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Review Article

Gamma-hydroxybutyrate (GHB) for narcolepsy in adults: an updated systematic review and meta-analysis

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ABSTRACT

Background: Narcolepsy is a chronic and debilitating sleep disorder characterized by cataplexy and excessive daytime sleeping. Gamma-hydroxybutyrate (GHB) has been widely used to treat narcolepsy, and new findings have been published in recent years.
Objective: A meta-analysis was conducted to assess the efficacy and tolerability of GHB treatment in adults with narcolepsy.
Methods: A systematic search of PubMed, Cochrane, Embase, Web of Science, and clinical-trials.gov from inception to June 2018 was performed. Change in daily diaries and polysomnographic data of narcoleptic patients were defined as the efficacy outcomes. The tolerability and acceptability outcomes were the rates of adverse events and dropping out for adverse effects or other reasons.
Results: Fifteen randomized controlled trials involving 2104 participants were identified. GHB was found to improve cataplexy attacks ($P = 0.001$), subjective daytime sleepiness ($P < 0.0001$), daytime sleep latency ($P < 0.0001$), inadvertent naps/sleep attacks ($P < 0.00001$), effective rates (Clinical Global Impression of change) ($P < 0.00001$), hypnagogic hallucinations ($P = 0.004$), sleep paralysis ($P = 0.004$), stage 1 sleep ($P = 0.04$), slow wave sleep ($P = 0.003$), REM sleep ($P = 0.0006$), sleep shifts ($P = 0.005$), nocturnal awakenings ($P = 0.004$), quality of nocturnal sleep ($P < 0.00001$), chin muscle activity, and quality of life, but had no effect on stage 2 sleep ($P = 0.88$). GHB was less well tolerated than placebo because of side effects that occurred in a dose-dependent fashion (RR = 6.08; 95% CI = 2.18 to 16.97; $P = 0.0006$).
Conclusions: GHB was effective in improving narcolepsy-cataplexy and related symptoms in adults but was less well tolerated than placebo because of dose-dependent side effects.

1. Introduction

Narcolepsy is a chronic and debilitating sleep disorder that results from dysregulation of the sleep–wake cycle [1]. It is characterized by excessive daytime sleeping (EDS), cataplexy, sleep paralysis, hypnagogic or hypnopompic hallucinations, and disrupted nighttime sleep [2]. Cataplexy is considered to be the pathognomonic marker for narcolepsy, and EDS is the hallmark symptom that presents in all narcoleptic patients [3].

Narcolepsy is subcategorized into two types. Type 1 narcolepsy is characterized by EDS and cataplexy, while type 2 narcolepsy is characterized by EDS and the absence of cataplexy [4]. Narcolepsy causes extreme interference with nearly every aspect of life [2,5,6], resulting in an economic burden [7–10] and significant reductions in quality of life [9,11,12].

A diagnosis of narcolepsy is often apparent from clinical history and is confirmed by an overnight polysomnography (PSG) and a multiple sleep latency test (MSLT) [13]. Currently, there is no cure for narcolepsy, and the management of this disorder focuses on symptom control [14]. Sodium oxybate (SXB), a sodium salt of gamma-hydroxybutyrate (GHB), is approved by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) to treat cataplexy and EDS in narcoleptic adults with cataplexy [15–17]. Although a few review articles

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Abbreviations

CGI	Clinical Global Impression
CGI-C	Clinical Global Impression of change
CI	Confidence interval
EDS	Excessive daytime sleeping
EMA	European Medicines Agency
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration
FOSQ	Functional Outcomes of Sleep Questionnaire
GHB	Gamma-hydroxybutyrate
LMI	Long muscle activity index
MD	Mean difference
MeSH	Medical Subject Headings
MSLT	Multiple sleep latency test
MWT	Maintenance of wakefulness test
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
RCT	Randomized controlled trial
RR	Risk ratio
SF-36	Short form 36
SMI	Short muscle activity index
SSS	Stanford Sleepiness Scale
SWS	Slow wave sleep
SXB	Sodium oxybate

[14,17] have discussed this issue in the past, a number of new studies have been published in recent years. Therefore, our meta-analysis was conducted to evaluate the efficacy and tolerability of GHB in adults with narcolepsy based on latest scientific evidence. Outcome parameters such as cataplexy, daytime sleepiness, inadvertent naps, nocturnal awakenings, response rates, quality of sleep, PSG data, and side effects were identified and analyzed.

2. Methods

2.1. Data sources and search strategy

A systematic search of PubMed, Cochrane, Embase, and Web of Science databases from inception to June 2018 was performed to identify relevant available data sources. The search terms were (Narcolepsy or Cataplexy or "Paroxysmal Sleep") AND (Xyrem or GHB or "Gamma-hydroxybutyrate" or "γ-hydroxybutyric acid" or oxybate). Both Medical Subject Headings (MeSH) and free-text words were used to search PubMed. Only free-text words relating to SXB for narcolepsy were used to search the Cochrane, Embase, and Web of Science databases because of interface limitations. Details of the search strategies are presented in the Supplemental Table. Only studies in English were included in this investigation. To avoid omitting relevant trials, clinical trial registries (www.clinicaltrials.gov), conference abstracts, and reference lists of all identified related publications were also scanned.

2.2. Selection criteria

The inclusion criteria for our analyses were as follows: (i) randomized controlled trials (RCTs) with GHB or placebo taken regularly as a narcolepsy treatment; (ii) adults (≥16 years) with a clinical diagnosis of narcolepsy; and (iii) a clinical trial that reported complete efficacy outcome(s). When multiple studies reported different outcomes in a mutually exclusive way from the same cohort of populations, all reports meeting the inclusion criteria were included.

Exclusion criteria were as follows: (i) studies that compared two or more interventions with each other but did not contrast with placebo; (ii) reviews, animal studies, and duplicate or secondary analyses; or (iii) case reports, dissertations, or outcome data that were unavailable or incomplete.

