

Intermittent and Long-Term Use of Sedative Hypnotics

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Abstract: In this review, the context and evidence base for intermittent and long term dosing with hypnotics is critically evaluated. The context provided includes addressing two questions: “why has long term or maintenance therapy not been a standard for practice for the treatment of chronic insomnia?”; and “why is intermittent dosing thought to represent a potential solution for the problem of chronic insomnia?”. The data from the systematic review suggests, over all, that: 1) while intermittent dosing can be conducted without resulting in rebound insomnia on non-med nights, there is insufficient data to show that the strategy is equal, or superior, to nightly dosing on a long term basis; 2) long term therapy (up to 6 months) with intermittent or nightly dosing appears viable to the extent that clinical outcomes are stable over time and occur in the absence of dose escalation or increased adverse events. The discussion section of the review includes: an analysis of the future prospects for intermittent dosing (with or without placebos); the suggestion that the use of placebos in an intermittent dosing regimen presages the use of partial reinforcement principles to enhance the safety and efficacy of the approach; finally the discussion contains a challenge to re-think, from first principles, whether the underlying approach to the medical management of insomnia is rational. It is suggested that a more rational approach is possible and that medical therapy for insomnia needs to be re-assessed for its curative (vs palliative) potential.

Key Words: Insomnia, pharmacotherapy, intermittent dosing, long term therapy.

GENERAL APPROACH TO THE MEDICAL MANAGEMENT OF INSOMNIA

Up to the present day, the medical management of insomnia has been fraught with contradictions. In a very real sense the guiding principle for practice has been “treat” but best “not to treat”. This paradoxical sentiment is likely related to a variety of factors. First, and perhaps foremost, there is the general belief that insomnia is something that patients should just “deal with”. This point of view has been, to a large extent, corroborated by the medical community based upon three considerations: 1) the conviction that “insomnia is only a symptom”, 2) the concern that both classical (barbiturates and benzodiazepines) and contemporary (benzodiazepine receptor agonists¹) treatments have the potential to be addictive and/or abused [1,2] and 3) the U.S. Food and Drug Administration’s long standing stipulation that insomnia should be managed medically only for brief periods of time.

The patient and/or societal point of view regarding insomnia treatment has not been a subject of sociologic/anthropologic study. This said, several factors likely to contribute to the perspective that insomnia is something that patients

should just “deal with”. First, sleep falls within a class of behaviors (i.e., appetitive behaviors) that are voluntarily curtailed or accentuated. The fact that the behaviors are subject to, within limits, voluntary regulation probably contributes to the belief that good sleep simply requires better self regulation. Perhaps the best testament to, or proof of, the relevance of this factor is the mass appeal of Sleep Hygiene instructions. This intervention, which has been shown to have little to no efficacy as a monotherapy [3], is perhaps the best known approach to the management of chronic insomnia.

Second, as appetitive behavior, there is a reluctance to seek or accept medical therapies for problems that “should be” manageable *via* self control strategies. This same bias has plagued the effort to have patients (and society at large) seek and/or accept medical therapies for most Psychiatric Disorders. Interestingly, the societal willingness to accept psychiatric treatment has only recently become less of a problem. This is no doubt related to the re-conceptualization of these disorders as “chemical imbalances”.

Third, the first generation of hypnotics’ (e.g., barbiturates) potential for abuse, habituation, dose escalation, and adverse events from overdose (alone or in combination with alcohol) appears to be firmly embedded in the popular consciousness and has likely lead to the common belief that “the cure is worse than the disease”. This state of affairs may have been initiated by the catastrophe that occurred with thalidomide in the late fifties and the early sixties [4-6] and has been further aggravated by the recent wave of publicity regarding the occurrence of parasomnias with the use of zolpidem (e.g., the New York Times articles written by Stephanie Saul).

