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Original Article

Durability of treatment response to zolpidem using a partial reinforcement regimen: does this strategy require priming?☆

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ABSTRACT

Background: Previous research has shown that after one month of full dose nightly treatment with zolpidem (priming), subjects with chronic insomnia (CI) switched to intermittent dosing with medication and placebos were able to maintain their treatment responses. This approach to maintenance therapy is referred to as partial reinforcement. The present study sought to assess whether priming is required for partial reinforcement or whether intermittent dosing with placebos (50% placebos and 50% active medication) can, by itself, be used for both acute and extended treatment.
Method: 55 CI subjects underwent a baseline evaluation (Phase-1) and then were randomized to one of two conditions in Phase-2 of the study: one month of (1) nightly medication use with standard-dose zolpidem (QHS [n = 39]) or (2) intermittent dosing with standard-dose zolpidem and placebos (IDwP [n = 16]). In Phase-3 (three months), the QHS group was re-randomized to either continued QHS full dose treatment (FD/FD) or to IDwP dose treatment (FD/VD). Treatment response rates and Total Wake Time (TWT = [SL + WASO + EMA]) were assessed during each phase of the study.
Results: In Phase-2, 77% (QHS) and 50% (IDwP) subjects exhibited treatment responses ($p = 0.09$) where the average change in TWT was similar. In Phase-3, 73% (FD/FD), 57% (FD/VD), and 88% (VD/VD) of subjects exhibited continued treatment responses ($p = 0.22$) where the average improvement in TWT continued with FD/FD and remained stable for FD/VD and VD/VD ($p < 0.01$).
Conclusion: These results suggest that intermittent dosing with placebos can maintain effects but do not allow for the additional clinical gains afforded by continuous treatment.

1. Introduction

The characterization of insomnia as a chronic disorder suggests that some form of maintenance therapy is required when Cognitive Behavioral Therapy for Insomnia (CBT-I) is not available or accepted [1,2]. Presently, maintenance therapy is accomplished using an intermittent dosing approach (prn use of medication on 3–5 nights per week) [1,2]. When evaluated week-to-week, the sleep continuity effects with intermittent dosing in this way appear to be comparable to, and at least as durable as, those obtained with nightly dosing [3–5]. This said, there are no empirical data to support that intermittent dosing allows for comparable rates of treatment responding, the extension of the "efficacy half-life" of hypnotics, or fewer side effects. What is clear from the given data is that there are no "treatment effects" on non-medication nights [3].

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The recurrence of insomnia on non-medication nights is problematic for at least two reasons. First, the insomnia is not treated on 2–4 nights a week. Second, the recurrence of insomnia on 2–4 nights per week may lead to a form of the disorder that is especially persistent and/or may enhance the likelihood that patients become psychologically dependent on medication.

In 2015, our group evaluated a modified intermittent dosing regimen which included the provision of placebos on non-medication nights [6]. This approach, by virtue of expectancy alone, was expected to provide for better overall outcomes. This approach was thought to provide better outcomes on non-medication nights based on the concept that therapeutic responses could be extended to non-medication nights based on the principles of conditioning and reinforcement. That is, the medication vehicle (ie, the pill capsule) could become a conditioned stimulus for the pharmacotherapeutic effects of hypnotics, and that periodic re-exposure to active medication via intermittent dosing (along with placebos) could serve as partial reinforcement [7–9]. In the 2015 study, following the obtention of treatment responses with nightly dosing (10 mg zolpidem for 1 month), intermittent dosing with placebos (IDwP) was compared to nightly dosing (QHS-10), nightly half-dose (QHS-5), and standard intermittent dosing (without placebos). In the case of IDwP dosing, 50% of the nightly capsules were placebos. It was found that all four strategies maintained treatment response over time (ie, prevented or delayed relapse). For the subjects that remained in remission, the subjects in the standard intermittent dosing group exhibited poorer sleep continuity and tended to exhibit more medical symptoms than the subjects in the other treatment conditions. It was concluded that the partial reinforcement regimen represented an optimal way to secure the benefits of nightly dosing while using 50% less medication.

