FMS demonstrated significantly greater fMRI signal (measured as regional cerebral blood flow or rCBF) in the contralateral primary and secondary sensory cortices than controls when the same mild pressure stimulation was applied to their thumbnail. Patients with FMS also demonstrated attenuated rCBF in the thalamic nuclei compared with controls when both groups were presented with the same novel noxious stimulation. Thus using the fMRI's increased spatial resolution to investigate small areas of rCBF, patients with FMS were shown to exhibit physiological and anatomical evidence of diffuse hyperalgesia and allodynia [Gracely *et al.* 2002]. It is postulated that CNS sensitization of nociceptive neurons starts in the dorsal horn of the spinal cord through dysregulation of the *N*-methyl-D-aspartic acid (NMDA) receptor. In patients with FMS, pronociceptive neurotransmitters substance P, dynorphin A, calcitonin gene-related peptide (CGRP), and nerve growth factor have been found in higher concentrations in cerebrospinal fluid [Russell *et al.* 1992]. It is theorized that chronic pain causes up-regulation of these neurotransmitters with secondary activation of the NMDA receptor, leading to an amplification of the nociceptive input into the CNS [Staud, 2005].

In addition, low levels of serotonin (5-HT) and its metabolite 5-hydroxyindolacetic acid (5-HIAA) have been observed in the spinal fluid of patients with FMS [Russell *et al.* 1992]. This is important because of the role that 5-HT plays in presynaptically inhibiting release of pronociceptive neurotransmitters (e.g. substance P and CGRP) from the terminals of primary afferent neurons [Bourgoin *et al.* 1993]. Serotonin also plays an important role in the regulation of mood. Impaired 5-HT signaling, resulting in 5-HT dysregulation, has been associated with depression, anxiety and sleep abnormalities [Ressler and Nemeroff, 2000; Juhl, 1998].

Growth hormone deficiency in adults has a clinical picture that in many ways is similar to the symptom complex seen in patients with FMS: low energy, poor general health, reduced exercise tolerance, and impaired mood [Cuneo *et al.* 1992]. Approximately 33% of patients with FMS have low levels of insulin-like growth factor-1, which is a marker for growth hormone [Bennett *et al.* 1992]. In one small placebo-controlled study, the administration of growth hormone improved sleep in patients with FMS compared with those receiving placebo [Bennett *et al.* 1998], although this finding has yet to be replicated.

Another possible mechanism involves the imbalance between excitatory and inhibitory influences on sensory pathways. Excitatory neurotransmitters (e.g. glutamate) and substance P stimulate the peripheral nociceptive afferents entering into the spinal cord with second-order neurons projecting onto the thalamus and then getting distributed throughout the cortical network. However, there are endogenous substances that have

inhibitory influences on nociception, such as endorphins and enkephalins, both of which are found in decreased concentration in patients with FMS. Glycine, a CNS inhibitory neurotransmitter, is required for activation of the NMDA receptor and it has been found to be in higher concentration in patients with FMS [Larson *et al.* 2000].

Chronic stress produces a suppression of dopamine activity and may represent an important aspect of the pathophysiology of FMS. The reduction of dopamine metabolism in FMS has also been investigated using positron emission tomography scans [Wood *et al.* 2006].

The autonomic nervous system is also affected by FMS, with strong evidence there is dysfunctional chronic autonomic arousal as demonstrated by decreased 24 h heart rate variability when compared with healthy age-, sex- and weight-matched controls. Patients with FMS also demonstrate an aberrant circadian rhythm of autonomic nervous system tone, with persistent nocturnal sympathetic hyperactivity, along with impaired autonomic response to body position changes [Martinez-Lavin *et al.* 1998, 1997].

The interrelationship of pain and sleep

It has long been known a bidirectional relationship exists between sleep and pain perception, that is, pain disturbs sleep and disturbed sleep (fragmented or shortened sleep) enhances and/or changes the perception of pain. Whereas the former relationship is intuitive, numerous investigators have demonstrated the latter.

