Clarithromycin in γ-aminobutyric acid–related hypersomnolence: A randomized, crossover trial

Lynn Trotti, *Emory University*
Prabhjyot Saini, *Emory University*
Donald Bliwise, *Emory University*
Amanda Freeman, *Emory University*
Andrew Jenkins, *Emory University*
David Rye, *Emory University*

Copyright information:

Clarithromycin in GABA-related Hypersomnolence: A Randomized, Crossover Trial

Lynn Marie Trotti, MD, MSc[1],[*], **Prabhjyot Saini, MSc**[1], **Donald L. Bliwise, PhD**[1], **Amanda A. Freeman, PhD**[1], **Andrew Jenkins, PhD**[2], and **David B. Rye, MD, PhD**[1]

[1]Department of Neurology & Emory Sleep Center, Emory University School of Medicine

[2]Department of Anesthesia, Emory University School of Medicine

Abstract

Objective—Some central hypersomnolence syndromes are associated with a positive allosteric modulator of GABA-A receptors in cerebrospinal fluid. Negative allosteric modulators of GABA-A receptors, including clarithromycin, have been reported to reduce sleepiness in these patients. We sought to systematically assess the effects of clarithromycin on objective vigilance and subjective sleepiness.

Methods—This was a five-week, randomized, placebo-controlled, double-blind, crossover trial of clarithromycin 500 mg with breakfast and lunch, in patients with hypersomnolence syndromes (excluding narcolepsy with cataplexy) and evidence for abnormal cerebrospinal fluid potentiation of GABA-A receptors. The study occurred at a university-affiliated medical center. The primary outcome measure was median reaction time on the psychomotor vigilance task (PVT) at week 2 in each condition. Secondary outcomes included the Epworth Sleepiness Scale, Stanford Sleepiness Scale, Functional Outcomes of Sleep, Pittsburgh Sleep Quality Index, the SF-36, and additional PVT measures.

Results—Twenty-three patients began treatment. Three patients dropped out, and final analyses were performed on twenty complete cases. Median reaction time was not significantly different between clarithromycin and placebo. Subjective measures of sleepiness were significantly improved on clarithromycin versus placebo. Altered taste perception occurred, but was the only side effect more common on clarithromycin than placebo. No serious adverse events occurred.

[*]Corresponding Author: 1841 Clifton Rd Ne, Atlanta, GA 30329, Lbecke2@emory.edu, 404-728-4752 (phone), 404-712-8145 (fax).

Interpretation—Subjective sleepiness, but not psychomotor vigilance, improved during a two-week course of clarithromycin. Although additional studies are needed, this suggests that clarithromycin may be a reasonable treatment option in patients with treatment-refractory hypersomnolence. This trial was registered at clinicaltrials.gov (NCT01146600) and supported by the American Sleep Medicine Foundation.

Introduction

The central nervous system (CNS) hypersomnias manifest as pathologic daytime sleepiness that persists despite sufficient sleep time and in the absence of nocturnal sleep pathology. They include disorders such as idiopathic hypersomnia and narcolepsy. They result in substantial morbidity and impaired quality of life.[1–5] While there are FDA-approved treatments available for narcolepsy, no therapeutic agent has been approved for idiopathic hypersomnia. In patients with idiopathic hypersomnia, consensus opinion recommends the off-label use of wake-promoting medications such as modafinil, [6] but these are frequently inadequate to control symptoms [7–9] and clinical trial data are scarce. At the time this study was initiated, there were no published randomized, controlled trials evaluating any wake promoting medication for idiopathic hypersomnia, although two trials of modafinil including idiopathic hypersomnia patients have recently been published. [10, 11]

Recent work has demonstrated that many CNS hypersomnia patients have an endogenous, positive allosteric modulator of GABA-A receptors in their cerebrospinal fluid (CSF), which enhances inhibitory chloride currents when applied in combination with GABA in vitro.[5] This effect is seen in patients with a variety of CNS hypersomnia syndromes, including those with narcolepsy without cataplexy, those with idiopathic hypersomnia with or without long sleep time, and those with reported sleepiness despite long habitual sleep times and normal diagnostic testing (i.e, Multiple Sleep Latency Test, MSLT). Because this abnormality is seen across several different hypersomnia diagnoses, we classify patients as having "GABA-related hypersomnia" if they are diagnosed with a CNS hypersomnia syndrome and demonstrate the presence of this CSF biomarker. Negative allosteric modulators of the GABA-A receptor, such as flumazenil, reverse the effect of this endogenous modulation in vitro and may improve vigilance in vivo.[5] The macrolide antibiotic clarithromycin also exhibits negative allosteric modulation of GABA-A receptors in vitro and the majority of patients with GABA-related hypersomnia demonstrate improved subjective sleepiness on clarithromycin in clinical practice.[12] The current trial systematically evaluated for objective and subjective improvements in sleepiness using clarithromycin in patients with GABA-related hypersomnia. We also sought to determine the safety and tolerability of a two week course of clarithromycin in this clinical population.

Methods

This was a randomized, double-blind, placebo-controlled, crossover study conducted at a single site, the Emory Sleep Center in Atlanta, Georgia. The majority of subjects were recruited from the Emory patient population. The study was registered at clinicaltrials.gov (NCT01146600), and potential subjects who contacted us based on this registration information were also eligible for participation if they met the inclusion/exclusion criteria.

All patients carried diagnoses of GABA-related hypersomnia, defined as the presence of both: 1) abnormal potentiation of GABA-A receptors on an in vitro assay of their spinal fluid, defined as 55% or greater;[5] and 2) a clinical diagnosis of a hypersomnia syndrome. Because idiopathic hypersomnia and narcolepsy without cataplexy can only be objectively differentiated based on number of sleep onset REM periods,[13] a diagnostic feature that may not be stable over time,[14,15] we included both patients with idiopathic hypersomnia and patients with narcolepsy without cataplexy. In light of the known role of hypocretin loss in patients with narcolepsy with cataplexy, patients with cataplexy or abnormal hypocretin values were excluded. Idiopathic hypersomnia and narcolepsy without cataplexy were defined following International Classification of Sleep Disorders, 2nd edition (ICSD-2) criteria. The ICSD-2 cutoff of a mean sleep latency of < 8 minutes has been shown to exclude a substantial proportion of patients who otherwise meet clinical criteria for a hypersomnolence syndrome.[8, 16] Therefore, we also prespecified inclusion of patients with hypersomnia symptoms and habitually long sleep times (greater than 70 hours per week) who met clinical but not Multiple Sleep Latency Test criteria for an ICSD-2 hypersomnia syndrome. This latter group of subjects was referred to as having a diagnosis of "subjective hypersomnia" (similar to ref[17]). Those subjects taking wake-promoting medications at the time of enrollment (n = 14) were allowed to continue on these medications for the duration of the study. Enrollment required stable dosing of any wake-promoting medications for at least 30 days prior to enrollment and throughout the five week study period.