2.3. Outcome measures

For efficacy analyses, outcomes included relief of EDS, cataplexy attacks, inadvertent naps/sleep attacks, sleep latencies, hypnagogic hallucinations, sleep paralysis, Clinical Global Impression of change (CGI-C), arousals, quality of nocturnal sleep, quality of life, muscle tone, and nocturnal PSG data. The continuous outcome was defined as the mean change from baseline to endpoint.

For feasibility analysis, the outcome measures were assessed by the number of adverse events per treatment group, the proportion of patients who prematurely terminated the study for any reason, and the proportion of dropouts because of side effects.

2.4. Data extraction and quality assessment

Two independent authors screened the titles and abstracts of each paper and verified that all potentially relevant trials fulfilled the inclusion criteria. Potential articles were then reviewed in full and verified for eligibility. Extracted data included the key characteristics of studies, therapy designs, and outcomes. The methodological quality of trials was assessed using the Risk of Bias Assessment Tool from the Cochrane Handbook for Systematic Reviews of Interventions [18]. Any discrepancies were resolved by discussion or following arbitration with a third reviewer if necessary.

2.5. Statistical analysis

All statistical analyses were conducted using RevMan 5.3 software (Cochrane Management System). We calculated standardized mean differences (SMDs) or mean differences (MDs) with 95% confidence intervals (CIs) for continuous outcomes, and risk ratios (RRs) with 95% CIs for dichotomous data. Statistical significance was defined as $P < 0.05$ unless otherwise stated. Meta-analyses were carried out on the intention-to-treat population when possible. Heterogeneity was evaluated with I^2 and χ^2 statistics [18]. When substantial heterogeneity for outcome data was detected ($I^2 > 50\%$ or $P < 0.10$), a random-effects model was used to calculate pooled estimates. Otherwise, a fixed-effect model was chosen.

3. Results

3.1. Study selection and characteristics

Overall, 346 records were identified through the initial database search (40 from PubMed, 114 from Embase, 74 from Cochrane, 51 from Web of Science, and 67 from clinical-trials.gov). After removing duplicates, there were 300 records. Of those, 266 were excluded based on independent screening of the titles and abstracts by two reviewers. Thirty-four full texts were then reviewed further for eligibility, and 15 RCTs fulfilled the selection criteria (Fig. 1).

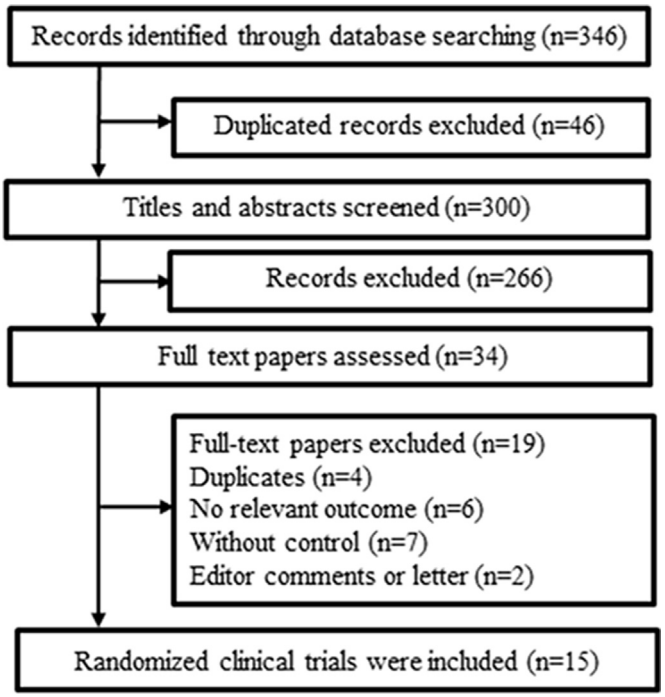

Fig. 1. Flowchart of study selection.

Table 1 summarizes the general characteristics of each included article. The 15 trials, published between 1989 and 2017, involved 2104 participants in total (computing patients from the same cohort as separate, in relation to different outcomes). The average age of patients was 34.56 years old (range 16–75 years). Sample sizes ranged from 20 to 228, with more females than males (61.68% versus 38.32%). The GHB dose ranged from 3.0 to 9.0 g, with treatment durations ranging from four to eight weeks. Twelve trials used parallel designs [3,19–29] while three used crossover designs [30–32]. Moreover, 12 out of 15 were multicentric trials [3,19–29], and three were unicentric [30–32].

3.2. Quality assessment and publication bias

The overall quality of included studies was rated as moderate using the Cochrane risk-of-bias method (Fig. S1). Inverted funnel plots of the included studies were generated for all evaluated comparisons, and these generally demonstrated symmetry around the vertical axis.

3.3. Efficacy outcomes

3.3.1. Cataplexy attacks

Cataplexy, which is considered pathognomonic for narcolepsy [23], is characterized by sudden, emotionally triggered episodes of muscle paralysis with preserved consciousness [13]. Five studies [19,21,28,30,31] reported cataplexy attacks and four of these [19,28,30,31] provided available data. Pooled analyses showed that patients receiving GHB therapy experienced a significant reduction in cataplexy attacks compared with those receiving placebo (SMD = −0.26; 95% CI = −0.42 to −0.11; P = 0.001), with low heterogeneity (I^2 = 0%; P = 0.43). The effect size was dose-dependent (3–4.5 g SMD = −0.16, 95% CI = −0.40 to 0.08, P = 0.19; 6 g SMD = −0.27, 95% CI = −0.56 to 0.02, P = 0.07; 9 g SMD = −0.42, 95% CI = −0.73 to −0.12, P = 0.006; Fig. 2a) but not time-dependent (four weeks (9 g) MD = −10.24, 95% CI = −17.32 to −3.16, P = 0.005; eight weeks (9 g) SMD = −10.31, 95% CI = −24.47 to 3.85, P = 0.15).