Sleep loss of 4 h with specific REM sleep loss is hyperalgesic the following day as measured by finger withdrawal to a painful stimulus [Roehrs *et al.* 2006].

The application of noxious stimuli during sleep causes a decrease in delta (0.5–3.5 Hz) and sigma (12–14 Hz) frequencies consistent with deep sleep. At the same time there is an increase in alpha (8–10 Hz) and beta (14.5–25 Hz) frequencies that are consistent with lighter and more fragmented sleep [Lavigne *et al.* 2004]. The decrease in sigma frequencies is associated with a decrease in spindle activity.

Moldofsky and colleagues used noxious auditory stimulation to disrupt slow wave sleep (SWS also called N3) (2–3.5 Hz) in normal individuals. In the morning these individuals reported their sleep was unrefreshing and they developed daytime fatigue, body aches and increased tender points in many of the same areas as patients with FMS [Moldofsky *et al.* 1975]. In patients with selective REM sleep deprivation, no changes were observed in terms of development of pain or tenderness [Moldofsky and Scarisbrick, 1976]. Other researchers have also shown that SWS disruption results in a 'generalized hyperalgesic state' [Lentz *et al.* 1999; Older *et al.* 1998]. It has also been shown that the restoration of SWS increases next day mechanical pain thresholds, strongly suggesting that improvement of SWS induces an analgesic effect [Hakkionen *et al.* 2001].

Fibromyalgia and sleep

It has been estimated that over 90% of patients with FMS describe their sleep as 'disturbed'. Descriptions vary, including light sleep, unrefreshing sleep, frequent nocturnal awakenings, sleep-related increase in pain, restlessness, jerking, twitching, kicking or snoring [Moldofsky, 2008].

There are demonstrable electroencephalogram abnormalities present in a high percentage of patients with FMS. These include the finding of alpha frequency waves over-riding slower background rhythms during non-REM sleep (alpha-delta or A-D sleep); in particular, the slower wave frequencies of stage N3 or SWS [Moldofsky *et al.* 1975]. The presence of this alpha activity that is associated with wakefulness is thought to be indicative of a 'hypervigilent' state of sleep. This, in turn, results in the subjective feeling of nonrefreshing or nonrestorative sleep [Anch *et al.* 1991].

In addition to A-D sleep, other electro-cortical abnormalities have been associated with FMS. These include decreased number of sleep spindles [Chervin *et al.* 2009], shorter periods of stage N2 sleep [Landis *et al.* 2004] and an elevated frequency of cyclic alternating pattern (CAP) (identified using computer-aided frequency and pattern recognition software). CAP has been proposed as an objective measure of sleep state stability with CAP phase A1 pattern indicating normal sleep architecture whereas CAP A2 and A3 patterns indicate progressively more disrupted and unstable sleep architecture [Rizzi *et al.* 2004].

The appearance of sleep spindles (12–14 Hz) represents the onset of stage N2 sleep. Sleep spindle activity is thought to originate in the thalamus and is associated with thalamic gating mechanisms [Jankel and Neidermeyer, 1985]. Through this mechanism, the flow of nociceptive input into the cortex and the cortical responses to the nociceptive stimuli are regulated and attenuated during sleep [Steriade, 2000, 1994; Steriade *et al.* 1993]. Reduced spindle incidence and frequency have been shown in women with FMS. This reduction in gating is hypothesized to represent an intrinsic impairment in the thalamocortical control of 'protecting' the sleeping brain, leading to a chronic 'hyperalgesic state' [Landis *et al.* 2004].

Fragmented sleep is noted in many patients with FMS and is commonly associated with sleep apnea syndrome and/or periodic limb movements of sleep. These produce a periodic arousal disturbance in sleep, known as K-alpha [MacFarland *et al.* 1996] or increased CAP, an EEG sleep pattern that is thought to be a measure of sleep stability [Rizzi *et al.* 2004; Older *et al.* 1998].