Subjects had to be age 18 or older. Subjects could not have contraindications to clarithromycin use (i.e., medical conditions or medications with severe drug interactions; see supplemental table 1 for full list). Subjects could not have moderate or severe sleep apnea, severe periodic limb movement disorder with arousals, metabolic disorders thought to explain their hypersomnia symptoms, hypocretin deficiency, or cataplexy. The presence of a circadian rhythm disorder, e.g., delayed sleep phase syndrome, was not an exclusion as long as the circadian disorder did not better explain sleepiness than did the diagnosed hypersomnolence disorder (e.g., a patient with insufficient sleep time related to a circadian rhythm disorder would be excluded, but a patient with a delayed sleep phase but sufficient duration of sleep could be included). Although not explicitly pre-specified in inclusion/exclusion criteria, we chose to exclude subjects for the following additional reasons: chronic use of clarithromycin and unwilling to discontinue for study purposes, chronic use of flumazenil (another negative allosteric modulator of the GABA-A receptor), and living out of town at a distance that would make weekly study visits impractical.

Eligible subjects were enrolled in a two-treatment, two-period (AB/BA) crossover trial comparing the effects of clarithromycin and matched placebo. The study consisted of five visits across five weeks, with each visit occurring at the same time on the same day of the week for a given subject (Figure 1). The first visit was a screening visit at which baseline measurements were collected. The subject then took a study drug (clarithromycin or placebo) twice daily for two weeks, with a study visit after each week on therapy. Following a one week washout period, during which subjects took no study medication, each subject then took the other study drug for two weeks. A one week washout was chosen: 1) to ensure ample time for the active drug, which has up to a 7 hour half-life in patients with normal renal function, to wash out; and 2) to ensure all study visits were on the same day of the

week for each individual patient, to limit any variability in sleepiness severity related to the individual's weekly schedule. Clarithromycin was dosed as 500 mg taken with breakfast and 500 mg with lunch. Placebo tablets were matched in appearance and dosing schedule.

The pre-specified primary outcome was change in median reaction time on the psychomotor vigilance task (PVT) at week two on each intervention. The psychomotor vigilance task is a ten minute, simple reaction task that requires subjects to rapidly press a button in response to a visual stimulus.[18] Pre-specified secondary outcome measures were: 1) median reaction times at week 1; 2) PVT lapses, *i.e.,* response times greater than 500 msec following presentation of a stimulus, at week 1 and week 2; 3) scores on the Epworth Sleepiness Scale, a widely used measure of subjective tendency to doze during the day,[19] at week 1 and 2; 4) Functional Outcomes of Sleep Questionnaire scores, a measure of the impact of sleepiness on daily activities,[20] at week 1 and 2; 5) the SF-36 questionnaire, a measure of both physical and emotional health outcomes,[21] at week 1 and 2; 6) the Stanford Sleepiness Scale, a measure of momentary level of sleepiness, at week 1 and 2;[22] 7) the Pittsburgh Sleep Quality Index scores [23] at weeks 1 & 2, scored using the database available at sleep.pitt.edu; and 8) subject-reported adverse events. Following the finalization of the protocol, work by Basner et al suggested that the reciprocal of reaction time (RRT) measure on the PVT was superior to median reaction time in detecting the effects of sleep deprivation,[24] so we included RRT as an exploratory outcome. Because of preliminary data suggesting substantial test-retest variability of PVT scores in our hypersomnia patients, we performed two PVT assessments at each study visit, separated by at least 30 minutes, which were averaged for each visit. Questionnaires were administered once at each study visit.

Research pharmacists dispensed all study medications (active and placebo) according to a computer generated randomization list,[25] with 1:1 randomization in blocks of four. The allocation sequence generated by pharmacy staff was not shared with study investigators, who enrolled patients. Subjects were randomized such that an equal number received each intervention first (*i.e.,* 10 received clarithromycin first, 10 received placebo first, with pharmacy staff maintaining this overall ratio despite drop outs). Identity of medication (clarithromycin versus placebo) was concealed by the pharmacy, using matched pills and labeled pill containers generated for each subject that were identical in appearance for placebo and clarithromycin weeks (other than sequential dates). Pharmacists and pharmacy staff were located in a separate building and had no interaction with subjects; medication was transferred from pharmacy to study staff via courier. All study investigators and study staff, as well as all subjects, remained blinded to randomization strategy, block size, and treatment allocation until study completion. All subjects gave informed consent and this study was approved by the Emory Institutional Review Board.

Statistical analysis

Sample size was determined using PVT data from six hypersomnolent patients before and after open label use of clarithromycin. Based on these data, 20 subjects completing the trial would provide 85% power to detect a 25 msec difference in median PVT reaction time between treatment arms, with alpha set at 0.05. There were no interim analyses or stopping guidelines.

To obtain the best estimate of the effect of clarithromycin in a crossover design, we pre-specified a complete case analysis, including only those subjects who completed assessments on both interventions and continuing enrollment until our complete-case sample size of 20 was reached. Those 20 subjects who completed assessments during both periods were then analyzed even in cases where subjects did not take all pills as prescribed during each intervention period. In the case of missing data points (SSS x 1 visit in one case, PSQI x 1 visit in one case), the other, available data point for that subject was used in lieu of the period average.

Prior to performing testing of the outcome measures, we evaluated for the presence of carryover and period effects. Carryover was assessed separately for each outcome, both for carryover of average scores from week 1 and week 2 between treatments and for scores at the end of week 2 and the beginning of week 4. Carryover was evaluated with unpaired t-tests comparing sum of the score for the two periods between those who started on clarithromycin and those who started on placebo.[26] A carryover effect is demonstrated if the summed values are different between the two treatment groups (*i.e.*, clarithromycin first and placebo first). Period effect was assessed separately for each outcome using average scores from weeks 1 and 2, via an unpaired t-test comparing the difference of score and score multiplied by a factor of −1. Evidence for a period effect would be indicated by a significant difference in the scores between these two groups.

For evaluation of treatment effects, we first compared scores on each outcome during week 1 on clarithromycin versus week 2 on clarithromycin using a paired t-test. For those secondary outcomes that were not different between week 1 and week 2, we collapsed across both weeks for subsequent testing. For those measures different between week 1 and week 2, individual weeks were evaluated separately.