Given the viability of the partial reinforcement strategy, a second study was undertaken to assess whether priming with one month of QHS dosing was required for maintenance of good clinical outcomes during extended treatment. In theory, priming is needed to maximize treatment responding and/or for the conditioning of pharmacologic responses to the medication vehicle (capsules). In the present study, these assumptions were tested by including both QHS and IDwP regimens into the acute treatment stage of the study. It was hypothesized that: 1) QHS dosing during acute treatment would result in more treatment responders with larger average sleep continuity effects than those treated with IDwP dosing and 2) those with QHS pre-treatment, when switched to the IDwP condition, would better maintain their treatment responses than those who had started their treatment regimen with IDwP. Confirmation of the latter would provide evidence that priming is required for maintenance therapy using a partial reinforcement regimen.

2. Methods

2.1. Study overview

The data presented here are from a larger study of partial reinforcement in the long-term management of insomnia. The parent study had a mixed model design with four phases and three groups. The study design and the conduct of the investigation was overseen by the Internal Review Board of the University of Pennsylvania and by an independent Data Safety and Monitoring Board. As can been seen in Fig. 1, the four phases were: Phase-1 (baseline assessment of sleep continuity); Phase-2 (nightly dosing with standard dose zolpidem [QHS] or intermittent dosing with placebos [IDwP]); Phase-3 (re-randomization of subjects in the QHS condition to either continued nightly dosing [FD/FD] or intermittent dosing with placebos administered on non-medication nights [FD/VD]).

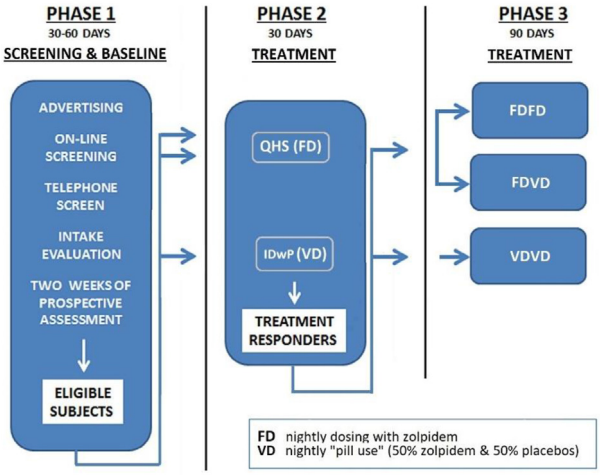

Fig. 1. Study design.

Phase-1 (Baseline) was conducted over 4–8 weeks and included an in-person interview, a history and physical, one overnight polysomnography (PSG) study and two weeks of evaluation with sleep diaries to ensure that subjects did not meet any of the exclusionary criteria and that each subjects' retrospective characterization of their sleep continuity meet inclusion criteria.

Phase-2 (Acute treatment) was conducted over 4 weeks where subjects were randomized on 2 to 1 basis to either nightly dosing with zolpidem (QHS) or intermittent dosing with active med and placebos (IDwP). In the case of the IDwP condition, ~50% of doses were standard dose and ~50% were placebos. The medication doses were 5 or 10 mg depending on age and sex considerations and all subjects were instructed to take a single capsule, each and every night, 30 min prior to bedtime. Subjects that exhibited a treatment response during Phase-2 continued on to Phase-3. Treatment non-responders were disenrolled from the study and offered CBT-I.

Phase-3 (Extended treatment) was conducted over 12 weeks. The QHS group was re-randomized to either continued QHS treatment (full dose in Phase 2 continuing with full dose in Phase 3 [FD/FD]) or to IDwP treatment (full dose in Phase 2 continuing with variable dose in Phase 3 [FD/VD]). The IDwP group continued forward without a change in the treatment regimen (variable dose-variable dose [VD/VD]).

During all phases of the study, all subjects completed a daily online sleep/pill-use diary and a weekly medical symptom checklist. During Phase-2 and Phase-3, medication was disbursed and collected on a monthly basis (foil packs). All subjects were assessed for their clinical status on a bi-weekly basis and continued in each phase of the study until they exhibited a relapse. Note: Unlike our prior study, both medication conditions (Phase-2 and Phase-3) were experimental. Phase-2 allowed for the contrast between nightly use of medications and intermittent dosing with placebos on treatment response and magnitude of sleep continuity effects during acute treatment. Phase-3 allowed an assessment of how "pre-treatment" (QHS or IDwP) affected long term outcomes with respect to maintenance of treatment response and magnitude of sleep continuity effects (ie, allowed for a three-way comparison of FD/FD vs. FD/VD vs. VD/VD).