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¹ Benzodiazepine receptor agonists (BZRAs) may be defined as including both benzodiazepines proper and the “non-benzodiazepine benzodiazepines”. For the purposes of this paper the BZRAs will refer to only the “non-benzodiazepine benzodiazepines (e.g., zolpidem, zopiclone, zaleplon, etc.).

Finally, the medical community at large has long made it clear that insomnia is not life threatening and that it does not confer risk for other adverse outcomes (e.g., medical or psychiatric illnesses). While there is now a fair amount of data to suggest otherwise [7] (esp., for insomnia as a risk factor for Major depression [8-11]), the prevailing wisdom for primary care practice continues to be 'insomnia is a symptom that, at worst, contributes to irritability and/or very modest impairments in interpersonal, social, and vocational functioning'.

The medical point of view that "insomnia is only a symptom" has been carried across the modern era without reservation, elaboration, or qualification. For example, in 1897 Otto Wetterstrand stated "Sleeplessness is no disease in itself, but a symptom of disease. It may be present in all diseases and commence and end with them." [12]. This same perspective, in almost identical terms, was echoed 90 years later by Patricia Lacks when she stated in 1987 "Insomnia is not a disease or a diagnostic category in itself; it is a symptom, like fever or chest pain..." [13]. In point of fact, this concept has not only persisted, but has been promulgated by sleep specialists since the early days of Sleep Medicine. Only in the present decade has this conceptualization been subject to scrutiny and revision [14-18]. The current position within the sleep medicine community is that insomnia is a disorder and one that may occur co-morbid with other illnesses [19,20]. This re-conceptualization (and corresponding evidence base), however, is sufficiently new that it has yet to inform day to day practice, inside or outside, of sleep medicine.

The general belief that hypnotics have the potential to be addictive (along with their use as palliative care) has lent substantial weight to the proposition that hypnotics should be used sparingly, even in the context of chronic insomnia. This perspective, as with the public point of view, most likely owed to the obvious problems that existed with barbiturates, thalidomide, and first generation benzodiazepines. The perspective did not owe to hard evidence demonstrating that regular and/or extended treatment with "non-benzodiazepine-benzodiazepines" resulted in habituation and/or dose escalation, abuse, or psychological dependence. This said, the lack of evidence is not the same as clear demonstrations that such problems do not reliably occur. The lack of evidence is such that there were no long term (>1 month) intermittent or nightly dosing studies (i.e., placebo controlled randomized trials which systematically assessed for adverse outcomes) until 2000 [21].

Finally, the United States' Food and Drug Administration's (FDA) stipulation that insomnia be treated as an acute condition has also fueled the inherently contradictory approach to the medical management of chronic insomnia. Their regulations for all hypnotics prior to 2004 were, on the one hand, that treatment should be limited to 7-10 days. This recommendation was, on the other hand, provided with the proviso that if hypnotics were to be taken for longer periods of time, they "should not be prescribed in quantities exceeding a 1-month supply" (PDR). Thus, the FDA guidelines themselves were somewhat contradictory. This situation persists to the present day by virtue of the fact that, while the short term indication for the two most recently evaluated BZRAs has been "repealed", no FDA approved hypnotic

(including ramelteon) has in its label an approval for the long term management of insomnia.

Given this context, it is not surprising that there has been only a limited amount of research on the long term treatment of insomnia. To date, the effort in this regard has proceeded along two dimensions: the evaluation of 1) intermittent dosing regimens over short and moderate term intervals and 2) nightly dosing over long term intervals (≥ 6 months). The literature for each of these areas is reviewed below. Following this, a discussion is provided regarding the future prospects for a rationale approach to the medical management of insomnia.

INTERMITTENT USE OF HYPNOTICS

To our knowledge there is no formal definition of what constitutes the intermittent use of hypnotics (otherwise referred to as non-nightly dosing, PRN scheduling, and as-needed use). A general rule of thumb might be that this form of "pill prescribing" and/or "pill taking" exists at the center of a continuum where periodic/irregular dosing (≤ 2 days per week) exists at one end of the spectrum and nightly dosing (6-7 days per week) exists at the other.