Treatment effects were assessed using analysis of variance, via a mixed model with fixed effects for treatment (two treatment conditions), period, and sequence (the treatment by period interaction). In all models, random effects included subjects nested within sequence as a sampling cluster.[27] The models were fitted using the restricted maximum likelihood estimation (REML) to obtain the best fitting variance-covariance matrix. The Kenward-Roger method was implemented to adjust the REML estimator of the standard error and degrees of freedom.[28, 29] The assumptions of the analysis of variance were verified with the Shapiro-Wilk test of normality,[30] Hartley's maximal F test,[31] and visual inspection of the residuals.

Post-hoc comparisons were performed on several subgroups of patients for each outcome that showed a significant effect of clarithromycin in the group as a whole. These subgroup comparisons included: subjects who were on versus off of other wake-promoting medications during the study; subjects who were on versus off of modafinil or armodafinil during the study; subjects who were on versus off of antidepressants for comorbid psychiatric disease; and subjects who had versus had not previously taken clarithromycin. The difference between each outcome measure on placebo and clarithromycin was calculated, and compared between the two groups using t-test (corrected for unequal variances when necessary). A post-hoc assessment for effects of clarithromycin on sleep

length was performed comparing question 4 of the PSQI ("during the past week, how many hours of actual sleep did you get at night") at baseline, on clarithromycin, and on placebo using a repeated measures ANOVA. Post-hoc comparisons were also made by diagnostic category. For baseline characteristics, diagnostic groups were compared using Welch ANOVA on ranked data [32] or Fisher exact test, as appropriate. For treatment response, in those variables significant for the group as a whole, the above mixed model was used, with the addition of a diagnosis term and removal of the period term (necessary for model to reach convergence). All tests were two-sided with significance set at $p < 0.05$. Data management and analyses were performed using Microsoft Excel 2010 (Redmond, WA) and SAS, version 9.3 (Cary, NC).

Results

Twenty subjects were randomized, completed both treatment periods, and were analyzed for primary and secondary outcomes (see Figure 2). There were 15 women, mean age 33.0 years (SD 13.3). Three subjects had comorbid diagnoses of circadian rhythm disorders (two of delayed sleep phase and one of irregular sleep-wake), but sleepiness in these three subjects persisted after obtaining sufficient habitual sleep time despite the circadian abnormality. Owl-Lark questionnaires were available for 16 of 20 subjects, and demonstrated one subject with a definite evening type, 5 subjects with moderate evening type, one subject with moderate morning type, and the remainder of neither type. In the group as a whole, average bedtime during the baseline week (based on question 1 of the PSQI) was 11:14 pm (range 9:00 pm until 1:00 am). Prior to enrollment in the study, patients had previously tried an average of 2.5 wake-promoting medications (range 1–5, SD 1.2) across an average of 2.3 medication classes (range 1–4, SD 1.0) for treatment of their hypersomnolence. Only three of twenty subjects endorsed reasonable symptom control with prior wake-promoting medications; the remainder (85%) had not found satisfactory control of their symptoms with available mediations. There were no significant differences in baseline characteristics by diagnosis category (except MSLT results, by definition; see Table 3). Four subjects were treated with antidepressant medications for comorbid psychiatric disease (one of whom had symptomatic hypersomnia; the remaining three all had abnormally short mean sleep latencies on their MSLTs).

Three additional eligible patients were randomized but not included in complete-case analyses because they dropped out during the first intervention period (two for side effects and one for unrelated financial concerns). Subjects who completed all five assessment visits were included in the complete-case analysis, even if they did not take all study medication as prescribed (*e.g.*, in the case of a subject who missed several days of placebo because of GI side effects). The first subject was recruited 3/15/11 and the final subject completed the final study visit 9/28/12, ending the trial at the planned completion point of twenty subjects completing both intervention periods. Baseline characteristics of the included subjects are shown in Table 1. Unpaired t-tests for carryover were non-significant for all outcome measures (all p-values > 0.05). There was no evidence of a period effect on any outcome measure (all p-values > 0.05). For all outcomes other than scores on the Stanford Sleepiness Scale, there was no significant difference between scores during week 1 of clarithromycin

and week 2 of clarithromycin (all p-values > 0.05). Stanford scores were significantly better during week 1 of clarithromycin (2.55 versus 3.15, p = 0.04).

The primary outcome measure, median reaction time on the psychomotor vigilance task (PVT), was no different between week 2 on clarithromycin and week 2 on placebo (279.1 +/− 77.3 on clarithromycin versus 311.6 +/− 114.1 on placebo, t = −1.47, p = 0.16, see Table 2 and Figure 3a). Other tested PVT measures were also not significantly different between groups (see Table 2). In contrast, subjective measures of sleepiness were significantly improved during treatment with clarithromycin. The Epworth Sleepiness Scale was four points lower on clarithromycin than placebo (10.1 +/− 5.4 versus 14.1 +/− 3.7, t = −4.99, p < 0.0001, Figure 3b). Functional Outcomes of Sleep Questionnaire scores significantly improved on clarithromycin (16.6 +/− 2.4 versus 14.4 +/− 2.7, t = 3.77, p = 0.01, Figure 3c). The SF-36 energy subsection was significantly improved on clarithromycin (48.9 +/− 26.9 versus 28.0 +/− 22.5, t = 3.93, p = 0.001, Figure 3d), as were several other subscales (Table 2). Stanford Sleepiness Scale scores were significantly lower on clarithromycin than placebo during week 1 (2.6 +/− 1.3 versus 4.3 +/− 1.6, t = −4.90, p = 0.0001) but not week 2 (3.2 +/− 1.6 versus 3.6 +/− 1.4, t = −1.30, p = 0.21).

Comparing those subjects who remained on wake-promoting medications (n = 14) during the trial to those not on wake-promoting medications (n = 6), there was a non-significant trend toward greater improvement on the FOSQ in those not taking other wake promoting medications (FOSQ 3.8 points higher on clarithromycin than placebo for those not on other medications versus 1.6 points higher for those on other medications, p = 0.09). There were no significant differences between these two groups on the other measures (all p-values > 0.05 for ESS, SSS, and SF-36 energy, role physical, social, and general subscales). Considering only modafinil and armodafinil, there were no significant differences in treatment effect between those on these medications (n = 5) and those not (n = 15) during the trial (all p-values > 0.05). There were no significant differences of the effect of clarithromycin in those subjects who were (n = 4) or were not (n = 16) taking an antidepressant for comorbid psychiatric disease during the trial (all p-values > 0.05). There were no significant differences of the effect of clarithromycin in those subjects who had (n = 11) or had not (n = 9) had prior exposure to clarithromycin (all p-values > 0.05). Sleep length was not significantly different by condition (7.8 hours at baseline, 7.0 hours on clarithromycin, and 7.4 hours on placebo, p = 0.39). There were no significant differences in treatment effect by diagnosis (Table 3).