3.3.2. Subjective daytime sleepiness

Both the Epworth Sleepiness Scale (ESS) and the Stanford Sleepiness Scale (SSS) were included to evaluate the extent of sleepiness. Eight studies evaluated the efficacy of GHB for treatment of daytime sleepiness [19–23,29–31] and six provided specific data [19,20,23,29–31]. The data from five articles were converted for meta-analysis [19,23,29–31], while data in another study was not suitable for conversion and was excluded [20]. GHB therapy significantly improved subjective daytime sleepiness compared with placebo (SMD = −0.50, 95% CI = −0.72 to −0.27, P < 0.0001; I^2 = 53%, P = 0.02) whether or not symptoms included cataplexy (with cataplexy, SMD = −0.46, 95% CI = −0.70 to −0.23, P = 0.0001; without cataplexy, SMD = −0.86, 95% CI = −1.41 to −0.31, P = 0.002). In addition, these effects were dose-related (3–4.5 g SMD = −0.20, 95% CI = −0.52 to 0.12, P = 0.23; 6 g SMD = −0.46, 95% CI = −0.85 to −0.08, P = 0.02; 9 g SMD = −0.81, 95% CI = −1.06 to −0.56, P < 0.00001; Fig. 2b) and time-dependent (four weeks SMD = −0.33, 95% CI = −0.72 to 0.07, P = 0.10; and eight weeks SMD = −0.62, 95% CI = −0.83 to −0.40, P < 0.00001).

3.3.3. Objective daytime sleepiness (daytime sleep latency)

Five studies published data regarding daytime sleep latency [20,23,29,30,32]; however, data in the Black et al., 2016 study [23] was duplicated from Black & Houghton 2006 [20]. Mean daytime sleep latencies were measured using the maintenance of wakefulness test (MWT) or multiple sleep latency test (MSLT). Two RCTs used MSLT [30,32] and three used MWT [20,23,29]. GHB treatment significantly increased sleep latency (SMD = 0.39; 95% CI = 0.21 to 0.57; P < 0.0001; heterogeneity I^2 = 25%; P = 0.25) compared with placebo. Patients receiving a 9 g dose of GHB displayed a robust effect (SMD = 0.66; 95% CI = 0.38 to 0.95; P < 0.00001), whereas no statistical change was seen in patients receiving 4–4.5 g (SMD = 0.26; 95% CI = −0.04 to 0.56; P = 0.09) or 6 g (SMD = 0.12; 95% CI = −0.25 to 0.50; P = 0.52) GHB doses (Fig. 2c). Narcoleptic patients without cataplexy (SMD = 0.62; 95% CI = 0.08 to 1.15; P = 0.02) were more likely to experience a reduction in objective daytime sleepiness than patients with narcolepsy-cataplexy (SMD = 0.36; 95% CI = 0.17 to 0.56; P = 0.0003).

3.3.4. Inadvertent naps/sleep attacks

Data on the effectiveness of GHB on inadvertent naps/sleep attacks were available in four studies [20,29–31]. Two trials reported such data on a daily basis [30,31], while two trials used a weekly reporting basis [20,29]. The overall pooled effect size showed a significant decrease in inadvertent naps/sleep attacks in the treatment arm compared with the placebo (SMD = −0.41; 95% CI = −0.58 to −0.25; P < 0.00001; I^2 = 22%; P = 0.26), which was treatment duration dependent. The subgroup analysis that was conducted based on GHD dose illustrated that all treatment doses had a statistical advantage over placebo (4–4.5 g SMD = −0.26, 95% CI = −0.52 to −0.01, P = 0.04; 6 g SMD = −0.63, 95% CI = −1.00 to −0.25, P = 0.001; 9 g SMD = −0.48, 95% CI = −0.75 to −0.20, P = 0.0008).

3.3.5. Hypnagogic hallucinations

Four included articles investigated the effect of GHB therapy on hypnagogic hallucinations in patients with narcolepsy-cataplexy [19,28,30,31], but only two studies were included in the meta-analysis [28,30]. The overall pooled effect size showed a significant advantage of GHB over placebo in the treatment of hypnagogic hallucinations, with an SMD of −0.38 (95% CI = −0.63 to −0.12; P = 0.004) and low heterogeneity (I^2 = 0%; P = 0.40).

Table 1
Clinical characteristics and outcomes of included randomized controlled trials.

