Narcolepsy is a sleep disorder characterized by excessive daytime sleeping (EDS) associated with irresistible attacks of sleep, sudden loss of muscle tone (cataplexy), disrupted nocturnal sleep, hypnagogic/hypnopompic hallucinations, and sleep paralysis. Cataplexy is specific to narcolepsy and is the most accurate diagnostic marker of the disease. It is characterized by a sudden, usually bilateral, partial or complete loss of muscle tone that is provoked by emotional stimuli. Studies have shown that 65% to 75% of patients with narcolepsy have cataplexy. The prevalence of narcolepsy with cataplexy is approximately 25 to 50 per 100,000 people, with an incidence of 0.74 per 100,000 person-years. It is often extremely incapacitating, interfering with every aspect of life, including work and social settings.

Currently there is no cure for narcolepsy, with treatment focusing on symptom control. Pharmacological management of EDS commonly involves medications that increase wakefulness, including non-sympathomimetic stimulants, (e.g., modafinil) and sympathomimetic stimulants (e.g., amphetamine, methamphetamine, dexamphetamine, and methylphenidate). Several drugs have been used to treat cataplexy, such as tricyclic antidepressants and serotonin norepinephrine reuptake inhibitors; however, none of these medications are Food and Drug Administration (FDA) approved for cataplexy treatment. SXB was recently approved by the FDA to treat patients diagnosed with narcolepsy and symptoms of cataplexy. It is currently authorized by the European Medicines Agency to treat narcolepsy with cataplexy as a whole disease in adults, and by the FDA to treat cataplexy in patients with narcolepsy, with an “expanded indication” for the treatment of excessive daytime sleepiness. It is the sodium salt of γ-hydroxybutyrate (GHB), an endogenous cerebral inhibitory neurotransmitter. Its mode of action is uncertain, but it may involve stimulation of γ-aminobutyric acid B (GABA [B]) receptors. SXB is rapidly absorbed and eliminated, having a mean elimination half-life of 30-60 minutes. Strict regulations have been established with regard to the prescription and dispensing of the drug and patients usually receive extensive education on its use.

In this article, we aimed to systematically review the efficacy and safety of SXB on EDS, cataplexy, quality of life, and the associated side effects among people with narcolepsy and cataplexy through a systematic review and meta-analysis.
METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement was used to guide the reporting of this review.11

Eligibility Criteria

The inclusion criteria were randomized controlled trials (RCTs) of participants with narcolepsy and cataplexy, which examined the use of SXB. We did not limit inclusion by comparator, language, publication status (i.e., unpublished reports could be included), or year of publication. When multiple study publications reported data from the same population (i.e., companion reports), the trial reporting the primary outcome of interest was considered the major publication and the other report(s) was used for supplementary data.

The primary outcome was elimination of excessive daytime sleepiness (EDS) according to subjective or objective indicators. Objective laboratory tests included the multiple sleep latency test (MSLT), which is a validated objective measure of the ability or tendency to fall asleep.12,13 In addition, it allows documentation of sleep onset rapid eye movement sleep (SOREM). Another objective laboratory test is the maintenance of wakefulness test (MWT), which is a validated objective measure of the ability to stay awake for a defined time that measures the mean time latency of falling asleep during 4 to 5 sessions of trying to stay awake.12 Subjective validated scales included the Epworth Sleepiness Scale (ESS), which is a specialized, validated sleep questionnaire containing 8 items that ask for self-reported disclosure of the expectation of dozing in a variety of situations. Scores ≥ 10 indicate an abnormal result.14 The subjective outcome of elimination of cataplexy or reduction of the symptoms by > 50% from patient diaries was also included.

Secondary outcomes included quality of life using the short-form (SF-36) scale, Clinical Global Impression of change (CGI-C), and harms, including the type of adverse event and number of adverse events per treatment group.