No serious adverse events occurred during the trial. Two patients dropped out of the study because of adverse events during clarithromycin treatment. Minor adverse events were common in both treatment periods (reported by 21 of 22 participants while taking clarithromycin and 15 of 20 participants while taking placebo, Fisher's test p = 0.09; see Table 4). Of the reported events, only alterations in taste and/or smell was more common with clarithromycin than placebo (15/22 subjects on clarithromycin vs 0/20 subjects on placebo, Fisher's test p = 0.0001)

Discussion

This pilot, randomized, double-blind, placebo controlled trial did not demonstrate a significant improvement in psychomotor vigilance in hypersomnolent subjects on 500 mg of clarithromycin twice daily (with breakfast and lunch). In contrast, clarithromycin consistently improved subjective measures of sleepiness. The benefit observed is large enough to be clinically meaningful, and is of the same magnitude or higher than that reported with modafinil in narcolepsy and shiftwork trials (*i.e.*, a decrease in of 4 points on ESS with clarithromycin versus 2.4–4.1 with modafinil, increase in FOSQ of 2.2 points on clarithromycin versus 0.7 points with modafinil, increase in SF-36 energy subscale of 20.9 points with clarithromycin versus 9.5–10 points with modafinil).[33–37]

This study was placebo-controlled and double blinded. However, dysgeusia or dysosmia was noted in two thirds of our subjects while on clarithromycin, which may have resulted in some inadvertent un-blinding and placebo effect. Another limitation was the drop-out rate (14%). Our decision to perform a complete case analysis does limit the intention-to-treat principle, although this was preserved to the extent possible (*i.e.,* patients were analyzed as randomized if they attended all follow up appointments, even if they did not take the medication as prescribed). Although drop outs are undeniably a limitation of crossover trials, others have argued that complete-case analyses at least allow assessment of effect in the subgroup of patients who are able to tolerate the medication,[38] which might be particularly relevant with this medication. Post-hoc analyses in this study should be interpreted with caution, especially in light of the small sample size in some groups.

Our study population was recruited predominantly through our tertiary referral Sleep Center, and as such may not be fully representative of hypersomnolent patients in general. In particular, eighty-five percent of our patients had failed to find an adequate medication regimen to control their symptoms prior to enrollment, despite having tried multiple other classes of wake-promoting medications. Seventy percent of our subjects had persistent sleepiness despite the wake-promoting medications they were on at the time of enrollment (and remained on throughout the trial). Continuation of wake-promoting medications during our trial may have decreased our ability to detect a benefit of clarithromycin (by partially treating sleepiness), as suggested by the trend to greater improvement on FOSQ in those not on other medications. We focused on subjective measures of sleepiness and objectively measured vigilance. The central disorders of hypersomnolence encompass other important symptomatology, including sleep inertia and long sleep times in many patients, which require evaluation in future treatment studies. When clarithromycin is used for indications other than hypersomnolence, some children appear to develop hypersomnia [39]. Our post hoc evaluation of sleep time in this study of adults did not demonstrate increased nocturnal sleep time, suggesting that the disparate effects of clarithromycin in our study and that reported by Baranowski might reflect differences in age or indication for use in the two groups.

Our two week treatment period was not long enough to comprehensively assess for possible wearing off of medication effectiveness over time, which we and others have reported may be problematic in some hypersomnia patients treated with clarithromycin.[12, 40] The difference between weeks 1 and 2 on SSS might suggest the development of tolerance,

although this was not seen in any other measure. Clarithromycin was relatively well tolerated in this study. However, the duration was too short to assess for potential long term complications of antibiotic use, including antibiotic resistance and superinfection. Clearly, the long term use of an antibiotic must be justified by clinical benefit that exceeds these potential risks, as we have elaborated elsewhere.[12]

It is attractive to postulate that the benefits of clarithromycin seen in this study are mediated by clarithromycin's action as a negative allosteric modulator of GABA-A receptors. However, at present the mechanism behind improved sleepiness with clarithromycin is unknown. It might be mediated by anti-inflammatory effects of clarithromycin. For example, clarithromycin decreases plasma interleukin-6 levels [41] and this cytokine has been implicated as a potential cause of excessive daytime sleepiness and a component of the homeostatic regulation of sleep. [42] Alternatively, recent work has highlighted the potential role of the gastrointestinal microbiome in the expression of neuropsychiatric conditions,[43] and it could be speculated that clarithromycin affects sleepiness through an alteration in gut flora composition. Even a short, 7–10 day course of clarithromycin at the dose used in our study results in measurable changes in the composition of the gastrointestinal microbiome.[44, 45] We were not able to directly assess for changes in cytokines or gut flora in the present study. Clarithromycin is a strong inhibitor of the cytochrome P450 CYP3A4 enzyme, and both modafinil and armodafinil are partially metabolized by this enzyme.[46–48] Therefore, clarithromycin might have part of its effect by decreasing metabolism of modafinil and armodafinil. This is, however, unlikely to explain the majority of the treatment benefit produced by clarithromycin in this study, given that a similar benefit was seen in patients not taking these medications, and because patients taking these medications had already found them to be ineffective in controlling their sleepiness. Future studies of clarithromycin, potentially including patients with sleepiness from known causes such as hypocretin-deficient narcolepsy or experimental sleep deprivation, would be useful in differentiating the extent to which the benefit observed in this study was mediated through a GABA-ergic mechanism.

This preliminary study suggests that there is a subjective treatment benefit from clarithromycin for idiopathic hypersomnia, narcolepsy without cataplexy, and subjective hypersomnia, consistent with the benefit previously reported in clinical practice.[12] Larger studies that include additional objective measures of sleepiness (such as the maintenance of wakefulness test) and longer treatment duration are needed. In the interim, clarithromycin might be considered, especially in cases that are otherwise treatment-refractory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. Billiard M, Dauvilliers Y. Idiopathic Hypersomnia. Sleep Med Rev. 2001; 5(5):349–58. [PubMed: 12530998]

2. Ozaki A, Inoue Y, Hayashida K, et al. Quality of life in patients with narcolepsy with cataplexy, narcolepsy without cataplexy, and idiopathic hypersomnia without long sleep time: comparison between patients on psychostimulants, drug-naive patients and the general Japanese population. Sleep Med. 2012; 13(2):200–6. [PubMed: 22137109]

3. Ozaki A, Inoue Y, Nakajima T, et al. Health-related quality of life among drug-naive patients with narcolepsy with cataplexy, narcolepsy without cataplexy, and idiopathic hypersomnia without long sleep time. J Clin Sleep Med. 2008; 4(6):572–8. [PubMed: 19110887]

4. Bayon V, Leger D, Philip P. Socio-professional handicap and accidental risk in patients with hypersomnias of central origin. Sleep Med Rev. 2009; 13(6):421–6. [PubMed: 19493688]

5. Rye DB, Bliwise DL, Parker K, et al. Modulation of Vigilance in the Primary Hypersomnias by Endogenous Enhancement of GABAA Receptors. Sci Transl Med. 2012; 4(161):161ra51.