Study	Study design	Duration	Treatment Groups	Intervention vs placebo	Mean age	Female %	With- vs without cataplexy	Race(White/ Black/Asians/ other)	Sponsor	Outcomes
Scrima 1989 [31]	Randomized, Double-Blind, Placebo-Controlled, crossover, single center	29 days	GHB(50 mg/kg) vs placebo	20 vs 20	47.5	50%	20 vs 0	NR	Orphan Products Grant(FDA)	Cataplexy per day, sleep attacks per day, SSS, daytime naps, subjective nocturnal arousals, Subjective sleep onset latency, Subjective Total sleep time, hypnagogic hallucinations[b], sleep paralysis[b]; advert events[b], withdraws for advert event
Scrima 1990 [32]	Randomized, Double-Blind, Placebo-Controlled, crossover, single-center	29 days	GHB(50 mg/kg) vs placebo	20 vs 20	47.5	50%	20 vs 0	NR	Orphan Products Grant(FDA)	MSLT(Sleep latency, No. of REM naps, Sleep stages, Stage shifts); PSG(Total sleep time, No. of wakes, Stage 1, Stage 2, Stage 3, Stage 4, Delta, REM sleep, Stage shifts, Latency to Sleep),
Lammers 1993 [30]	Randomized, Double-Blind, Placebo-Controlled, crossover, single-center	4 weeks	SXB(60 mg/kg) vs placebo	24 vs 24	36	45.8%	24 vs 0	NR	Stichting Phoenix (non-profit educational organization)	Hypnagogic hallucinations, daytime sleep attacks, severity of subjective daytime sleepiness, cataplexy, awakenings at night, sleep latency, Mood ratings, global therapeutic impression; PSG(Stage 1, Stage 2, Stage 3 + 4, Stage REM, Sleep stage shifts); advert events
Xyrem 2002 [19]	Randomized, Double-Blind, Placebo-Controlled, Parallel, Multicenter	4 weeks	SXB(3 g) vs SXB(6 g) vs SXB(9 g) vs placebo	34 vs 33 vs 35 vs 34	43.1	58.1%	136 vs 0	124 vs 9 vs 1 vs 2	Orphan Medical, Inc	ESS, CGI-c, Cataplexy[a], hypnagogic hallucinations[b], inadvertent naps/sleep attacks[b], nocturnal awakenings[b], sleep paralysis[b]; adverse events
Xyrem 2005a [29]	Randomized, Double-Blind, Placebo-Controlled, Parallel, Multicenter	8 weeks	SXB(4.5 g) vs SXB(6 g) vs SXB(9 g) vs placebo	64 vs 58 vs 47 vs 59	40.5	65.4%	228 vs 0	196 vs 25 vs 2 vs 4	Orphan Medical, Inc	ESS, MWT, weekly inadvertent naps/sleep attacks, CGI- C; advert events[b], withdraws for advert event
Xyrem 2005b [28]	Randomized, Double-Blind, Placebo-Controlled, Parallel, Multicenter	8 weeks	SXB(4.5 g) vs SXB(6 g) vs SXB(9 g) vs placebo	64 vs 58 vs 47 vs 59	40.5	65.4%	228 vs 0	196 vs 25 vs 2 vs 4	Orphan Medical, Inc	Hypnagogic hallucinations, sleep paralysis, Cataplexy[a]; advert events, withdraws for advert event, withdraws for any reason
Weaver 2006 [27]	Randomized, Double-Blind, Placebo-Controlled, Parallel, Multicenter	8 weeks	SXB(4.5 g) vs SXB(6 g) vs SXB(9 g) vs placebo	64 vs 58 vs 47 vs 59	40.5	65.4%	228 vs 0	196 vs 25 vs 2 vs 4	Orphan Medical, Inc	FOSQ; advert events[b], withdraws for advert event[b]
Black 2010 [21]	Randomized, Double-Blind, Placebo-Controlled, Parallel, Multicenter	8 weeks	SXB(4.5 g) vs SXB(6 g) vs SXB(9 g) vs placebo	64 vs 58 vs 47 vs 59	40.5	65.4%	228 vs 0	196 vs 25 vs 2 vs 4	Jazz Pharmaceuticals, Inc	Cataplexy attacks[b], ESS[b], MWT[b], quality of life[b]; PSG(Sleep Latency[a], Total Sleep Time[a], nocturnal awakenings[a], Wake after Sleep Onset[a], Stage 1[a], Stage 2[a], Stage 3+4[a], Sleep Stage Shifts[a], Delta Power[a], NREM Sleep, REM Sleep); advert events[b], withdraws for advert event[b]

(*continued on next page*)

Table 1 (*continued*)

Study	Study design	Duration	Treatment Groups	Intervention vs placebo	Mean age	Female %	With- vs without cataplexy	Race(White/ Black/Asians/ other)	Sponsor	Outcomes
Bogan 2016 [24]	Randomized, Double-Blind, Placebo-Controlled, Parallel, Multicenter	8 weeks	SXB(4.5 g) vs SXB(6 g) vs SXB(9 g) vs placebo	64 vs 58 vs 47 vs 59	40.5	65.4%	228 vs 0	196 vs 25 vs 2 vs 4	Jazz Pharmaceuticals, Inc	SF-36
Roth 2017 [26]	Randomized, Double-Blind, Placebo-Controlled, Parallel, Multicenter	8 weeks	SXB(4.5 g) vs SXB(6 g) vs SXB(9 g) vs placebo	64 vs 58 vs 47 vs 59	40.5	65.4%	228 vs 0	196 vs 25 vs 2 vs 4	Jazz Pharmaceuticals, Inc	Quality of nocturnal sleep; PSG(Stages N2/3/REM to Stage N1/Wake, Stage N2/3 to Stage N1/Wake, REM to Stage N1/ Wake)
Mayer 2017 [25]	Randomized, Double-Blind, Placebo-Controlled, Parallel, Multicenter	8 weeks	SXB(4.5 g) vs SXB(6 g) vs SXB(9 g) vs placebo	34 vs 33 vs 22 vs 27	40.3	62.9%	116 vs 0	90 vs 13 vs 1 vs 1	UCB Pharma, Brussels	PSG (sleep stages N1 + N2, sleep stage N3, REM), SMI, LMI
Black 2006 [20]	Randomized, Double-Blind, Placebo-Controlled, Parallel, Multicenter	8 weeks	SXB(6 g) vs SXB(9 g) vs placebo	50 vs 50 vs 55	38.2.	52.4%	46 vs 59	90 vs 13 vs 1 vs 1	Orphan Medical Inc	MWT, Weekly Inadvertent Naps/Sleep Attacks, CGI-c, ESS[a]; withdraws for advert event, advert events[b]
Black 2009 [22]	Randomized, Double-Blind, Placebo-Controlled, Parallel, Multicenter	8 weeks	SXB(6 g) vs SXB(9 g) vs placebo	50 vs 50 vs 55	38.2	52.4%	46 vs 59	90 vs 13 vs 1 vs 1	Jazz Pharmaceuticals, Inc	MWT[b], ESS[b]; PSG (Total sleep time[a], Total non-REM sleep[a], Total REM sleep[a], Stage 1[a], Stage 2[a], Stage 3 and 4[a], Delta power[a], Nocturnal awakenings[a]); advert events[b], withdraws for advert event
Black 2016 [23]	Randomized, Double-Blind, Placebo-Controlled, Parallel, Multicenter	8 weeks	SXB(9 g) vs placebo	50 vs 55	38.2	52.4%	46 vs 59	90 vs 13 vs 1 vs 1	Jazz Pharmaceuticals, Inc	MWT, ESS, CGI-c; advert events
Dauvilliers 2017 [3]	Randomized, Double-Blind, Placebo-Controlled, Parallel, Multicenter	8 weeks	SXB(9 g) vs placebo	50 vs 55	38.2	52.4%	46 vs 59	90 vs 13 vs 1 vs 1	Jazz Pharmaceuticals, Inc	PSQI; PSG(Stages 2/3/REM to Stage N1/Wake, Stages REM to Stage N1/Wake, Stage N1/Wake to Stage REM)