Information Sources

Medical Subject Headings and text words related to SXB for narcolepsy with cataplexy were used to search MEDLINE (OVID interface, 1950 to October 2010), EMBASE (OVID interface, 1980 to October 2010), CINAHL (EBSCOhost interface, 1997 to October 2010), PsycInfo (Scholar’s Portal interface, 1806 to October 2010), and the Cochrane Central Register of Controlled Trials (Wiley interface, inception to October 2010). To supplement the search, we searched a clinical trial registry (www.clinicaltrials.gov), scanned the reference lists of included studies, searched the authors’ personal files, and contacted narcolepsy experts via email to identify further studies to be included, as well as the manufacturer of SXB (Jazz Pharmaceuticals).

Search

An experienced information specialist conducted all of the literature searches. The search strategy for the main electronic search (MEDLINE) is presented in the appendix; details on the other searches are available from the authors on request.

RESULTS

Study Selection

To ensure reliability, a training exercise was conducted prior to commencing the screening process. Two independent reviewers screened the search results for inclusion using a predefined relevance criteria form and obtained the full text of potentially relevant articles and screened them to determine inclusion, independently. Discrepancies at any stage were resolved by discussion or the involvement of a third reviewer. The level of agreement during screening was assessed using a κ statistic.15 We determined a priori that an acceptable level of agreement would be > 60%.15

Data Collection Process

A draft data extraction form was developed, piloted, and modified as necessary. Two reviewers assessed study quality and extracted all of the data using the standardized data extraction form, independently. Discrepancies were resolved by discussion or the involvement of a third reviewer.

Data Items

The extracted data included study characteristics (e.g., study period, sample size, geographic location, setting), participant characteristics (e.g., population, narcolepsy diagnosis, mean age, gender), and results from the primary and secondary outcomes.

Risk of Bias in Individual Studies and Across Studies

The risk of bias in individual studies was assessed using the Cochrane risk of bias tool.16 This tool consists of 6 items pertaining to sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. The risk of bias across studies was assessed using the outcome reporting bias criterion from the Cochrane risk of bias tool. Publication bias was to be assessed using funnel plots,17 but there were too few studies included in each meta-analysis to assess publication bias sufficiently.

Summary Measures

The summary measures were the relative risk (RR) and the mean difference (MD).

Synthesis of Results

The studies were plotted in a forest plot to examine heterogeneity visually. Statistical heterogeneity was examined using the I² and χ² statistics.18 Pooled estimates were derived using a random-effects model, and 95% CIs were derived based on a normal distribution.19 All analyses were conducted in Review Manager Version 5 (The Cochrane Collaboration, available from http://ims.cochrane.org/revman/download).
full-text articles were retrieved and examined for relevance, and 6 RCTs fulfilled the inclusion criteria along with 5 companion reports (Figure 1). Two articles were excluded at the full-text level of screening because they were not RCTs, and one study was excluded because it did not report any relevant outcomes. There was excellent agreement between reviewers at level 1 screening (κ = 0.92, 95% CI: 0.81 to 1.03), and lower agreement at level 2 screening, due to the small number of studies included at this level (κ = 0.46, 95% CI: −0.08 to 1.00).

Study and Patient Characteristics

Except for 2 studies, all studies were published after 2002 (Table 1). Most of the studies were conducted in clinics in the USA, Canada, and Europe. Duration of the RCTs ranged from 4-8 weeks, except for one study that lasted for 12 weeks. SXB at a dose range between 4.5 to 9 g/night was the dose examined in most of the studies. The number of patients ranged from 20 to 228, and the percentage of females ranged from 50% to 65% (Table 2). The diagnosis of narcolepsy was based on classical symptoms of narcolepsy and an MSLT showing ≥ 2 SOREM periods. MSLT in one study was conducted at home. All studies excluded patients with other sleep disorders. One study that assessed the effect of SXB on excessive daytime sleepiness did not include cataplexy as an enrollment criterion. No paper analyzed all of the clinical features of narcolepsy or performed all diagnostic tests.