6. Morgenthaler TI, Kapur VK, Brown T, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. Sleep. 2007; 30(12):1705–11. [PubMed: 18246980]

7. Ali M, Auger RR, Slocumb NL, Morgenthaler T. Idiopathic hypersomnia: clinical features and response to treatment. J Clin Sleep Med. 2009; 5(6):562–8. [PubMed: 20465024]

8. Anderson KN, Pilsworth S, Sharples LD, Smith IE, Shneerson JM. Idiopathic hypersomnia: a study of 77 cases. Sleep. 2007; 30(10):1274–81. [PubMed: 17969461]

9. Wise MS, Arand DL, Auger RR, Brooks SN, Watson NF. Treatment of narcolepsy and other hypersomnias of central origin. Sleep. 2007; 30(12):1712–27. [PubMed: 18246981]

10. Philip P, Chaufton C, Taillard J, et al. Modafinil improves real driving performance in patients with hypersomnia: a randomized double-blind placebo-controlled crossover clinical trial. Sleep. 2014; 37(3):483–7. [PubMed: 24587570]

11. Mayer G, Benes H, Young P, Bitterlich M, Rodenbeck A. Modafinil in the treatment of idiopathic hypersomnia without long sleep time-a randomized, double-blind, placebo-controlled study. J Sleep Res. 2015; 24(1):74–81. [PubMed: 25196321]

12. Trotti LM, Saini P, Freeman AA, et al. Improvement in daytime sleepiness with clarithromycin in patients with GABA-related hypersomnia: Clinical experience. J Psychopharmacol. 2013; 28(7): 697–702. [PubMed: 24306133]

13. Heier MS, Evsiukova T, Vilming S, Gjerstad MD, Schrader H, Gautvik K. CSF hypocretin-1 levels and clinical profiles in narcolepsy and idiopathic CNS hypersomnia in Norway. Sleep. 2007; 30(8):969–73. [PubMed: 17702265]

14. Trotti LM, Staab BA, Rye DB. Test-retest reliability of the multiple sleep latency test in narcolepsy without cataplexy and idiopathic hypersomnia. J Clin Sleep Med. 2013; 9(8):789–95. [PubMed: 23946709]

15. Goldbart A, Peppard P, Finn L, et al. Narcolepsy and predictors of positive MSLTs in the Wisconsin Sleep Cohort. Sleep. 2014; 37(6):1043–51. [PubMed: 24882899]

16. Vernet C, Arnulf I. Idiopathic hypersomnia with and without long sleep time: a controlled series of 75 patients. Sleep. 2009; 32(6):753–9. [PubMed: 19544751]

17. Pizza F, Moghadam KK, Vandi S, et al. Daytime continuous polysomnography predicts MSLT results in hypersomnias of central origin. J Sleep Res. 2012

18. Dinges DF. Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. Behav Res Methods Instrum Comput. 1985; 17:652–5.

19. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991; 14(6):540–5. [PubMed: 1798888]

20. Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. Sleep. 1997; 20(10):835–43. [PubMed: 9415942]

21. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical care. 1992; 30(6):473–83. [PubMed: 1593914]

22. Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC. Quantification of sleepiness: a new approach. Psychophysiology. 1973; 10(4):431–6. [PubMed: 4719486]

23. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989; 28(2):193–213. [PubMed: 2748771]

24. Basner M, Dinges DF. Maximizing sensitivity of the psychomotor vigilance test (PVT) to sleep loss. Sleep. 2011; 34(5):581–91. [PubMed: 21532951]

25. Urbaniak, GC.; Plous, S. Research Randomizer (Version 4.0) [Computer software].

26. Wellek S, Blettner M. On the proper use of the crossover design in clinical trials: part 18 of a series on evaluation of scientific publications. Deutsches Arzteblatt international. 2012; 109(15):276–81. [PubMed: 22567063]

27. Stevens, JP. Intermediate statistics : a modern approach. 3. New York: Lawrence Erlbaum; 2007.

28. Jones, B.; Kenward, MG. Design and Analysis of Cross-Over Trials. 2. Taylor & Francis; 2003.

29. The SAS Institute Inc. SAS/STAT® User's Guide, Version 9.3. Cary, NC: SAS Institute Inc; 2011.

30. Shapiro SS, Wilk MB. An analysis of variance test for normality (complete samples). Biometrika. 1965; 52:591.

31. Hartley HO. The maximum F-ratio as a short-cut test for heterogeneity of variance. Biometrika. 1950; 37(3–4):308–12. [PubMed: 14801057]

32. Cribbie RA, Wilcox RR, Bewell C, Keselman HJ. Tests for treatment group equality when data are nonnormal and heteroscedastic. Journal of Modern Applied Statistical Methods. 2007; 6(1):117–32.

33. Erman MK, Rosenberg R. Modafinil Shift Work Sleep Disorder Study G. Modafinil for excessive sleepiness associated with chronic shift work sleep disorder: effects on patient functioning and health-related quality of life. Primary care companion to the Journal of clinical psychiatry. 2007; 9(3):188–94.