Treatment of fibromyalgia

Historically, treatment regimens have been primarily targeted to reduce the pain complaints of patients with FMS. However, an Outcome Measures in Rheumatology (OMERACT) Delphi exercise identified other aspects of FMS that occur in over 50% of the affected patients [Mease *et al.* 2008]. These include fatigue, sleep disturbance, poor concentration, stiffness, disorganized thinking, tenderness, depression and poor memory. As such, optimal therapy should involve both pharmacological and nonpharmacological pathways to address most if not all of these multifaceted signs and symptoms. The nonpharmacological treatment paradigms include physical therapy, counseling and education for the patient and the family. Cognitive behavioral therapy is a useful modality to help change both habits and ideas that through long-term negative conditioning re-enforce the hyperalgesic state [Richards and Cleare, 2000].

From a pharmacological standpoint the primary agents that have been approved by the US Food and Drug Administration (FDA) to treat FMS are geared to reduce pain, as noted above. However, it is clear that an agent(s) that can improve the other comorbid symptoms, for example, reduction in fatigue, improvement in the quality and quantity of nocturnal sleep, and improve cognitive and affective symptoms is needed.

Currently there are three agents that are FDA approved to treat FMS: pregabalin, an α_2-δ (type 1) calcium channel blocker that has analgesic, anxiolytic and anticonvulsant properties [Crofford *et al.* 2005]; duloxetine, an antidepressant with both serotonergic and noradrenergic reuptake inhibition [Arnold *et al.* 2004]; and milnacipran, also an antidepressant with dual serotonergic and noradrenergic reuptake inhibition, which has a somewhat greater effect on norepinephrine [Clauw *et al.* 2008]. In pivotal registration trials conducted on these agents, all three agents showed statistically significant improvements in pain scores.

The subjective and objective effects of these medications on sleep have been studied in small numbers of patients. Pregabalin has been shown to increase SWS and decrease REM sleep in healthy individuals [Hindmarch *et al.* 2005]. Duloxetine has been reported to increase slow wave sleep and decrease total REM sleep time along with an increase in REM sleep latency in patients with major depression [Kluge *et al.* 2007]. Milnacipran, administered to patients with depression, demonstrated a reduction in REM sleep as a percentage of total sleep time along with an increase in REM latency [Lemoine and Faivre, 2004]. The overall positive effects of these medications on sleep are modest at best. Their ability to improve both subjective and objective measures of sleep at the same time as decreasing pain in FMS remains to be ascertained.

Sodium oxybate

SXB is the sodium salt of gamma-hydroxybutyrate (GHB), an endogenous metabolite of gamma-aminobutyric acid (GABA) a major inhibitory neurotransmitter [Pardi and Black, 2006]. GHB is thought to function as a neurotransmitter with evidence that it is synthesized in neurons, distributed throughout the CNS, stored in vesicles, released via potassium-dependent depolarization into the synaptic cleft and undergoes reuptake into the nerve terminal. Like GABA, GHB interacts with its own specific receptors (two types of binding sites have been identified): high-affinity sites located mainly in the cerebral cortex and brain stem, and low-affinity sites mainly found in peripheral tissues (kidney, liver, muscle, and heart) [Maitre *et al.* 1983].

GABA and GHB receptors are both G-protein-coupled receptors. In addition to binding at its own receptor, GHB also binds to $GABA_B$ receptors [Mathivet *et al.* 1997; Snead and Liu, 1984].

SXB is FDA approved for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy [Jazz Pharmaceuticals, 2005]. It is not approved for the treatment of fibromyalgia.