![Figure 1 — Study flow](image)

---

**Table 1 — Study characteristics**

<table>
<thead>
<tr>
<th>Articles</th>
<th>Type of trial</th>
<th>n</th>
<th>Setting</th>
<th>Duration of trial in weeks (longest duration of FU)</th>
<th>Trial arms (dose in grams)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xyrem Int. Group 2005</td>
<td>RCT</td>
<td>228</td>
<td>42 sleep clinics in USA, Canada, and Europe</td>
<td>8 (8)</td>
<td>1) Sodium oxybate (4.5) 2) Sodium oxybate (6) 3) Sodium oxybate (9) 4) Placebo</td>
</tr>
<tr>
<td>Xyrem Int Group</td>
<td>RCT</td>
<td>55</td>
<td>14 clinical sites (location NR)</td>
<td>2 (2)</td>
<td>1) Sodium oxybate (3) 2) Sodium oxybate (4.5) 3) Sodium oxybate (6) 4) Sodium oxybate (7.5) 5) Sodium oxybate (9) 6) Placebo</td>
</tr>
<tr>
<td>U.S. Xyrem Multicenter Study Group, 2002</td>
<td>RCT</td>
<td>136</td>
<td>18 clinical sites (location NR)</td>
<td>4 (4)</td>
<td>1) Sodium oxybate (3) 2) Sodium oxybate (6) 3) Sodium oxybate (9) 4) Placebo</td>
</tr>
<tr>
<td>Black et al.</td>
<td>RCT</td>
<td>278 (222 ITT)</td>
<td>44 clinical sites in USA, Canada, and Europe</td>
<td>4 (8)</td>
<td>1) Sodium oxybate (6 titrated to 9)/modafinil 2) Modafinil/placebo 3) Sodium oxybate (6 titrated to 9)/placebo 4) Placebo/placebo</td>
</tr>
<tr>
<td>Lammers et al.</td>
<td>Cross-over RCT*</td>
<td>24</td>
<td>Leiden University Hospital, Netherlands</td>
<td>4 (4)</td>
<td>1) Sodium oxybate (60 mg/kg/night) 2) Placebo</td>
</tr>
<tr>
<td>Scrima et al.</td>
<td>Cross-over RCT*</td>
<td>20</td>
<td>Sleep Disorders Center, University of Arkansas for Medical Sciences</td>
<td>4 (12)</td>
<td>1) Sodium oxybate (50 mg/kg/night) 2) Placebo</td>
</tr>
</tbody>
</table>

*Data from crossover RCTs were abstracted prior to the groups crossing over to make the data consistent with the other RCTs. CR, companion report; FU, follow-up; Int, International; ITT, intention-to-treat; N, no; RCT, randomized controlled trial; U, unclear; USA, United States of America; Y, yes.
Risk of Bias
None of the included RCTs were assessed as having adequate sequence generation or allocation concealment (Table 3). All of the studies adequately blinded participants and addressed incomplete outcome data. Five of the 6 studies were free from selective outcome reporting.22 All of the studies scored unclear on other biases, as they involved private-industry funding. Four of the included studies were sponsored by the manufacturing company.20-23

Efficacy Meta-Analysis Results
Four studies reported cataplexy attacks,21,23,25,26 and 2 were included in the meta-analysis (Figure 2).25,26 The 2 other studies could not be included in the meta-analysis because the standard error was not reported and these data could not be obtained from the SXB manufacturer.21,23 The first study23 comprised 20 subjects, and the other study26 included 104 subjects. Compared with placebo, cataplexy attacks were statistically significantly decreased with 4.5 g/night of SXB (pooled results: MD: −8.5, 95% CI: −15.3 to −1.6). No statistical heterogeneity was observed, with an I² of 0% and a χ² p-value of 0.36 on the test.