34. Broughton RJ, Fleming JA, George CF, et al. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. Neurology. 1997; 49(2):444–51. [PubMed: 9270575]

35. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. Ann Neurol. 1998; 43(1):88–97. [PubMed: 9450772]

36. Dauvilliers Y, Bassetti C, Lammers GJ, et al. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. The Lancet Neurology. 2013; 12(11):1068–75. [PubMed: 24107292]

37. Beusterien KM, Rogers AE, Walsleben JA, et al. Health-related quality of life effects of modafinil for treatment of narcolepsy. Sleep. 1999; 22(6):757–65. [PubMed: 10505821]

38. Ho WK, Matthews JN, Henderson R, Farewell D, Rodgers LR. Dropouts in the AB/BA crossover design. Stat Med. 2012; 31(16):1675–87. [PubMed: 22362410]

39. Baranowski WJ. Clarithromycin-induced hypersomnia in children. International journal of clinical pharmacology and therapeutics. 2011; 49(5):297–9. [PubMed: 21543032]

40. Rezvanian E, Watson NF. Kleine-levin syndrome treated with clarithromycin. J Clin Sleep Med. 2013; 9(11):1211–2. [PubMed: 24235906]

41. Demartini G, Esposti D, Marthyn P, Lapidari A, Fraschini F, Scaglione F. Effect of multiple doses of clarithromycin and amoxicillin on IL-6, IFNgamma and IL-10 plasma levels in patients with community acquired pneumonia. J Chemother. 2004; 16(1):82–5. [PubMed: 15078004]

42. Vgontzas AN, Pejovic S, Zoumakis E, et al. Daytime napping after a night of sleep loss decreases sleepiness, improves performance, and causes beneficial changes in cortisol and interleukin-6 secretion. American journal of physiology Endocrinology and metabolism. 2007; 292(1):E253–61. [PubMed: 16940468]

43. Gonzalez A, Stombaugh J, Lozupone C, Turnbaugh PJ, Gordon JI, Knight R. The mind-body-microbial continuum. Dialogues in clinical neuroscience. 2011; 13(1):55–62. [PubMed: 21485746]

44. Jakobsson HE, Jernberg C, Andersson AF, Sjolund-Karlsson M, Jansson JK, Engstrand L. Short-term antibiotic treatment has differing long-term impacts on the human throat and gut microbiome. PLoS One. 2010; 5(3):e9836. [PubMed: 20352091]

45. Edlund C, Beyer G, Hiemer-Bau M, Ziege S, Lode H, Nord CE. Comparative effects of moxifloxacin and clarithromycin on the normal intestinal microflora. Scandinavian journal of infectious diseases. 2000; 32(1):81–5. [PubMed: 10716083]

46. Clarithromycin Prescribing Information (FDA). 2013. [1/28/2015]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050662s052lbl.pdf

47. Modafinil FDA approved labeling. 2007. [1/28/15]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/020717s020s013s018lbl.pdf

48. Armodafinil Prescribing Information (FDA). 2010. [1/28/15]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021875s005s008s015lbl.pdf

49. Trotti LM, Saini P, Freeman AA, et al. Clarithromycin for the treatment of hypersomnia: a randomized, double-blind, placebo-controlled crossover trial. Sleep. 2013; 36:A248.
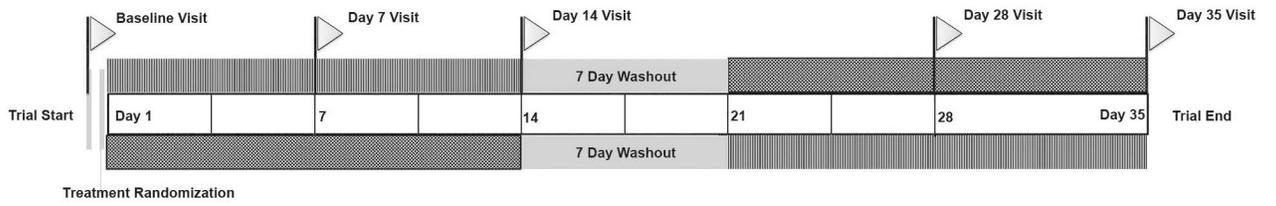
Figure 1. Study protocol

Subjects were randomized to order of presentation of clarithromycin (vertical lines) and placebo (checkerboard).
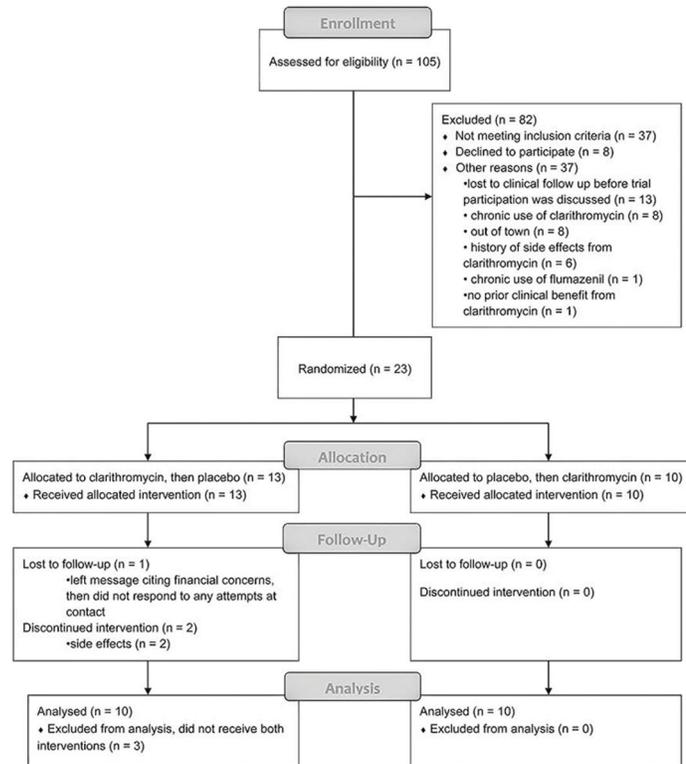
Figure 2.
Flow diagram of study participants
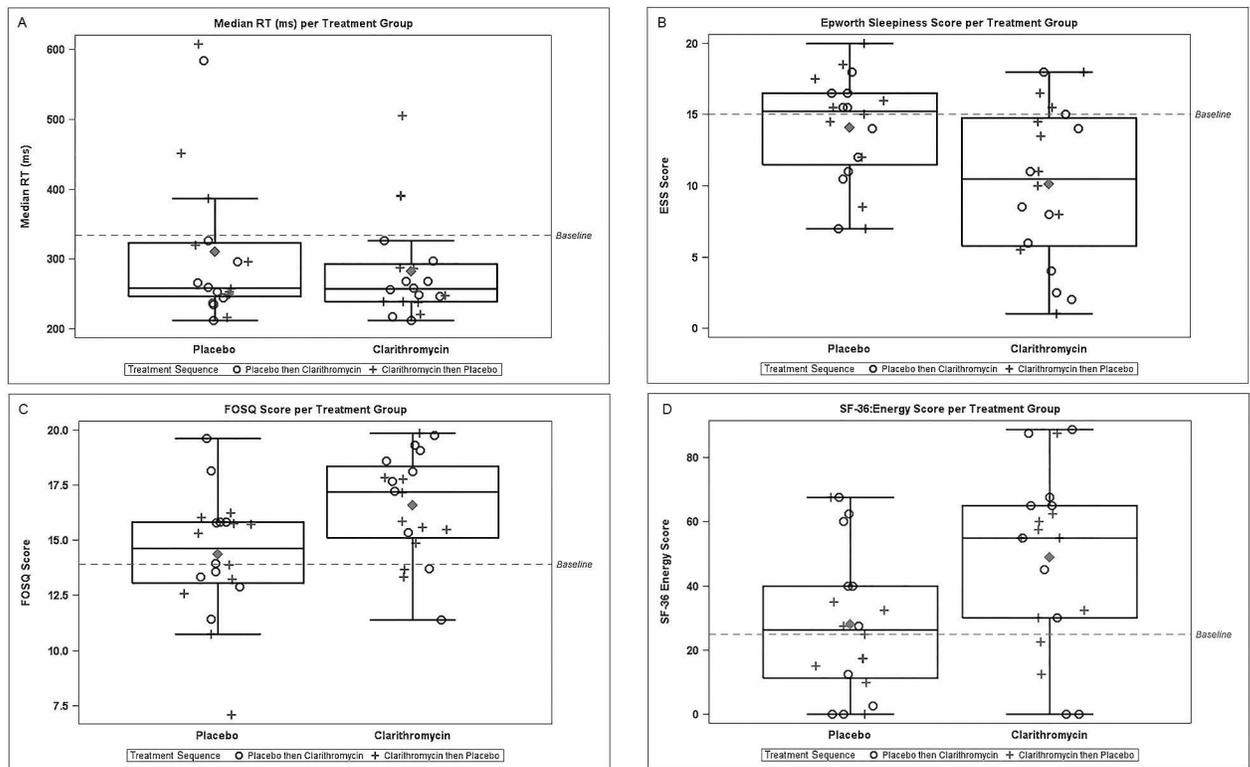
Figure 3. Clarithromycin versus placebo