Abbreviations: CGI, Clinical Global Impression-changes; ESS, Epworth Sleepiness Scale; FDA, Food and Drug Administration; FOSQ, Functional Outcomes of Sleep Questionnaire; GHB, gamma-hydroxybutyrate; LMI, long (>0.5 s) muscle activity indices; MWT, maintenance of wakefulness test; NR, not reported; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; SF-36, short form 36 (health survey questionnaire); SMI, short(<0.5 s) muscle activity indices; SSS, Stanford Sleepiness Scale; SXB, sodium oxybate.

[a] = Reported data are unsuitable for meta-analysis as they lack common statistical reference.

[b] = No specific data can be extract.

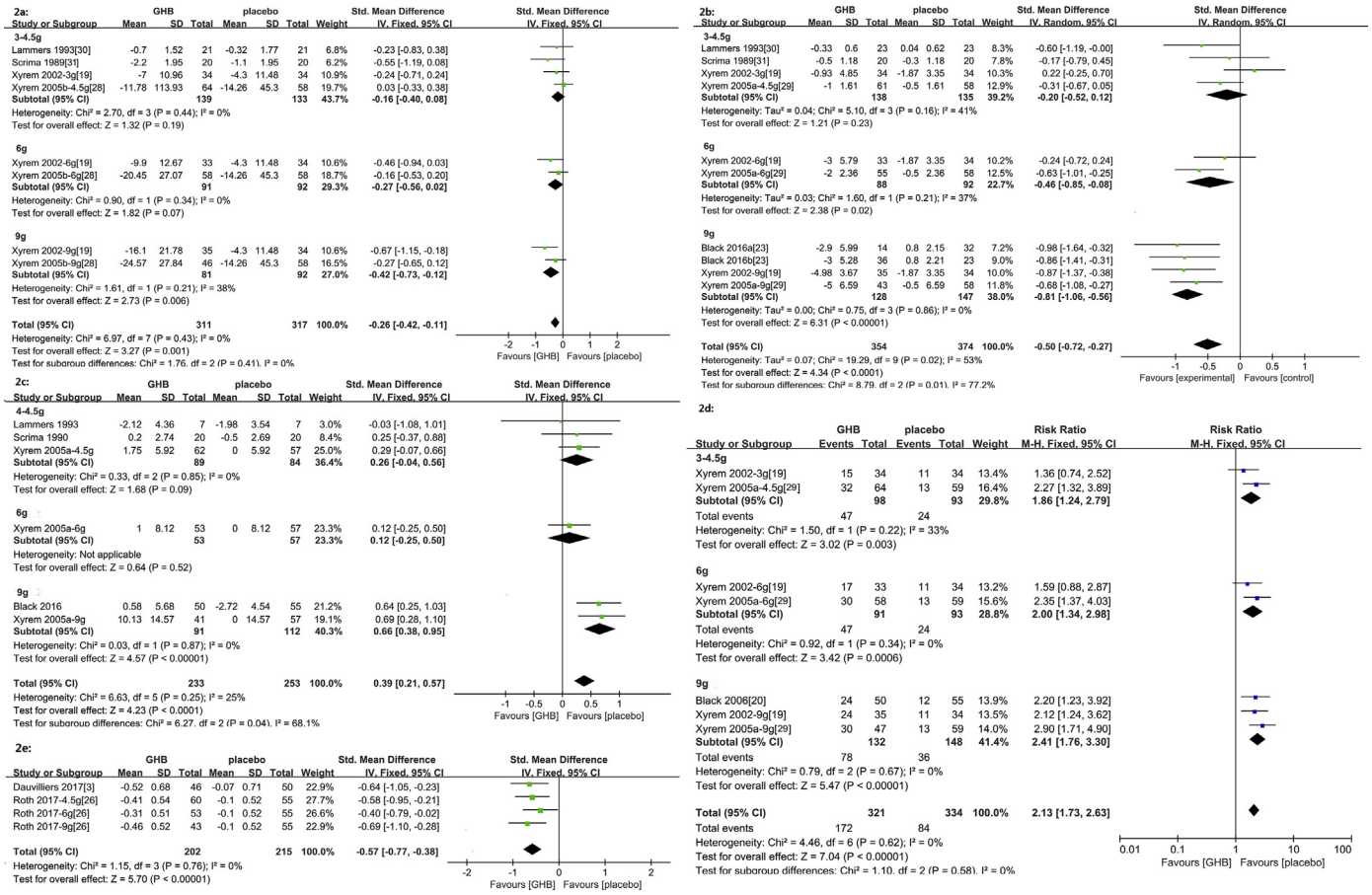

Fig. 2. a. Subgroup analysis of GHB in the treatment of cataplexy attacks based on the dose. b. Subgroup analysis of GHB in the treatment of subjective daytime sleepiness based on the dose. c. Subgroup analysis of GHB in the treatment of objective daytime sleepiness(daytime sleep latency) based on the dose. d. Subgroup analysis of effective rate (CGI-c) based on the GHB dose. e. Effect of GHB in nocturnal sleep quality compared with placebo.