Two studies reported the benefit of SXB on excessive daytime sleepiness which was measured by MWT and both were included in the meta-analysis (n = 101 and 91 subjects; Figure 3).20,22 At a dose of 9 g/night, SXB increased sleep latency significantly in the MWT compared to placebo (pooled results: MD: 5.18, 95% confidence interval, CI: 2.59-7.78). No statistical hetero-

Table 2—Patient characteristics

<table>
<thead>
<tr>
<th>Articles</th>
<th>N</th>
<th>% female</th>
<th>Age in years: mean (SD)</th>
<th>Weight in kg: mean (SD)</th>
<th>Narcolepsy diagnosis</th>
<th>Occurrence of cataplexy and/or sleep attacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xyrem Int. Group 2005</td>
<td>228</td>
<td>65.4</td>
<td>42.5 (range: 16 to 75)</td>
<td>87.5 (range: 46.3 to 170.6)</td>
<td>PSG, MSLT in past 5 years</td>
<td>Daily for at least 3 months</td>
</tr>
<tr>
<td>Xyrem Int. Group21</td>
<td>55</td>
<td>58.0</td>
<td>47.7 (NR)</td>
<td>80.5 (NR)</td>
<td>American Academy of Sleep Medicine criteria</td>
<td>5 or more per week</td>
</tr>
<tr>
<td>U.S. Xyrem Multicenter Study Group, 200223</td>
<td>136</td>
<td>58.1</td>
<td>43.1 (NR)</td>
<td>82.9 (NR)</td>
<td>PSG within previous 5 years</td>
<td>3 or more per week over a 2-week baseline period</td>
</tr>
<tr>
<td>Black et al.22</td>
<td>278 (ITT 222)</td>
<td>51.8</td>
<td>38.6 (14.6)</td>
<td>81.6 (17.4)</td>
<td>American Academy of Sleep Medicine criteria</td>
<td>Cataplexy not considered as enrollment criteria</td>
</tr>
<tr>
<td>Lammers et al.24</td>
<td>24</td>
<td>45.8</td>
<td>36 (NR)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Scrima et al.25</td>
<td>20</td>
<td>50.0</td>
<td>45 (20.6)</td>
<td>85.1 (23.3)</td>
<td>PSG, MSLT</td>
<td>10 or more on a daily log during a 2-week baseline period</td>
</tr>
</tbody>
</table>

ITT, intention-to-treat; MWT, multiple sleep latency test; NR, not reported; PSG, polysomnogram; SD, standard deviation.

Table 3—Risk of bias results

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Xyrem Int Group 2005</td>
<td>No</td>
<td>unclear</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>unclear</td>
</tr>
<tr>
<td>Xyrem Int Group21</td>
<td>No</td>
<td>unclear</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>unclear</td>
</tr>
<tr>
<td>U.S. Xyrem Multicenter Study Group, 200223</td>
<td>Unclear</td>
<td>unclear</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>unclear</td>
</tr>
<tr>
<td>Black et al.22</td>
<td>Unclear</td>
<td>unclear</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>unclear</td>
</tr>
<tr>
<td>Lammers et al.24</td>
<td>No</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Scrima et al.25</td>
<td>Unclear</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>

Figure 2—Mean weekly cataplexy attacks meta-analysis

Risk of Bias
None of the included RCTs were assessed as having adequate sequence generation or allocation concealment (Table 3). All of the studies adequately blinded participants and addressed incomplete outcome data. Five of the 6 studies were free from selective outcome reporting.22 All of the studies scored unclear on other biases, as they involved private-industry funding. Four of the included studies were sponsored by the manufacturing company.20-23

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Geneity was observed, with an I² of 0% (χ² p-value = 0.69). The above 2 studies used different protocols for the MWT. While the Xyrem International Study group used the 40-min version of the protocol, Black and Houghton used the 20-min version of the protocol. Theoretically, this may influence the sleep latencies obtained, particularly in patients who do not fall asleep very fast.

One of the included trials examined combination therapy trial of SXB and modafinil. The mean MWT values statistically different in the SXB monotherapy and modafinil monotherapy and combination therapy (SXB + modafinil) compared to placebo. The median ESS scores decreased significantly in a dose-related manner in the international trial in patients receiving SXB (4.5 g, 6 g, and 9 g/night) compared to placebo. Black and Houghton (combination-therapy trial) reported a significant reduction by 20% and 27% in the median ESS scores in the SXB monotherapy and SXB + modafinil combined therapy recipients, respectively. On the other hand, the ESS scores did not change significantly in the placebo or modafinil monotherapy recipients. However, we could not conduct a meta-analysis on the ESS score because the standard error was not reported, and these data could not be obtained from the SXB manufacturer.