GHB was first described as a possible precursor of GABA that could cross the blood–brain barrier [Laborit, 1964]. Further elucidation proved it an endogenous metabolite of GABA [Roth and Giarman, 1969] with a turnover of 0.16% of GABA being converted to GHB [Maitre, 1997]. GHB exhibited strong hypnotic effects and there was no apparent tolerance with long-term use [Vickers, 1969]. GHB has been shown to robustly increase slow wave sleep and improve sleep consolidation in narcolepsy [Mamelak *et al.* 2004], a condition of excessive daytime sleepiness, episodic attacks of muscle weakness (cataplexy), and fragmented night-time sleep, manifested by episodic intrusions of REM sleep throughout the day and night. GHB was found to decrease nocturnal arousals, improve daytime sleepiness, and significantly decrease the number and severity of the cataplectic attacks [Broughton and Mamelak, 1980, 1979, 1976].

The effects of GHB on CNS neurotransmitter/hormonal systems

GHB has been demonstrated to affect the signaling of monoaminergic, opioid and hormonal systems within the central nervous system.

Dopamine. Exogenous administration of GHB raises concentrations of GHB significantly in specific dopaminergic regions of the brain (nigrostriatal and mesocorticolimbic areas) [Shumate and Snead, 1979; Lettieri and Fung, 1979]. When GHB is first administered there appears to be an initial inhibition of dopamine release, but at the same time, there is an increase in dopamine synthesis. When GHB washes out there is an increase in dopamine release [Tunnicliff, 1992].

Serotonin. GHB has been shown to induce an increase in serotonin turnover in the striatum and mesolimbic areas of the brain [Waldmeier and Fehr, 1978].

Growth hormone. Some of the earliest studies of the effects of GHB demonstrated a dramatic increase in growth hormone secretion (doubling) in healthy individuals treated with even low doses of the drug (2.5 g/night). Stimulation of growth hormone secretion was correlated with a simultaneous increase in slow wave sleep [Van Cauter *et al.* 1997].

Opioids. GHB has also been found to increase endogenous opioids, dynorphin, and encephalin after both acute and chronic administration [Schmidt-Mutter *et al.* 1999; Lason *et al.* 1983].

Noradrenergic system. $GABA_B$ receptors have been shown to be active in the regulation of noradrenergic afferents from the locus coeruleus (LC). Studies have shown that with chronic GHB administration there is an inhibition of LC noradrenergic firing as long as there is an adequate concentration of GHB within the CNS. During GHB washout there is an enhancement of LC noradrenergic firing which may help explain the clinical effect of increased wakefulness during the day in patients with narcolepsy [Szabo *et al.* 2004; Persson and Henning, 1980].

Pharmacology

SXB is a short-chain fatty acid that is rapidly absorbed after an oral dose. It has a half life of 30–60 min and is metabolized by the tricarboxylic acid (Krebs) cycle to water and carbon dioxide [Palatini *et al.* 1993]. Less than 5% of the ingested drug is eliminated unchanged in the urine [Jazz Pharmaceuticals, 2005]. SXB is typically taken at bedtime, with half the dose taken at the beginning of the night and the second half 2–4 h later. The drug needs to be taken on a relatively empty stomach because administration with a high-fat meal will seriously impede its absorption [Borgen *et al.* 2003].

Sodium oxybate and sleep

SXB has been shown to decrease sleep onset latency, increase slow wave sleep, increase growth hormone secretion, consolidate sleep by increasing sleep efficiency and promote a normal sequence of non-REM and REM sleep [Van Cauter *et al.* 1997; Mamelak, 1989; Marcus *et al.* 1967].

SXB is a potent CNS depressant and as such carries a black-box warning from the FDA in its labeling for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy [Jazz Pharmaceuticals, 2005]. The most common adverse events include confusion, nausea, vomiting, headache, and next day somnolence. Other adverse events include urinary

incontinence and sleep waking (thought to be due to the enhanced SWS with resultant confusional arousals and/or frank parasomnias).