From a clinical point of view, it is a common practice to recommend less than nightly usage of hypnotics [22-25]. Presumably this recommendation represents the effort to limit patient exposure to medication and thereby increase the likelihood of a longer clinical efficacy "half life" and reduce the risk of habituation, dose escalation, and/or abuse. The practice of using hypnotics on an intermittent basis also appears to be a strategy that is favored by patients when using hypnotics ad libitum. Despite the fact that the "intermittent dosing" approach may be both the recommended and preferred standard of practice, only five Randomized Controlled Trials (RCTs) [26-30] have been conducted to evaluate the efficacy and safety of non-nightly use of hypnotics. These studies have been supplemented by two large scale open label studies. Each study is individually summarized below.

Intermittent Use of Sedative Hypnotics - RCTs

Cluydts *et al.* 1998 [26]. Intermittent dosing was compared to nightly medication use in a multi-center out-patient study. 160 adult patients (mean age = 45 yrs) with chronic insomnia took part in the investigation. The patients were treated for 2 weeks with zolpidem (10 mg), either continuously or intermittently (five consecutive nights zolpidem and two consecutive nights placebo per week). At the end of the two-week treatment, patients in the nightly use condition estimated their nightly total sleep time as 6.96 +/- 1.19 hrs (vs 6.07 +/- 1.25 hrs. at baseline). Patients in the intermittent dosing group estimated their nightly total sleep time as 6.94 +/- 1.30 h (vs 5.72 +/- 1.46 h). These results suggest that the effects of zolpidem (10 mg) are comparable whether the drug is administered every night or intermittently.

While the first of its kind, the limitations of this study include: the use of retrospective estimates, less than the full compliment of sleep continuity² variables, the use of a fixed

² Sleep continuity refers to the collection of variables that correspond to sleep initiation and maintenance, including sleep latency (SL), number of awakenings (NOA), wake after sleep onset (WASO), and total sleep time (TST). While the term is not formally

intermittent dosing scheme, and the absence of a placebo control group.

Walsh *et al.* 2000 [21]. Intermittent dosing with zolpidem was compared with intermittent dosing with placebo in an acute application. 160 adult patients (mean age = 45 yrs) with DSM-IV-defined primary insomnia took part in this multi-center, out-patient, study. The patients received either zolpidem or placebo for a period of eight weeks. Over the course of each two week period patients received "10 capsules, either zolpidem 10mg or identically appearing placebos". Patients were instructed to take a single capsule at bedtime (as needed) and that the medication should be taken at least three, but no more than five, nights per week. Sleep was assessed with both global assessments (patient and investigator ratings) and with daily sleep/wake diaries. On the nights that pills were taken, patients in the intermittent use condition exhibited approximately a 50% reduction in sleep latency (75 vs 36 min.) and approximately a 30% increase in total sleep time (320 vs 415 min). Patients in the placebo condition exhibited approximately a 25% reduction in sleep latency (67 vs 50 min.) and approximately a 14% increase in total sleep time (320 vs 363 min). The medication effects were stable across the 8 week treatment period and there was no evidence of discontinuation effects or an increased frequency of pill taking.

The limitations of the investigation include: an analysis of less than the full compliment of the standard sleep continuity variables and an analytic strategy that did not allow for the clear resolution of group-by-time effects.