3.3.6. Sleep paralysis

Although three articles referred to sleep paralysis [19,28,31], only one study was included in the current analysis [28], and this suggested that a significant improvement in sleep paralysis only occurred at a 6 g dose of GHB ($P = 0.005$).

3.3.7. Clinical Global Impression of severity and change

Effective rates were defined as the proportion of patients who qualified their condition as "much improved" or "very much improved" as measured by the Clinical Global Impression of Severity and Change (CGI) scale. Four articles reported the effectiveness of GHB using the CGI scale [19,20,23,29], but the data in Black et al., 2016 [23] was duplicated from Black & Houghton 2006 [20]. Compared with placebo, GHB-treated patients showed a significantly higher treatment effectiveness rate (RR = 2.13; 95% CI = 1.73 to 2.63; $P < 0.00001$; heterogeneity $I^2 = 0\%$; $P = 0.51$), in a dose-dependent (3–4.5 g RR = 1.86, 95% CI = 1.24 to 2.79, $P = 0.003$; 6 g RR = 2.00, 95% CI = 1.34 to 2.98, $P = 0.0006$; 9 g RR = 2.41, 95% CI = 1.76 to 3.30; $P < 0.00001$; Fig. 2d) and time-dependent (four weeks RR = 1.69, 95% CI = 1.22 to 2.36, $P = 0.002$; and eight weeks RR = 2.42; 95% CI = 1.84 to 3.18; $P < 0.00001$) fashion. No significantly effective rates were observed in type-2 narcolepsy (type-1: RR = 2.18; 95% CI = 1.76 to 2.71; $P < 0.00001$; type-2: RR = 1.6; 95% CI = 0.73 to 3.52; $P = 0.24$).

3.3.8. Quality of nocturnal sleep

Sleep quality was reported in two studies [3,26] and was evaluated using the four-point Likert-type scale or Pittsburgh Sleep Quality Index (PSQI). Results from the two trials showed that GHB therapy significantly improved patient-reported sleep quality relative to placebo (SMD = −0.57; 95% CI = −0.77 to −0.38, $P < 0.00001$; heterogeneity $I^2 = 0\%$; $P = 0.76$; Fig. 2e).

3.3.9. Muscle tone

To date, only one study has examined the effectiveness of SXB on chin muscle tone in sleep in patients with narcolepsy-cataplexy [25]. The intervention lasted for eight weeks and resulted in a dose- and sleep-stage-dependent effect on muscle activity. GHB, especially at high doses (9 g), significantly decreased the short muscle activity index (SMI) and long muscle activity index (LMI) in REM and light sleep stages, while low doses of GHB (4.5 g and 6 g) may increase short muscle activity in slow wave sleep (SWS). However, because conclusions were based on just one study, further investigation is recommended.

3.3.10. Quality of life

The change in quality of life was measured using the SF-36 and Functional Outcomes of Sleep Questionnaire (FOSQ). The nocturnal administration of GHB within eight weeks in patients with narcolepsy-cataplexy was associated with improved SF-36 [24] and total FOSQ scores [27] in a dose-dependent manner, and the 9 g/night dose provided the greatest effect size. The significant improvement domains included vitality, general health, and physical and social functioning in the SF-36, and vigilance, activity level, general productivity, and social outcome subscales in the FOSQ.

3.4. Diary- and PSG-based nighttime sleep features

3.4.1. Sleep stages

3.4.1.1. NREM sleep. Regarding the effectiveness of GHB on NREM sleep, extractable data were available from three studies [25,30,32], while another two studies presented non-adjustable data [21,22]. The reported pattern of changes in nocturnal sleep included a decreased amount of stage 1 sleep (MD = −4.40; 95% CI = −8.64 to −0.16, $P = 0.04$) and an increased amount of SWS (SMD = 0.62; 95% CI = 0.21 to 1.03, $P = 0.003$; Fig. 3a) in a dose-dependent (4–4.5 g SMD = 0.41, 95% CI = 0.08 to 0.73, $P = 0.01$; 6 g SMD = 0.50, 95% CI = −0.02 to 1.02, $P = 0.06$; 9 g SMD = 1.61, 95% CI = 0.95 to 2.26, $P < 0.00001$) and time-dependent (four weeks SMD = 0.57, 95% CI = 0.15 to 0.98, P = 0.008; eight weeks SMD = 0.77, 95% CI = 0.04 to 1.51, $P = 0.04$) manner. In contrast, no change was observed in the duration of stage 2 sleep (MD = 0.32; 95% CI = −3.69 to 4.34, $P = 0.87$).

3.4.1.2. REM sleep. Extractable data regarding REM sleep were available from four articles [21,25,30,32]. Two studies presented data as minutes with treatment durations of eight weeks [21,25] and two presented data as percentages with treatment durations of four weeks [30,32]. The pooled results revealed a positive effect of GHB treatment on REM sleep (SMD = −0.38; 95% CI = −0.60 to −0.17, $P = 0.0006$; Fig. 3b). However, a meta-analysis based on the change of REM percentage did not show a significant effect (SMD = −0.07; 95% CI = −0.50 to 0.35, $P = 0.74$), while analysis based on minutes showed a statistically significant reduction in REM duration (SMD = −0.49; 95% CI = −0.75 to −0.24, $P = 0.0001$).

3.4.2. Stage shifts

Five of the included studies assessed stage shifts [3,21,26,30,32]. Data from one study were not convertible and the study was thus excluded from the current analysis [21]. A significantly greater reduction from baseline was observed in the number of total sleep shifts in groups treated with GHB compared with the placebo group (MD = −10.47; 95% CI = −17.72 to −3.22, $P = 0.005$), with low heterogeneity ($I^2 = 0\%$; $P = 0.39$). According to the two most recent studies [3,26], treatment with GHB significantly decreased the shifts from stages N2/3/REM to stage N1/Wake (MD = −3.36; 95% CI = −5.67 to −1.05, $P = 0.004$; Fig. 3c) and from REM stage to Stage N1/Wake (MD = −3.99; 95% CI = −5.65 to −2.34, $P < 0.00001$; Fig. 3d) compared with placebo.