Because SXB is a sodium salt of GHB, and illicit GHB is a street drug with a history of abuse and criminal misuse, there has been a perception among some physicians and patients that all the risks associated with illicit GHB also apply to SXB. To investigate this further, a cumulative postmarketing and clinical safety analysis was carried out on approximately 26,000 patients who received SXB from 2002 (the year in which SXB was approved by the FDA) until March 2008 [Wang *et al.* 2009]. In the United States, SXB is available only through a central pharmacy that tracks drug initiation, refills, and discontinuation. In 14 other countries where SXB is approved for use, postmarketing spontaneous adverse event reports were reviewed. Incidents of misuse and/or abuse were investigated, which included reports of *Diagnostic and Statistical Manual of Mental Disorders* volume IV (DSM-IV) abuse criteria, DSM-IV dependence criteria, and withdrawal symptoms following discontinuation of SXB. Incidents involving SXB-facilitated sexual assault, overdose with suicidal intent, traffic accidents involving drivers taking SXB, and any deaths related to SXB were recorded. Because of the need for a signature at the time of delivery of SXB in the United States, instances of diversion of the drug have been well documented and available for review. There were a total of 10 cases (0.039%) meeting criteria for abuse, four cases (0.016%) of dependence, eight cases (0.031%) with withdrawal symptoms following discontinuation of SXB, two confirmed cases (0.008%) of SXB-facilitated sexual assault, eight cases (0.031%) of overdose with suicidal intent, 21 deaths (0.08%) in patients receiving SXB treatment with one death known to be related to SXB, and three cases (0.01%) of traffic accidents involving drivers taking SXB. During the timeframe studied, there were approximately 600,000 bottles of SXB distributed with five incidents of diversion (0.0009%). The conclusion was that SXB is a safe medication with very low risk of abuse and or misuse.

Sodium oxybate and fibromyalgia

The first open-label trial of SXB for the treatment of patients with 'widespread musculoskeletal pain in all 4 quadrants' was carried out in 1998. Eleven patients were evaluated after 1 month of SXB administration. The results suggested improvement in all clinical spheres of FMS with subjective improvement in terms of overall wellness, decrease in pain, and decrease in fatigue. Objectively there was a 'dramatic' reduction in the percentage of non-REM alpha intrusion based on overnight polysomnographic recordings [Scharf *et al.* 1998].

This study was followed up with a 30-day double-blind placebo-controlled trial (with a 2-week washout) enrolling 24 patients, all of whom were women (56 patients were screened and a total of six withdrew) to evaluate the effects of SXB on subjective symptoms of pain, fatigue and sleep quality, and objective polysomnographic data looking at alpha intrusion, slow wave sleep and sleep efficiency in patients meeting the ACR diagnostic criteria for FMS. There was statistically significant improvement in the treated group in terms of the following: a decrease in the TPCs; overall pain, pain at rest, pain during movement, end of day fatigue, overall fatigue, and morning fatigue improved; decreased sleep latency; decreased alpha intrusion; decreased REM sleep; and increased slow wave sleep [Scharf *et al.* 2003].

A larger study was reported [Moldofsky *et al.* 2010; Russell *et al.* 2009] involving 195 patients who met the 1990 ACR criteria for FMS. The trial was conducted at 21 clinical sites by practitioners experienced in diagnosing and caring for patients with FMS (OMC-SXB-26 FMS Study Group). Of the 320 patients who were screened, 209 underwent polysomnography and 195 were randomized into three groups: SXB at 4.5 g, SXB at 6 g and placebo. The intent-to-treat (ITT) analysis included 188 patients. The enrollees were washed out of their prestudy medications and were enrolled for a total of 8 weeks. A total of 147 or 78% of the ITT population completed the protocol (94% were women with mean age of 47.6 years). The trial medication was taken in two doses: half of the full night-time dose was taken at bedtime and the second half 4 h later. The primary outcome variable was a composite score for changes from baseline in three self-reported measures: pain rating on a visual analog scale (pain-VAS) as recorded daily in an electronic diary, the Fibromyalgia Impact Questionnaire (FIQ) score, and the Patient Global Impression of Change (PGI-C). Secondary measures included the Jenkins Sleep Scale (JSS), and quality-of-life measures.