Two studies reported the number of weekly sleep attacks and both were included in the meta-analysis with a total of 105 and 98 participants. Sleep attacks were statistically significantly decreased with 9 g/night of SXB compared to placebo (pooled results: mean difference, MD: −9.65, 95% confidence interval, CI: −17.72, −1.59); low heterogeneity was observed, with an I² of 13% (χ² p-value = 0.28).

Three studies reported the Clinical Global Impression of severity and Change (CGI) of “very much improved” and all were included in the meta-analysis (n = 106, 69, and 105). CGI scores significantly increased with 9 g/night of SXB (pooled results: mean difference, MD: 2.42, 95% confidence interval, CI: 1.77-3.32). No statistical heterogeneity was observed, with an I² of 0% and a p-value of 0.7 on the χ² test. In the combination-therapy trial “very much improved” was seen only in the arms SXB monotherapy and the combination therapy (SXB + modafinil), while the modafinil monotherapy arm did not differ from that in the placebo arm.

Two studies reported the percentage of REM sleep before and after SXB and were included in the meta-analysis with a sample size of 22 subjects and 20 subjects, but there were no significant differences between groups (pooled results: MD −0.49, 95% confidence interval, CI: −3.90, 2.92). No statistical heterogeneity was observed, with an I² of 0% (χ² p-value = 0.37).

**Harms Meta-Analysis Results**

All harms meta-analyses included SXB at 9 g/night versus placebo. Patients receiving SXB had statistically more adverse events versus placebo, including nausea (3 studies, relative risk...
Figure 6—Polysomnographic data for nocturnal sleep meta-analysis (REM)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sodium oxybate (55mg/kg) Mean</th>
<th>SD</th>
<th>Placebo Mean</th>
<th>SD</th>
<th>Total</th>
<th>Risk Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lammers 1993</td>
<td>13.4</td>
<td>6.8</td>
<td>11</td>
<td>15.5</td>
<td>12</td>
<td>-2.10 [-7.01, 2.81]</td>
<td></td>
</tr>
<tr>
<td>Scoril 1990</td>
<td>20.9</td>
<td>5.3</td>
<td>10</td>
<td>19.9</td>
<td>5.5</td>
<td>1.00 [-3.73, 5.73]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 21

Heterogeneity: Tau² = 0.00; Chi² = 0.79; df = 1 (P = 0.37); I² = 0%

Test for overall effect: Z = 0.28 (P = 0.78)

Figure 7—Adverse events: gastrointestinal/nausea

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sodium oxybate (9g) Events</th>
<th>Total</th>
<th>Placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black 2006</td>
<td>12</td>
<td>55</td>
<td>1</td>
<td>56</td>
<td>20.1%</td>
<td>12.22 [1.64, 90.80]</td>
<td></td>
</tr>
<tr>
<td>US Xyrem multicentre 2002</td>
<td>12</td>
<td>35</td>
<td>2</td>
<td>34</td>
<td>40.2%</td>
<td>5.83 [1.41, 24.13]</td>
<td></td>
</tr>
<tr>
<td>Xyrem int 2005</td>
<td>15</td>
<td>55</td>
<td>2</td>
<td>60</td>
<td>39.7%</td>
<td>8.18 [1.96, 34.17]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 145

Total events: 5

Heterogeneity: Tau² = 0.00; Chi² = 0.36; df = 2 (P = 0.83); I² = 0%

Test for overall effect: Z = 4.45 (P < 0.00001)