2.2. Subjects

Subjects were recruited from the local sleep disorders center, from advertisements in local newspapers, TV and radio stations, and via the Penn EMR and social media (eg, Facebook ads). Interested

individuals were referred to www.sleeplessinphilly.com for initial online screening. Subjects that continued to be eligible were further screened with an in person interview, a history and physical, one overnight PSG study, and two weeks of sleep diaries. Medically stable subjects, 40 years and older who had a preferred sleep phase between 9:00 PM and 9:00 AM and who met criteria for DSM-5 criteria for Insomnia Disorder and ICSD-3 & RDC criteria for Psychophysiologic Insomnia were eligible for the study. The age limit was restricted to minimize circadian rhythm influences on the diagnoses of insomnia and to focus the study on middle aged and older adults. In addition to the age limits and diagnostic criteria, all subjects were required to have a sleep initiation complaint (≥30 min to fall asleep) with a problem frequency ≥3 nights/week and a problem duration ≥6 months). Middle (ie, difficulty staying asleep) and late insomnia (ie, early morning awakenings) were free to vary. This profile had to be evident at both intake (based on retrospective reports) and as an average profile from the two weeks of baseline diaries.

Exclusionary criteria (based on an intake interview, the history and physical, and a single night of polysomnography [PSG]) were as follows.

- Inadequate language comprehension.
- Unstable medical or psychiatric illness.
- Symptoms suggestive of sleep disorders other than insomnia.
- Past history of treatment failure with zolpidem or discontinuation of zolpidem owing to side effects.
- Past history of parasomnias (no more than 1 incident in last 10 years).
- Polysomnographic data indicating sleep disorders other than insomnia (eg, AHI or PLMI >10).
- Evidence of active illicit substance use or alcohol abuse and/or dependence.
- Current use of CNS active medications (eg, antidepressants and hypnotics other than zolpidem).
- Pregnancy or the intention to become pregnant within the study period (8–10 months).
- Any first-degree relatives with bipolar disorder or schizophrenia.

In total, 99 subjects were consented and enrolled into Phase-1 (mean age 61.6 ± 9.4, 57% female, and 76% white). As can be seen in Table 1, 44 of these subjects were lost to follow-up owing to baseline fails (prospective assessment failed to show sufficient illness severity), PSG screen fails, voluntary withdraw from the study, or simply discontinued participation. Table 1 also provides data about subject status for Phases 2 and 3.

Table 1
Subject enrollment at each study phase.

Study Enrollment			
	Phase-1	Phase-2	Phase-3
Enrolled	99	55	37
Completed	55	37	26
Relapse/Treatment Fail	0	15	6
Attrition	44	3	5
LTFU	9	0	0
Withdrew	9	3	5
Baseline Fail	9	n/a	n/a
PSG Fail	17	n/a	n/a

LTFU = Loss to Follow-Up; Withdrew = Voluntary Withdrawal; Baseline Fail = Did not meet inclusion/exclusion criteria; PSG Fail = sleep disorder other than insomnia present.

2.3. Study medication

Zolpidem tartrate (trade name Ambien) is a non-benzodiazepine hypnotic whose primary indication is for sleep initiation problems. The recommended initial dose is 5 mg for women and 10 mg for non-elderly men. Medication is to be taken immediately before bedtime with at least 7–8 h remaining before the planned time of awakening. Older adults and patients with mild to moderate hepatic impairment are instructed to use 5 mg. Zolpidem interacts with the GABA-BZ receptor complex, appears to bind selectively to the BZ1 receptor, is metabolized by the human liver cytochrome P450, has a T^{max} of 1.6 h, and a $T^{1/2}$ of 2.6 h.

2.4. Study medication acquisition, formulation and dispensation

Zolpidem was purchased through, and managed by, the Investigational Drug Services of the University of Pennsylvania. An over encapsulation technique was used to ensure that the drug doses and placebo formulations appeared identical. Over encapsulation was accomplished using green and yellow capsules (coni-snap #1 - yellow/green [opaque]: mfr. Medisca Inc., product no: 1115). Placebo capsules were filled with lactose monohydrate powder (mfr. Fagron Inc., Product no. 804964). Medication was packaged in foil packs which contained 35 pills per pack where each blister was numbered and placebos were interspersed according to one of four randomly selected sequences. In all cases, 50% of the capsules contained zolpidem and 50% contained only inert filler and no placebo sequence lasted longer than 2 days. Blister packs were returned once a month. A nurse practitioner or the study coordinator dispensed and received the foil packs and queried subjects about compliance and side effects.