In this study, significant benefit was observed with both of the trial doses of SXB (4.5 and 6 g).

There were statistically significant improvements in all primary outcome variables for both doses of SXB (overall function, pain and PGI-C) as well as improvement in the secondary measurements (daytime fatigue and subjective quality of sleep as measured by the JSS).

The SXB-26 FMS study was the first to assess objective and subjective measures of disrupted sleep in a large number of patients with FMS [Scharf *et al.* 2003]. Polysomnographic intrepration utilizing standard visual scoring rules was performed on 209 patients, of whom 195 were randomized and 151 completed the 8-week study. Computer-aided CAP analysis was performed on 88 of 195 randomized patients and 47 of 151 patiets who completed the study. Subjective assessments of sleep and fibromyalgia severity were assessed throughout the study. These included the JSS (looking at sleep disturbance and daytime tiredness), the Epworth Sleepiness Scale (ESS) (which assesses the liklihood of falling asleep in eight different scenarios), the fatigue VAS (F-VAS), the Functional Outcome of Sleep Questionnaire (FOSQ) (evaluates the effects of daytime sleepiness on daily activities and function), the Short Form-36 Health Survey (SF-36) (which evaluates energy levels) and the FIQ (morning and general tiredness subscales).

Baseline polysomnographic data corroborated previous findings that patients with FMS exhibited a high prevalence of A-D sleep (alpha EEG intrusion > 24 min/h of sleep) (66%), as well as showing significant non-REM sleep disruptions, periodic limb movements of sleep (20% with more than five per hour), and moderate to severe obstructive sleep apnea (15%).

Findings of the baseline subjective scales and scores revealed significant sleep complaints with shortened sleep duration ($\leq$6 h sleep/night) in 74% of patients, multiple nocturnal awakenings (at least three per night), and light or very light sleep in 66% of patients. The ESS was elevated at 11, indicating excessive daytime sleepiness with a propensity for inadvertant or unintentional sleep episodes. JSS, FOSQ and SF-36 scores all indicated significant daytime fatigue with worsening symptoms as the day progressed.

Treatment with SXB resulted in a dose-dependent decrease in fatigue measured by F-VAS, with significant reductions compared with placebo throughout the day for SXB 6 g and for morning only with the 4.5 g dose. Dose-dependent improvements were seen in JSS and ESS scores and were statistically significantly better than placebo. Polysomnographic findings revealed that the SXB 6 g dose statistically increased stages N2 and N3 sleep individually and collectively there was an increase in total non-REM sleep. Both SXB 4.5 g and SXB 6 g significantly reduced total REM sleep compared with placebo. Total sleep time and sleep efficiency (total time asleep divided by time from sleep onset to sleep offset) increased with SXB 6 g by an amount that fell just short of statistical significance. A stitistically significant improvement was seen in the reduction of wakefulness after sleep onset for the SXB 6 g dose with near statistical significance for the SXB 4.5 g dose. A1 CAP rate (the more stable sleep state) showed improvement for both doses of SXB but the increase was not statistically significant. However, decreases in the phase A2/A3 CAP rates for both doses of SXB were seen, with statitistical significance being demonstrated for the SXB 6 g dose only.

Treatment-emergent adverse events were reported in all three treatment groups: placebo 60%, SXB 4.5 g 68%, and SXB 6 g 78%. There were no clinically significant changes in vital signs, laboratory measures, general and neurological examinations or electrocardiograms. Two patients experienced serious adverse events (one experienced a respiratory infection with an exacerbation of asthma and the other experienced a manic episode as part of an undisclosed bipolar disorder with transient hypertension and tachycardia). None of the adverse events were judged to be related to study drug. No deaths were reported in this study. Most of the adverse events were mild to moderate with a dose-dependent pattern. These included nausea, dizziness, headache, paresthesias, somnolence, restlessness, renal and urinary disorders, and urinary incontinence. Ten patients (5%) reported experiencing either anxiety (2%) or depression (3%) as adverse events. One of these 10 patients reported both anxiety and depression and one of the six patients with depression expressed suicidal ideation. Nine of the 10 patients were taking one of the two doses of SXB and all the patients reporting depression were dropped from

the study. No signs of dependence or withdrawl symptoms were noted during the washout period.