Figure 8—Adverse events: vomiting

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sodium oxybate (9g) Events</th>
<th>Total</th>
<th>Placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Xyrem multicentre 2002</td>
<td>5</td>
<td>35</td>
<td>0</td>
<td>34</td>
<td>17.3%</td>
<td>10.69 [0.61, 186.26]</td>
<td></td>
</tr>
<tr>
<td>Xyrem int 2005</td>
<td>8</td>
<td>55</td>
<td>4</td>
<td>60</td>
<td>62.7%</td>
<td>2.18 [0.76, 6.44]</td>
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</tbody>
</table>

Total (95% CI): 90

Total events: 4

Heterogeneity: Tau² = 0.13; Chi² = 1.11; df = 1 (P = 0.29); I² = 10%

Test for overall effect: Z = 1.69 (P = 0.09)

Figure 9—Adverse events: dizziness

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sodium oxybate (9g) Events</th>
<th>Total</th>
<th>Placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black 2006</td>
<td>7</td>
<td>53</td>
<td>0</td>
<td>56</td>
<td>50.8%</td>
<td>15.83 [0.93, 270.57]</td>
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<tr>
<td>US Xyrem multicentre 2002</td>
<td>4</td>
<td>35</td>
<td>0</td>
<td>34</td>
<td>49.2%</td>
<td>8.75 [0.49, 165.57]</td>
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</tbody>
</table>

Total (95% CI): 88

Total events: 0

Heterogeneity: Tau² = 0.00; Chi² = 0.08; df = 1 (P = 0.77); I² = 0%

Test for overall effect: Z = 2.39 (P = 0.02)

Figure 10—Adverse events: enuresis

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Sodium oxybate (9g) Events</th>
<th>Total</th>
<th>Placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black 2006</td>
<td>4</td>
<td>55</td>
<td>3</td>
<td>56</td>
<td>36.5%</td>
<td>1.36 [0.32, 5.79]</td>
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</tr>
<tr>
<td>US Xyrem multicentre 2002</td>
<td>12</td>
<td>35</td>
<td>2</td>
<td>34</td>
<td>37.2%</td>
<td>5.83 [1.41, 24.13]</td>
<td></td>
</tr>
<tr>
<td>Xyrem int 2005</td>
<td>13</td>
<td>55</td>
<td>1</td>
<td>60</td>
<td>26.3%</td>
<td>14.18 [1.92, 104.87]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 145

Total events: 6

Heterogeneity: Tau² = 0.72; Chi² = 4.17; df = 2 (P = 0.12); I² = 52%

Test for overall effect: Z = 2.15 (P = 0.03)

[RR]: 7.74, 95% CI: 3.2, 19.2; Figure 7), vomiting (2 studies, RR: 11.8, 95% CI: 1.6, 89.4; Figure 8), and dizziness (3 studies, RR: 4.3, 95% CI: 1.1, 16.4; Figure 9). Enuresis was not significantly different from placebo (2 studies, RR: 2.6, 95% CI: 0.8, 9.8; Figure 10), yet there was a trend towards favoring placebo versus SXB. In the US Xyrem study, 10 patients (7.4%) withdrew because of adverse events.21 Side effects were significantly more common in the SXB recipients compared to
placebo and included nausea, vomiting, dizziness, and urinary incontinence. In the international Xyrem trial, 21 (9.2%) patients withdrew due to adverse events; however, in that trial, there was no difference in the incidence of urinary incontinence between SXB and placebo recipients. In the combination therapy trial, adverse events were reported in 70% of placebo, 54% of modafinil monotherapy, 60% of SXB monotherapy, and 79% of SXB + modafinil combination therapy. In this latter trial 1, 2, 4, and 6 patients withdrew from the placebo, modafinil monotherapy, SXB monotherapy, and SXB + modafinil combination therapy, respectively, due to adverse events. Serious side effects were reported infrequently. Acute confusion was reported in one patient in the US trial at a dose of SXB 6 g/night. In the combination therapy trial, one patient developed a serious psychotic disorder related to narcissistic personality disorder.