2.5. Instructions regarding study medication

All subjects were told to take each and every pill and to do so in sequence. All subjects were told to take the pills approximately 30 min before bed. The medication protocol was explained in the informed consent document as follows: "… you will be randomly assigned (like choosing numbers from a hat) to treatment. The treatment groups will differ in the amount of zolpidem received at any given time over the course of the 7 month study. The 28 weeks of treatment will include 4 weeks of treatment with a stable dose of medication and then 24 weeks with a stable and/or a variable amount of medication (range from 0 mg to 10 mg per night)." Subjects were not informed or reminded regarding the switch from Phase 1 to Phase 2 of the study at the fifth week of the investigation.

2.6. Data acquisition

An online questionnaire system was designed, developed, and implemented for this program of research. All questionnaire data was acquired via this system (referred to as an Internet Data Portal [IDP]). Data acquisition via the IDP allowed for time and date stamps (to know if subjects were adherent with the assessment schedules), the detection of responses to questions that were out of range (which result in queries to the subject), and automated monitoring and notification (both to investigators and subjects) regarding flagged items such as suicidality.

2.7. Measures

Several instruments were administered via the internet data portal on a daily, weekly, monthly, or pre-post basis to track relapse (primary outcome), assess sleep continuity (secondary outcome), and to quantify the incidence of medical symptoms (tertiary outcome). The questionnaires included a set of validated measures and a set of measures that are specific to our laboratory. The

validated measures included the insomnia severity Index (ISI) [10] and the Epworth Sleepiness Scale (ESS) [11]. The measures specific to our laboratory included questionnaires re: subject demographics (DEMO), daily sleep continuity (AM Sleep Diaries), and medical symptoms checklist (MS-CL).

The AM sleep diaries included questions pertaining to Time to Bed (TTB), Sleep Latency (SL), Number of Awakenings (NWAK), Wake After Sleep Onset (WASO), Time out of Bed (TOB), Total Sleep Time (TST), and whether or not study medication was taken. In addition to these self-reported variables, Time in Bed (TIB), Total Sleep Time - Calculated (TST-C), and Sleep Efficiency (SE%) were auto-calculated.

2.8. Outcome variables

Traditional sleep continuity variables as assessed with daily sleep diaries were used in two ways. First, bi-weekly profiles of sleep continuity (SL, WASO, NWAK, TST and SE%) were used to assess each subject for "response to treatment" during Phase-2 of the study (4 weeks) and for continued response (no relapse) during Phase-3. Second, upon completion of the study, sleep continuity (SL, WASO, NWAK, TST-C, TIB, and SE%) by group by phase were used to assess each subject for the magnitude of their response to treatment.

Treatment response and relapse were defined as follows.

Treatment Response - an average of ≥37.5% improvement on SL and/or WASO and/or a SE% of ≥90% per week for two weeks.

NOTE: The 37.5% benchmark was taken from a meta-analytic study conducted in 2002 [12]. It represents the average change in SL and WASO. The SE of ≥90% benchmark is the standard often used by behavioral therapists to represent significant treatment gains [13–15].

Relapse - the first day of a two week average of SL and/or WASO where the subject showed a ≥50% loss of SL and/or WASO gains (where the SL and WASO were greater than 30 min) and/or a SE of less than 80%.

NOTE: The SE of ≤80% benchmark is the standard often used by therapists to represent a loss of significant gains) [13–15].

Phase 2 & 3 Data Analyses**.** Selection bias was assessed by comparing demographic characteristics (sex, age, and race/ethnicity) between the group completing Phase-1 and those lost to follow-up during Phase-1. T-test for continuous measures and an exact test for categorical measures were applied. In preliminary descriptive analyses, TWT = (SL + WASO + EMA) as aggregated and summarized with means and standard deviations by group and phase. Due to the skewed distribution of TWT, the primary analysis proceeded by modeling daily measurements using generalized estimating equations with a gamma distribution and log link. In addition to randomized group indicators, the model included an indicator for phase and phase−group interactions. Model estimated mean TWT was obtained at each phase by group. A statistically significant phase−group interaction indicated a difference in TWT within a phase by group. In separate analyses, response rates were compared across groups in each phase using an exact test. All statistical analyses were performed in Stata v16.1 (College Station, TX).