Allain *et al.* 2001 [31]. This was a multistage design whose final phase entailed three weeks of intermittent dosing with either zolpidem (10mg) or placebo. Stage 1 was a placebo run-in. During Stage 2 subjects received 2 consecutive nights of zolpidem. During Stage 3 subjects received two tablets of active medication over 5 days "to accustom the patients to using the drug discontinuously". During Stage 4 subjects were randomized to either zolpidem or placebo and all subjects were instructed to use as few tablets as possible. 245 subjects participated in the investigation who met criteria for "chronic insomnia" (at least 3 sleep disturbed nights per week for at least 4 weeks). The findings from the study were as follows. The two groups did not significantly differ with respect to frequency of tablet intake; the placebo group took a mean of 4.8 tablets per week and the zolpidem group took a mean of 5.2 tablets per week. On the nights which the patients took study medication (+ pill) the mean increase in sleep diary assessed TST (from baseline to the end of the study) was significantly greater with zolpidem than placebo (82.7 min vs 62.8 min). The groups did not differ on TST, however, for the average across all nights ("+ pill" and "-pill"). On the pre-post CGI measure (in this case the Clinical Global Improvement scale) 54% of the patients in the zolpidem group were "much or very much improved" vs 24% in the placebo as needed group. Finally, while the two groups did not differ with respect to adverse events, the drop out rates were significantly lower in the zolpidem group (0%) as compared with the placebo group (6%).

The limitations of the investigation include: a lack of clarity re: the placebo run-in phase (how long this lasted and whether placebo responders removed or analyzed separately); a presentation of less than the full compliment of the standard sleep continuity variables; and the presentation of data in a manner that did not allow for the clear resolution of group-by-time effects. This said, the multi-stage "priming" approach to initiating intermittent dosing was interesting. It would be useful in future studies to compare this strategy to "straight up" intermittent dosing. Such a study would allow an assessment of the value of priming with placebo, the effects of initial exposure, and the effects of a intermittent dosing accommodation phase. Such strategies may serve to sensitize patients to treatment gains.

Hajak, Cluydts *et al.* 2002 [32]. Intermittent dosing (5 nights/week [zolpidem 10 mg] and placebo 2 nights/week) was compared to nightly use of zolpidem 10 mg for a 2 week period. The study was conducted across seven European countries in 789 primary care population patients with chronic insomnia (>4 weeks duration). Subjects were randomized to one or the other conditions after a 14 day placebo run-in period. All subjects received medication and/or placebo for a treatment period of two weeks. It is important to note that in this protocol 1) the intermittent group received placebos on non-active med nights (vs no pill), 2) the placebos were "randomly" distributed throughout each 7 day block, and 3) all the zolpidem-placebo sequences for each 7 day block were initiated so that active drug was provided for at least the first two days of each week. The primary outcome was assessed using a Clinical Global Impression improvement score (CGI-II) which showed that 65.2% of patients in the continuous and 58.6% in the intermittent group were rated 'much' or 'very much' improved. These improvement rates corresponded to a mean 59% reduction in sleep latency and a 35% increase in total sleep time for the continuous treatment group and a mean 45% reduction in sleep latency and a 34% increase in total sleep time for the intermittent treatment group. Both groups exhibited comparable rates of adverse events. The comparability (non-inferiority) between the two conditions appears to support the proposition that, on average, intermittent dosing is as effective as nightly use of hypnotics.

The limitations of the investigation include: the use of retrospective estimates, and less than the full compliment of sleep continuity variables. An additional complicating factor for this study is the use of placebos on "non-pill" nights. While a thoughtful and novel approach to dealing with "med discontinuation", the discovery of non-inferiority between intermittent and nightly dosing may have more to do with expectancy and conditioning effects from partial reinforcement than the use of a so called intermittent dosing schedule. (For an explication of this point, please see the Future Directions section of this paper).

Perlis *et al.* 2004 [33]. Patients who met DSM-IV criteria for primary insomnia participated in a large scale, double-blind, randomized placebo-controlled trial (12 weeks) comparing an intermittent dose schedule with zolpidem (10mg) to placebo. Study Medication was provided in foil packs on an every-other-week basis, and patients were instructed to take no fewer than 3 and no more than 5 pills per week.

part of the sleep lexicon, it has the heuristic value of being a global term whose meaning may be contrasted with the class of variables that correspond to sleep architecture.