**DISCUSSION**

This systematic review assessed the efficacy and safety of SXB in narcolepsy patients and included six randomized controlled trials. All patients were diagnosed as having narcolepsy based on established criteria. This is the first meta-analysis that we are aware of to assess the effect of SXB in narcolepsy patients. Due to the short follow-up (2 to 12 weeks), we were unable to investigate long-term efficacy and harms.

We found that SXB in all trials resulted in significant reduction in cataplexy attacks and EDS. SXB reduced the frequency of cataplexy in a dose-related manner compared to placebo. Two studies have demonstrated beneficial effects on cataplexy attacks even with a smaller dose of SXB (4.5 g/night). EDS was reduced and sleep latency increased when evaluated by MWT in the SXB arm compared to placebo. The improvement was dose-related; however, the benefits documented in the MWT were statistically significant only in the higher dose (9 g/night). The improvement in the EDS appeared after 8 weeks of treatment. Although SXB reduces the frequency of sleep attacks, it did not eliminate them completely. Surprisingly, in the study by Black and Houghton, modafinil monotherapy had no significant effect on sleep latency completely. Surprisingly, in the study by Black and Houghton, modafinil monotherapy had no significant effect on sleep latency, increased stage N1, increased stage shift, and reduced stage N3. Several studies have shown that nightly SXB improves subjective and objective measures of nocturnal sleep and sleep architecture, with robust increases in stage N3 and delta power. Two recent randomized trials have shown that SXB resulted in significant dose-related improvements in slow wave sleep, total sleep time, and a decrease in stage N1, wake after sleep onset, and nighttime awakenings. SXB is generally well tolerated, with mild-to-moderate side effects that are dose-related. There is a concern about a narrow margin between efficacy and toxicity of SXB. In general, the incidence of side effects increases with dose, and most side effects subside upon reducing the dose.

Long-term follow-up data on adverse events are limited. A 12-month extension study reported adverse events in 93% of patients, including dizziness, headache, nausea, urinary incontinence, viral infection, somnolence, and pain. Dizziness was the only adverse event that was statistically more common in the SXB group.

All of the trials included in this systematic review excluded patients with sleep disordered breathing. Therefore, caution is advised when treating narcoleptics with concurrent SDB, and physicians should confirm that patients with concurrent obstructive sleep apnea are compliant with positive airway pressure therapy before starting SXB.

We identified two review articles assessing the efficacy and tolerability of SXB in patients with narcolepsy. The authors did not conduct a systematic literature search or meta-analysis and included fewer trials than we do here. The findings of both reviews were consistent with the findings of this systematic review. Both reported improvement in cataplexy and daytime sleepiness and good tolerability of SXB. Evidence-based practice parameters of the American Academy of Sleep Medicine for the treatment of narcolepsy and other hypersonias of central origin considered SXB as an acceptable patient-care strategy that reflects a high degree of clinical certainty for cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy; our review supports this recommendation. For the treatment of hypnagogic hallucination and sleep paralysis, they considered the evidence as uncertain.

There are a number of limitations of this report. One limitation is the fact that the included studies have a relatively short follow-up period. Nevertheless, the effect of SXB in the assessed outcomes was obvious during the follow-up periods. Another limitation is the small sample sizes of the included trials. Limitations in the systematic review process include that it was limited to the English language; no unpublished trials were identified (although we did contact trial authors and searched for unpublished material), we could not obtain data for all the outcomes from the SXB manufacturer, and we were unable to formally assess for publication bias because too few trials were included in the meta-analyses.

On the basis of this review, it can be concluded that patients with narcolepsy on SXB have a significant reduction in cataplexy.
based on diaries and significant improvement in daytime sleepiness based on objective (MWT) and validated subjective (ESS) assessment methods. Reviewed data suggest that SXB is well tolerated in patients with narcolepsy, and most adverse events were mild to moderate in severity. The study raises further questions that need to be explored in the future including: the long-term efficacy and tolerability of SXB, the effect of SXB in patients with concurrent sleep disordered breathing, and the effect of different dosages on patients with milder form of narcolepsy.

REFERENCES


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DISCLOSURE STATEMENT

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