3. Results

Table 2 provides data profiling the sample of subjects at baseline, those that were lost to the study, and the sample that completed the study (all phases or relapsed during Phase-2 or Phase-3). The groups were not significantly different with respect to sex, age, or race.

Table 2
Demographic information for all subjects, subjects who dropped out or were disenrolled from the study, and subjects who completed Phase-2 of the study.

Factor	Level	All	Drop-Out	Phase 2
N		99	44	55
Age, mean (SD)		61.6 (9.4)	62.0 (10.9)	61.2 (8.1)
Sex	Male	43 (43%)	23 (52%)	20 (36%)
	Female	56 (57%)	21 (48%)	35 (64%)
Race	White	75 (76%)	35 (80%)	40 (73%)
	Black or African-American	22 (22%)	8 (18%)	14 (25%)
	Asian or Asian-American	2 (2%)	1 (2%)	1 (2%)
Hispanic/LatinX	No	97 (98%)	43 (98%)	54 (98%)
	Yes	2 (2%)	1 (2%)	1 (2%)

Phase 2 (Acute Treatment). 55 subjects (age 61.2 ± 8.1, 64% female, and 73% white) were enrolled into Phase-2; 39 were randomized to the QHS condition and 16 to the IDwP condition. The two groups did not differ with respect to sex, age, or race. 77% of the QHS subjects and 50% of the IDwP subjects exhibited treatment responses but the difference between groups was not statistically significant ($p = 0.09$). Mean reduction in TWT also did not significantly differ between the two groups (QHS, −43min [CI -76,-9] and IDwP, −76min [CI -138,-14]; $p = 0.35$). The lack of significant differences may be taken as evidence that the two treatment conditions produced "comparable" outcomes on weekly measures, despite one condition's use of 50% less medication (see Fig. 2). This is consistent with prior work on intermittent dosing [3–5].

Phase-3 (Extended Treatment). 37 of the 55 subjects continued on to Phase-3; 15 were randomized to the FD/FD condition, 14 to the FD/VD condition and 8 VD/VD condition. 73% (FD/FD), 57% (FD/VD), and 88% (VD/VD) exhibited continued treatment responses ($p = 0.22$) where the mean improvement of TWT continued with FD/FD and remained stable for FD/VD and VD/VD ($p < 0.01$). Please also refer to Fig. 2.

4. Discussion

4.1. Summary

It was found that QHS dosing, as compared to other conditions, tended to produce more treatment responders and similar effects on sleep continuity during acute treatment (Phase-2), comparable maintenance of treatment response over time (Phase-3), and continued improvement on sleep continuity during extended treatment (Phase-3).

4.2. Study strengths and limitations

The primary strength of the study is its design which allowed for the experimental assessment of two forms of partial reinforcement: Nightly pill use 1) with 100% medication (FD) vs. 50% medication (VD); and 2) under three sequential conditions (FD/FD vs VD/VD vs FD/VD). FD/FD corresponds to QHS dosing; VD/VD corresponds to intermittent dosing where placebos are given on non-medication nights; and FD/VD corresponds to the approach to partial reinforcement that was used in our 2015 study (nightly dosing for one month followed by intermittent dosing with placebos). The primary limitation of the study is its sample size, particularly for Phase-3 of the study. This not only provided less statistical power to resolve small differences and prevented the assessment of how the partial reinforcement regimen fared in