To further examine the clinical utility of SXB in patients with FMS, two larger studies were conducted. The first involved a 14-week randomized double-blind placebo-controlled study from multiple sites in the United States involving 548 patients who met the ACR criteria for FMS [Russell *et al*. 2011]. The patients were randomized into three groups: placebo, SXB 4.5 g/night and SXB 6 g/night (all doses were split with half of the dose taken at bedtime and the second half taken 2.5–4 h later). The primary outcome measure was the percentage of patients who reported a reduction of at least 30% on the pain-VAS from baseline to week 14. Other measures included the F-VAS, JSS and PGI-C. Safety was measured via treatment-emergent adverse events, vital signs, laboratory, and electrocardiogram measures.

The results revealed both doses of SXB resulted in significantly more patients reporting an improvement of at least 30% on the pain-VAS compared with placebo (54.2% and 58.5% respectively *versus* 35.2%, $p \leq 0.001$). Compared with PBO, treatment with SXB 4.5 g and SXB 6 g produced significantly greater reductions in mean JSS scores (−6.1 and −6.2 respectively *versus* −2.9, both $p \leq 0.001$) and significantly greater reductions in mean daytime fatigue measured as a linear VAS assessment score (F-VAS) (−27.94 and −30.02 respectively *versus* −17.57, both $p \leq 0.001$). In addition, a significantly greater percentage of patients in the treated groups perceived meaningful improvement in multiple symptom domains compared with placebo ($p < 0.001$).

Similar treatment-emergent adverse events (at least twofold that of placebo) were reported in this study as were reported in the OMC-SXB-26 study, that is, headache, nausea, dizziness, vomiting, diarrhea, anxiety, and sinusitis. Patients on SXB 6 g exhibited more adverse events than patients on SXB 4.5 g. As an adverse event, depression was reported in four patients in the placebo group, three in the SXB 4.5 g group and give in the SXB 6 g group. Anxiety was considered as an adverse event in two patients in the placebo group, 12 in the SXB 4.5 g group and 10 in the SXB 6 g group. No suicidal ideation was reported in any patient. Of note was the finding that weight loss was found to occur in a dose-dependent fashion, with 8% of patients on SXB 4.5 g and 14% of patients on SXB 6 g experiencing a weight loss of at least 7%. Apnea was reported in one patient on SXB 6 g and 'hypoventilation' was reported in one patient on SXB 4.5 g (both were dropped from the study).

The conclusion was that this study was corroborative of earlier studies that demonstrated that SXB 4.5 g/night and SXB 6 g/night dosing taken as split nocturnal aliquots were safe and efficacious in the treatment of pain, sleep disturbance, fatigue, and in the composite of the PGI-C in patients with FMS [Russell *et al.* 2009].

The last study involved 573 patients meeting ACR criteria for FMS enrolled from eight countries at multiple sites The results of this study are currently being tabulated and the findings will be published in the near future.

These studies provide further evidence that SXB is efficacious and well tolerated in patients with FMS with substantial effect on pain, fatigue, sleep, and patient global status.

Discussion

FMS is a relatively common disorder that is manifested by signs and symptoms encompassing both physical and psychological spheres. The most common patient complaints are chronic widespread pain, overwhelming fatigue, nonrefreshing nocturnal sleep and a variety of mood disorders. New diagnostic criteria should make it easier to diagnose and formulate a treatment plan.

To date, treatment has been geared to the modulation of the CNS nociceptive system that in a best-case scenario provides some degree of pain relief. However, it is clear that the sleep complaints of patients with FMS are severe and play a significant part in the underlying CNS mechanisms demonstrated by the studies that corroborated the bidirectionality of pain/sleep pathological interaction.