3.4.3. Nocturnal awakenings

Six articles investigated the effect of GHB on nocturnal awakenings [19,21,22,30–32], but only three of them provided data suitable for extraction [30–32]. The number of awakenings per night was measured by PSG (objective awakenings) or daily diaries (subjective awakenings). Meta-analysis showed a significant reduction (SMD = −0.53; 95% CI = −0.89 to −0.17; $P = 0.004$; heterogeneity $I^2 = 0\%$; $P = 0.84$) in both objective nocturnal awakenings (SMD = −0.65; 95% CI = −1.29 to −0.01; $P = 0.05$) and subjective nocturnal awakenings (SMD = −0.47; 95% CI = −0.91 to −0.03; $P = 0.03$) in patients treated with GHB.

3.5. Acceptability outcomes

3.5.1. Adverse events

Compared with placebo treatment, patients receiving GHB treatment may experience more side effects such as headache, nausea, vomiting, dizziness, and enuresis. In our analysis, we calculated the data regarding nausea and vomiting (RR = 6.50; 95% CI = 3.71 to 11.39; $P < 0.00001$), dizziness (RR = 4.76; 95% CI = 2.57 to 8.80; $P < 0.00001$), and enuresis (RR = 2.33; 95% CI = 1.25 to 4.34; $P = 0.008$), and found that adverse events were significantly more common in GHB recipients than in the placebo group. In addition, data regarding nausea and vomiting (3–4.5 g RR = 2.30, 95% CI = 0.74 to 7.19, $P = 0.15$; 6 g RR = 5.21, 95% CI = 1.87 to 14.52, $P = 0.002$; 9 g RR = 11.05, 95% CI = 4.56 to 26.80, $P < 0.00001$) and enuresis (3–4.5 g RR = 1.32, 95% CI = 0.39 to 4.47, $P = 0.65$; 6 g RR = 2.47, 95% CI = 0.87 to 7.01, $P = 0.09$; 9 g RR = 3.18, 95% CI = 1.13 to 8.97, $P = 0.03$) showed dose dependency.

3.5.2. Withdrawals

There were significantly higher rates of dose-related withdrawals caused by adverse events in groups treated with GHB (RR = 6.08; 95% CI = 2.18 to 16.97; $P = 0.0006$; heterogeneity $I^2 = 5\%$; $P = 0.37$; 4–4.5 g RR = 0.88, 95% CI = 0.06 to 13.80, $P = 0.93$; 6 g RR = 3.81, 95% CI = 0.44 to 33.12, $P = 0.23$; 9 g RR = 10.11, 95% CI = 2.43 to 42.09, $P = 0.001$; Fig. 4). Similarly, moderately higher rates of withdrawal for any reason were observed in the treatment group (RR = 2.20; 95% CI = 1.31 to 3.71; $P = 0.003$; heterogeneity $I^2 = 0\%$; $P = 0.59$).

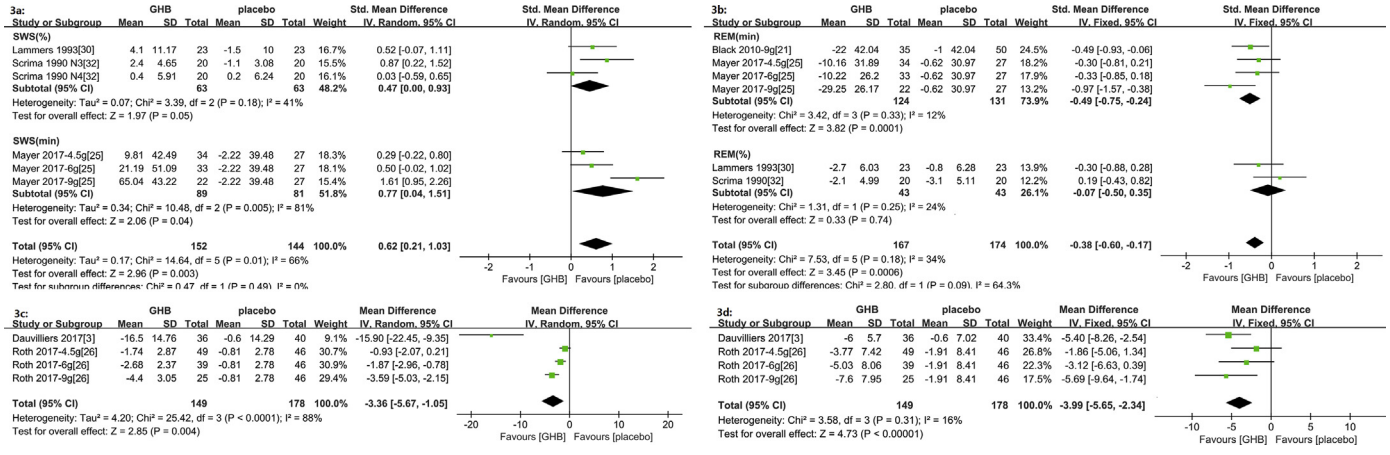

Fig. 3. a. Effect of GHB in the treatment of SWS compared with placebo. b. Effect of GHB in the treatment of REM sleep compared with placebo. c. Effect of GHB in the treatment of stage shifts from stages N2/3/REM to stage N1/Wake. d. Effect of GHB in the treatment of stage shifts from stage REM to Stage N1/Wake.