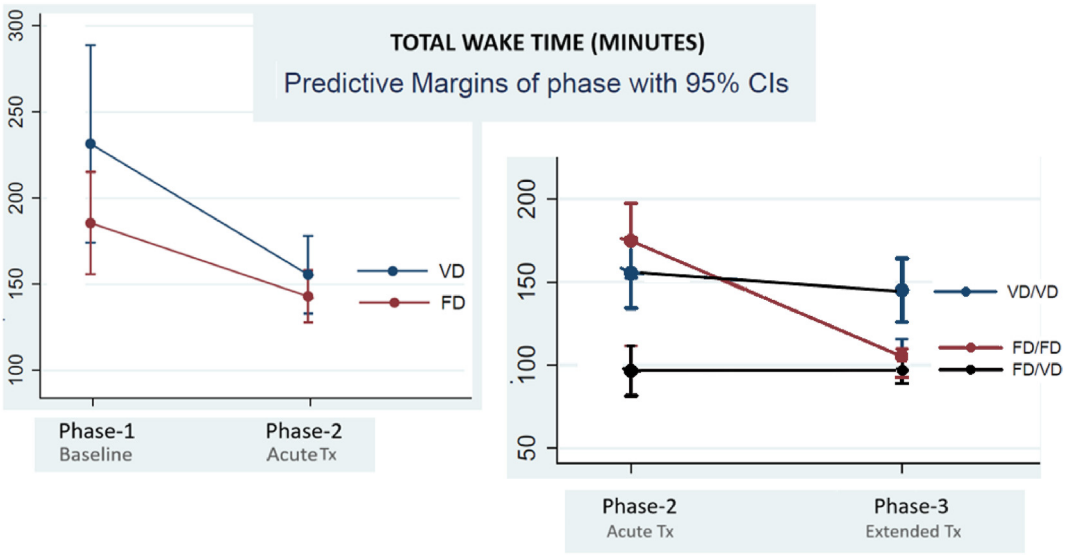

Fig. 2. Changes in total wake time (TWT) by condition. VD = variable dose; FD = full dose.

middle aged vs. older adults. Accordingly, the results from the present study must be considered preliminary.

4.3. Implications

The present study was undertaken to test whether priming (Phase-1 of the PR regimen) is needed 1) to maximize treatment responding and/or 2) for the repeated pairing of pharmacologic responses to the medication vehicle (capsule). The first test is straightforward: did the QHS condition produce more treatment responders and result in larger effects than the IDwP condition? The answer is less straightforward. The QHS condition tended to produce more responders but (contrary to our hypotheses) the average effect on sleep continuity was not significantly larger than the IDwP condition. The second test is more complicated: was it the case that those with priming in Phase-2 (QHS dosing in Phase-2 followed by variable dosing in Phase-3 [FD/VD]) fared better than those who had been in variable dosing all along (ie, did FD/VD subjects have more responders and/or greater treatment effects in Phase 3 than VD/VD)? The FD/VD and VD/VD conditions did not significantly differ with respect to percent treatment responders or TWT. If anything, and contrary to our hypotheses, those in the VD/VD condition tended to fare better with respect to maintenance of treatment response (VD/VD 88% vs. FD/VD 57%, $p = 0.22$). This suggests that QHS dosing may be required to maximize treatment responding during acute therapy but it is not required for maintenance therapy using partial reinforcement. While this may be taken as evidence against the idea that QHS dosing is necessary for partial reinforcement (required to condition pharmacologic effects to the medication vehicle), it does so only for contingent reinforcement over the course of four weeks. In hindsight, it may well be that variable interval reinforcement during acute treatment may be more optimal for maintenance of treatment effects during extended treatment (as it generally is with respect to extinction of conditioned effects) [16,17].

4.4. Conclusion

These results suggest that partial reinforcement can maintain effects but cannot allow for the additional clinical gains afforded by continuous treatment. Given this, it may be the case that the partial reinforcement technique could be improved upon by extending Phase-1 priming from one to two months. Such a change in protocol would be expected to maximize the percentage of treatment responders during acute treatment, allow for continued treatment gains during the second month of QHS dosing, and to preserve the percentage of those who remain treatment responders during extended therapy with intermittent dosing with placebos. Putting aside the issue of what is the optimal and what is the mechanism of action (what accounts for the efficacy) of intermittent dosing with placebos, it remains clear that effective acute and extended treatment can be accomplished with 50% less medication.

4.5. Future directions

The present study, along with our prior investigation, suggest multiple avenues for follow up research. Currently underway is a study addressing “how low can we go with partial reinforcement and how long can partial reinforcement be done for”. In the case of the former, we are evaluating variable dosing with one and three active doses per week (as compared to QHS and intermittent dosing without interspersion of placebos). In the case of the latter, we are evaluating extended therapy over 9 months. Beyond this, future research would also benefit from: 1) evaluating how med, placebo, and non-pill/med nights differ with respect to sleep continuity (ie, intermittent dosing with and without placebos needs to be compared); and 2) and to what extent the PR protocol is on dependent on over-encapsulation (vs. pairing placebos with active medication) and nondisclosure (patient lack of awareness of their treatment condition and/or night by night awareness of each pill's composition). Finally, it would be useful to determine if the PR regimen is equally successfully across age cohorts (ie, ideally young vs. middle aged vs. older adults).

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Conflict of interest

The authors declare no financial conflicts of interests.

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.2021.04.041.

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