All panels are boxplots demonstrating individual subject values while taking clarithromycin or placebo. Subjects randomized to clarithromycin first are indicated by pluses and those randomized to placebo first are indicated by open circles. Mean values are indicated by filled triangle and baseline values are indicated by the horizontal dashed line. Median values are indicated by the solid horizontal line inside the box, and the 25th and 75th percentiles are indicated by the upper and lower edges of the box. For median reaction time (A) and Epworth sleepiness scale (B), lower values indicate less impairment of vigilance/less sleepiness. For Functional Outcomes of Sleep (C) and SF-36 Energy (D), higher values indicate less severe impact of symptoms.

Table 1

Baseline characteristics by treatment allocation

	Placebo first, then clarithromycin	**Clarithromycin first, then placebo**
Age (in years)	34.7 (14.5)	31.2 (12.5)
Female gender	8 (80%)	7 (70%)
Hypersomnia diagnoses	Idiopathic hypersomnia with long sleep time: 3 Idiopathic hypersomnia without long sleep time: 1 Narcolepsy without cataplexy: 3 Subjective hypersomnia: 3	Idiopathic hypersomnia with long sleep time: 2 Idiopathic hypersomnia without long sleep time: 4 Narcolepsy without cataplexy: 1 Subjective hypersomnia: 3
In vitro potentiation of GABA-A receptor function by subject cerebrospinal fluid	80.9% (19.0)	86.2% (25.7)
Cerebrospinal fluid hypocretin level (pg/ml	273.3 (61.4)	313.1 (88.3)[*]
% on wake-promoting medications	6 (60%, including dextroamphetamine, modafinil, bupropion, and protriptyline)	8 (80%, including dextroamphetamine, dextroamphetamine-amphetamine, modafinil, and armodafinil)
PVT median reaction time	383.6 (409.5)	284.1 (49.6)
Epworth Sleepiness Scale	15.3 (1.6)	14.8 (3.0)
Multiple Sleep Latency Test, mean sleep latency	6.0 (3.0)	7.3 (5.1)
Multiple Sleep Latency Test, number of sleep onset REM periods	1.2 (1.5)	0.8 (1.0)
Respiratory disturbance index	4.5 (4.1)	2.0 (3.5)
Periodic limb movement arousal index	0.8 (1.3)	4.2 (7.5)

Values represent mean (standard deviation) for continuous variables, and number (percentage) for categorical variables. Median values are shown in Supplemental Table 2.

[*]
n = 9.

Abbreviations: PVT = psychomotor vigilance task; REM = rapid eye movement

Table 2

Treatment effects by condition

	Baseline	Placebo	Clarithro-mycin	Estimate	95% CI	t-value*	p-value
PSYCHOMOTOR VIGILANCE TEST							
-median RT week 2	333.8 (291.4)	311.6 (114.1)	279.1 (77.3)	−32.6	−79.2, 14.0	−1.47	0.16
-median RT week 1	333.8 (291.4)	308.4 (120.6)	285.4 (71.3)	−23.0	−15.9, −62.0	−1.24	0.23
-lapses**	6.5 (16.9)	10.3 (18.7)	5.7 (11.3)	−4.6	−11.3, 2.0	−1.46	0.16
-RRT	3.6 (0.9)	3.5 (0.8)	3.7 (0.7)	0.2	−0.03, 0.4	1.79	0.09
QUESTIONNAIRES							
-ESS	**15.0 (2.3)**	**14.1 (3.7)**	**10.1 (5.4)**	**−3.9**	**−5.6, −2.3**	**−4.99**	**<0.0001**
-FOSQ	**13.9 (2.0)**	**14.4 (2.7)**	**16.6 (2.4)**	**2.2**	**1.0, 3.5**	**3.77**	**0.001**
-SF-36: physical	84.0 (15.1)	82.8 (18.8)	87.5 (16.8)	4.7	−2.2, 11.5	1.43	0.17
-SF-36: role physical	**40.0 (38.4)**	**39.7 (44.2)**	**65.6 (40.5)**	**25.9**	**6.7, 45.1**	**2.84**	**0.01**
-SF-36: role emotional	78.3 (31.1)	73.3 (35.2)	84.2 (24.5)	10.8	−8.7, 30.4	1.16	0.26
-SF-36: energy	**25.0 (21.6)**	**28.0 (22.5)**	**48.9 (26.9)**	**20.9**	**9.7, 32.1**	**3.93**	**0.001**
-SF-36: emotional	72.0 (15.2)	72.0 (19.2)	73.5 (18.5)	2.4	−3.5, 6.5	0.63	0.54
-SF-36: social	**60.6 (27.6)**	**65.3 (24.7)**	**79.4 (23.0)**	**14.1**	**5.7, 22.5**	**3.51**	**0.003**
-SF-36: pain	82.8 (20.2)	80.8 (18.8)	85.3 (18.6)	4.5	−3.0, 12.0	1.26	0.22
-SF-36: general	**64.1 (19.1)**	**62.4 (19.0)**	**66.8 (18.4)**	**4.5**	**0.1, 8.9**	**2.14**	**0.046**
-SSS week 1	**4.3 (1.3)**	**4.3 (1.6)**	**2.6 (1.3)**	**−1.7**	**−2.4, −1.0**	**−4.90**	**0.0001**
-SSS week 2	4.3 (1.3)	3.6 (1.4)	3.2 (1.6)	−0.5	−1.3, 0.3	−1.30	0.21
-PSQI	6.7 (3.5)	6.3 (2.8)	5.8 (3.9)	−0.5	−1.6, 0.6	−0.92	0.37