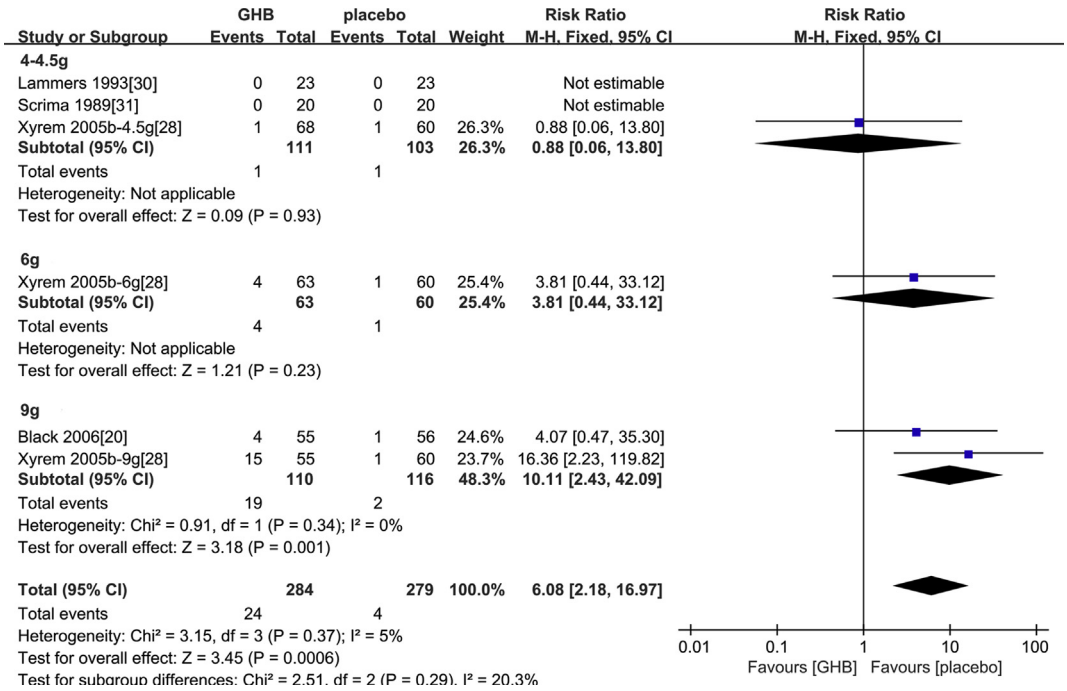

Fig. 4. Withdrawals for adverse events between GHB and placebo groups.

4. Discussion and conclusions

A valuable and relatively complete picture of the efficacy, acceptability, and tolerability of GHB treatment for adults with narcolepsy is presented in our systematic review. Overall, we identified 15 published trials comparing GHB with placebo, involving a total of 2104 narcolepsy patients. Amongst the outcomes that could be analyzed quantitatively, GHB was found to improve narcolepsy-cataplexy and related symptoms in adults. We also found that the effects of GHB on many aspects of narcolepsy were dose- and/or time-dependent. However, patients receiving GHB treatment were more likely to experience side effects such as dizziness, enuresis, and nausea or vomiting, and this resulted in dose-dependent higher rates of withdrawal.

Because cataplexy and excessive sleepiness are the hallmark symptoms of narcolepsy, we included all relevant studies in our meta-analysis, which was different from previous review articles [14,17]. Both subjective and objective daytime sleepiness were investigated. Our meta-analysis verified the role of GHB in improving cataplexy attacks and daytime sleepiness in narcolepsy patients, and its effect size was dose-dependent. We found that only treatment with 9 g/night resulted in a significant reduction of both cataplexy and objective daytime sleepiness, while other sub-therapeutic doses of GHB did not achieve an effective treatment effect. It is worth noting that the effect of GHB on cataplexy at a 6 g dose was close to statistically significant ($P = 0.07$), and so it may have potential therapeutic value, but its efficacy needs to be further verified. In addition, our pooled data did not show a time-dependent reduction in cataplexy attacks, with the greatest reduction achieved at four weeks of 9 g/night GHB treatment. Consistent with previous studies, a 6–9 g dose of GHB can significantly improve subjective daytime sleepiness.

Although previous review articles have investigated GHB treatment for narcolepsy, the most recent review was published in 2012, and since then five related studies have been published. From the updated pooled data analysis in the present study, we further confirmed the effect of GHB on improving subjective daytime sleepiness and SWS. It is noteworthy that the updated results also support the role of GHB in improving sleep shifts and REM sleep, which was not a statistically significant result in the previous review. In addition, data for different doses of GHB were included as mutually exclusive data in the current study, and a large number of subgroup analyses were conducted to investigate the dose- and time-dependent relationships of GHB in the treatment of cataplexy and related symptoms. We also included new data analyses of the quality of nocturnal sleep, hypnagogic hallucinations, sleep paralysis, muscle tone, objective awakenings (PSG), and adverse effects outcomes (withdrawals). All of these findings were closely correlated with clinical parameters and are therefore important for clinicians and patients to consider when making appropriate treatment decisions.

Moderately higher rates of dose-dependent adverse events and withdrawals due to side effects occurred with GHB treatment compared with placebo. The margin between efficacy and toxicity in GHB treatment is a critical issue for narcolepsy patients. Our analysis revealed that when the treatment dose did not exceed 6 g, there were no significant differences in the number of enuresis and withdrawal events between the treatment and placebo groups. When considering combined efficacy, GHB seemed to have a therapeutic effect on narcolepsy and related symptoms and was generally well tolerated. However, many studies reported that a 9 g/night dose of GHB provided the greatest effect size, so the balance of benefits and harms must be estimated when making clinical decisions for patients with narcolepsy.

Given the limitations of currently available clinical studies and the variability in study settings, our ability to draw definite and comprehensive conclusions on GHB treatment for narcolepsy was limited. In addition, the average treatment duration of included trials was not adequate to show long-term effects or the maximal response of GHB therapy in narcolepsy, and this may hinder our understanding of the role of GHB treatment of narcolepsy. Further robust and well-designed RCTs with larger sample sizes, rational

dosages, and adequate intervention durations are urgently needed.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.06.017.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2019.06.017.

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