SXB is a unique pharmacological agent, the exact mechanism of action of which has not been fully ascertained. However, all available evidence points to its ability to modulate the signaling of CNS monoaminergic transmitters, endogenous opioids, and increase growth hormone concentrations. In addition, the ability of SXB to decrease sleep fragmentation, increase slow

wave sleep and improve the patient's subjective assessment of restoring 'refreshing' sleep could produce an independent clinically significant analgesic effect. The capability of a single agent to modify and improve this complex interactive system represents a significant therapeutic advance in the treatment of this multifaceted syndrome.

In the studies cited, SXB was well tolerated, with adverse events occurring at approximately the same frequency as had been seen with prior studies that had been submitted to the FDA for approval of SXB to treat cataplexy and excessive daytime sleepiness in patients with narcolepsy.

Postmarketing analysis of SXB from 2002 through 2008 has shown there is an extremely low incidence of abuse/misuse and diversion of the drug [Wang *et al.* 2009]. This being said, SXB is a potent CNS and respiratory depressant and significant care needs to be taken that this drug should not be used in combination with alcohol or any other drug that causes CNS depression (i.e. opiates, sedatives, hypnotics, or tranquilizers) or depresses respiratory function.

A similar conclusion to the postmarketing analysis cited above was stated in a 2009 review of the literature concerning the tolerability and abuse potential of GHB for insomnia in patients with schizophrenia. This population has been prescribed and utilizes a high number of CNS active pharmaceutical agents and has a high comorbidity of substance abuse disorders. The authors of this review noted that the data supported previous findings that the actual numbers of adverse events as well as misuse and abuse of SXB/GHB are small and should not preclude the further development of GHB for indications beyond which it is already approved [Kantrowitz *et al.* 2009].

All the data support the overall safety of SXB, however in the population of patients who would be considered likely candidates for treatment with SXB there is a subset that needs to be carefully screened out to avoid those who are drug seekers, those who abuse narcotic analgesics, and those with a history of unstable depression.

SXB has also been reported to exacerbate untreated sleep-disordered breathing in a small number of patients [George *et al.* 2010a, 2010b]. In the studies cited above, the average body mass index (BMI) of patients was greater than 28 [Russell *et al.* 2009], and in the 8-week study that involved polysomnography, more than 15% of the screened patients were found to have an apnea/hypopnea index of at least 15 h (consistent with at least moderate obstructive sleep apnea syndrome) and were thus excluded from further participation in the trial [Moldofsky *et al.* 2010]. In patients with FMS with a history of snoring, elevated BMI, hypertension and/or diabetes it is prudent to evaluate for sleep apnea syndrome, and if present, treatment with Continuous Positive Airway Pressure (CPAP) should be initiated prior to starting treatment with SXB. If sleep apnea is not present at the start of therapy, vigilance is urged for the possible development of sleep-disordered breathing during long-term treatment with SXB [Feldman 2010, 2009]. As a cautionary note, the use of SXB should be carefully weighed in all patients with a history of respiratory dysfunction because of the drug's inherent potential as a respiratory depressant.

Patient education and physician education along with proper clinical follow up are essential components for successful prescribing of this medication.

In summary, the basic science and the clinical trials support the premise that SXB can safely and effectively improve most of the outcome measures as outlined by the OMERACT recommendations [Mease *et al.* 2008].

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Conflict of interest statement

Dr Swick has received research grant support from Jazz Pharmaceuticals, Pfizer, Cephalon, Boehringer-Ingelheim, Takeda Pharmaceuticals, Sanofi-Aventis, Somaxon, GlaxoSmithKline, UCB Pharma and Epix Pharmaceuticals. He is a consultant to Jazz Pharmaceuticals and is on the speaker's bureau of Jazz Pharmaceuticals and Sunovion (formally Sepracor). He was an investigator for the Jazz Pharmaceuticals OMC-SXB-26 funded study.

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