Values reflect mean (standard deviation). Median values are shown in Supplemental Table 3. Results in bold are significant at p < 0.05.

*
t-value reflects the model comparing clarithromycin and placebo treatments, as specified in the text.

**
Except as specified for median RT and SSS, all other measures were calculated for the average of week 1 and week 2 results on each treatment.

Abbreviations: RT = reaction time; RRT = reciprocal of the reaction time; ESS = Epworth Sleepiness Scale; SSS = Stanford Sleepiness Scale; PSQI = Pittsburgh Sleep Quality Index; FOSQ = Functional Outcomes of Sleep Questionnaire; SSS = Stanford Sleepiness Scale; PSQI = Pittsburgh Sleep Quality Index

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 3

Baseline characteristics and treatment response by diagnosis

	Narcolepsy without cataplexy (n = 4)	Idiopathic hypersomnia with long sleep (n = 5)	Idiopathic hypersomnia without long sleep (n = 5)	Subjective hypersomnia (n = 6)	F-value	p-value*
BASELINE DATA						
Age (in years)	29.8 (8.1)	32.0 (7.5)	39.4 (20.4)	30.5 (14.0)	0.25	0.86
Female gender	2 (50%)	5 (100%)	3 (60%)	5 (83%)	--	0.31
Bedtime at baseline, from PSQI	11:30 (65 min)	10:12 (44 min)	11:36 (68 min)	11:35 (29 min)	0.66	0.60
In vitro potentiation of GABA-A receptor function by subject cerebrospinal fluid	88.7 (20.1)	86.7 (21.4)	81.4 (21.8)	79.3 (28.7)	0.3	0.83
Cerebrospinal fluid hypocretin level (pg/ml)	331.8 (68.7)	269.0 (97.7)	324.8 (96.6)	263.3 (32.1)	1.2	0.38
% on wake-romoting medications	3 (75%)	2 (40%)	4 (80%)	5 (83%)	--	0.54
Number of wake-promoting medications previously attempted	2.0 (0.8)	2.0 (0.7)	2.2 (1.6)	3.3 (1.0)	2.14	0.17
PVT median reaction time (baseline)	261.0 (45.0)	527.9 (577.4)	299.0 (55.1)	249.8 (27.2)	1.84	0.22
Epworth Sleepiness Scale (baseline)	14.5 (1.3)	15.9 (2.2)	16.0 (1.9)	13.8 (3.1)	0.78	0.53
Multiple Sleep Latency Test, mean sleep latency	3.0 (0.9)	6.0 (1.6)	4.1 (2.5)	11.7 (3.0)	63.1	<0.0001 (groups different by definition)
Multiple Sleep Latency Test, number of sleep onset REM periods	3.3 (0.5)	0.2 (0.4)	0.4 (0.5)	0.7 (0.8)	30.0	<0.0001 (groups different by definition)
TREATMENT DATA						
Treatment difference**, Median RT week 2	-11.3 (16.5)	-78.0 (123.1)	-18.7 (158.7)	-20.5 (29.2)	1.7	0.20
Treatment difference, ESS	-6.5 (2.0)	-5.4 (4.1)	-1.2 (2.1)	-3.3 (3.5)	1.6	0.23
Treatment difference, FOSQ	3.9 (1.9)	3.5 (3.7)	0.3 (0.9)	1.7 (2.0)	0.15	0.92
Treatment difference, SF-energy	29.4 (5.9)	22.3 (21.3)	6.0 (11.8)	26.7 (35.3)	0.99	0.42
Treatment difference, SSS week 1	-3.0 (1.4)	-1.8 (1.8)	-1.0 (1.2)	-1.3 (1.4)	0.18	0.91

Values represent mean (standard deviation) for continuous variables, and number (percentage) for categorical variables.

*
P-values reflect comparisons across diagnosis groups using Welch ANOVA on ranked values, Fisher exact test, or mixed effects model (see text).

**
Treatment data values are reported as change scores comparing clarithromycin to placebo (i.e., values on clarithromycin minus values on placebo). For example, subjects with narcolepsy had an average ESS that was 6.5 points lower while on clarithromycin than on placebo.

Table 4

Adverse events experienced by more than one subject

	Clarithromycin	Placebo	p-value[*]
Any side effect	21/22 (95%)	15/20 (75%)	0.09
Dysgeusia or Dysosmia	**15/22 (68%)**	**0/20 (0%)**	**< 0.001**
Any gastrointestinal symptom	16/22 (73%)	9/20 (45%)	0.07
Abdominal pain	3/22 (14%)	1/20 (5%)	0.61
Bloating/gas	2/22 (9%)	1/20 (5%)	1.00
Diarrhea	4/22 (18%)	5/20 (25%)	0.71
Nausea	7/22 (32%)	3/20 (15%)	0.28
Other, unspecified gastrointestinal distress	5/22 (23%)	5/20 (25%)	1.00
Nose bleed	2/22 (9%)	0/20 (0%)	0.49
Upper respiratory infection symptoms	0/22 (0%)	3/20 (15%)	0.10
Dizziness	1/22 (5%)	1/20 (5%)	1.00
Feeling "jittery" or "hyper"	3/22 (14%)	1/20 (5%)	0.61
Headache	3/22 (14%)	5/20 (25%)	0.45
Insomnia	6/22 (27%)	3/20 (15%)	0.46
Anxiety	1/22 (5%)	1/20 (5%)	1.00
Change in appetite (increase or decrease)	2/22 (9%)	1/20 (5%)	1.00
Sweating, flushing, or feeling hot	2/22 (9%)	1/20 (5%)	1.00

[*]
Chi-square or Fisher exact test, as indicated. Results in bold are significant at $p < 0.05$.