Sleep continuity and pill use were evaluated on a daily basis with sleep diaries. By study end, 199 patients (mean +/- SD age = 41.0 +/- 12.8 years; 71% female) were randomly assigned to treatment. Patients receiving zolpidem on an intermittent basis exhibited (“+ pill”), on average, a 42% decrease in sleep latency, a 52% reduction in number of awakenings, a 55% decrease in wake time after sleep onset, and a 27% increase in total sleep time as compared to baseline. These positive clinical gains did not diminish with time. Patients receiving placebo on an intermittent basis exhibited (“- pill”), on average, a 12% decrease in sleep latency, a 23% reduction in number of awakenings, a 22% decrease in wake time after sleep onset, and a 8% increase in total sleep time as compared to baseline. These effects were stable with time. There was also no evidence that the zolpidem group (as compared to the placebo group) exhibited rebound insomnia on “non-pill” nights or dose escalation over time. Fig. (1) provides an example of the clinical outcomes for sleep latency by condition for each of the 12 weeks. Note that panel 1 of the figure represents the average data on “+ pill” nights; panel 2 of the figure represents the average data on “- pill” nights; and panel 3 represents the average data irrespective of whether or not a pill was taken. These data serve to illustrate 1) robust effects on “+ pill nights” for zolpidem, 2) an absence of rebound insomnia (or significant worsening) for both zolpidem and placebo on “- pill nights”, and 3) that the average clinical response across the conditions (“+ pill” and “- pill”) was good.

The primary limitation of this study is inherent in its design: the data may only be used to address absolute efficacy (vs placebo) and rebound issues. What remains to be tested, particularly in longer term designs, is the issue of relative efficacy, i.e., whether intermittent dosing confers an advantage over nightly use of hypnotics.

Intermittent Use of Sedative Hypnotics – Open Label Studies

Hajak, Bandelow *et al.* 2002 [28]. In this open label, three week, observational study, 2690 patients with chronic insomnia were treated with zolpidem according to an "as-

needed" administration treatment schedule (between zero and five tablets per week, as determined by the patient). Subjects were instructed to use Stimulus Control Procedures (SCP) during the medication-free nights. The mean age of the sample was 59 years of age and 66% were female. At study end, it was found that medication use was significantly reduced from baseline (28% reduction - 3.7 to 2.6 pills per week) while treatment efficacy, as assessed *via* Clinician Global Impression (CGI) scales, was not significantly changed. Subjective assessments of sleep continuity showed that, compared to baseline, sleep latency was significantly reduced (74 to 27 min) and total sleep time was increased (5.0 to 6.8 h). Mild adverse events were observed in 1.2% of patients. No serious adverse events occurred during the study period.

The primary limitation of this study is it was not clearly an investigation of intermittent dosing so much as it is was an evaluation of combination therapy (zolpidem + SCP). As such the present findings are consistent with prior RCT findings that acute therapy can be effectively conducted by adding CBT-I to a standing medical regimen (e.g., [34]).

Levy *et al.* 2004 [35]. This was a general practice multi-centre study designed to evaluate frequency of zolpidem use over time when the medication was prescribed on an ‘as-needed’ basis. 1938 patients were enrolled in this four week study. Each patient was provided a 3 week supply of medication (21 doses) and was instructed to take the medication ‘as needed’. All subjects kept a daily sleep diary for sleep latency (SL) and total sleep time (TST) and were evaluated by a clinician at the beginning (Day 0) and end of the study (Day 28). Sixty-four percent of the sample was female (mean age 48.9 ± 14.2 years). The mean duration of insomnia was 3.0 ± 15.2 months. Eighty percent of the sample reported problems with initial insomnia; 37% of the sample reported problems with middle insomnia; 10% of the sample reported problems with late insomnia.

When evaluating pill use on a week-by-week basis it was found that consumption decreased from 5.1 ± 1.9 doses/week during week 1 to 4.1 ± 2.3 doses/ week during week 2

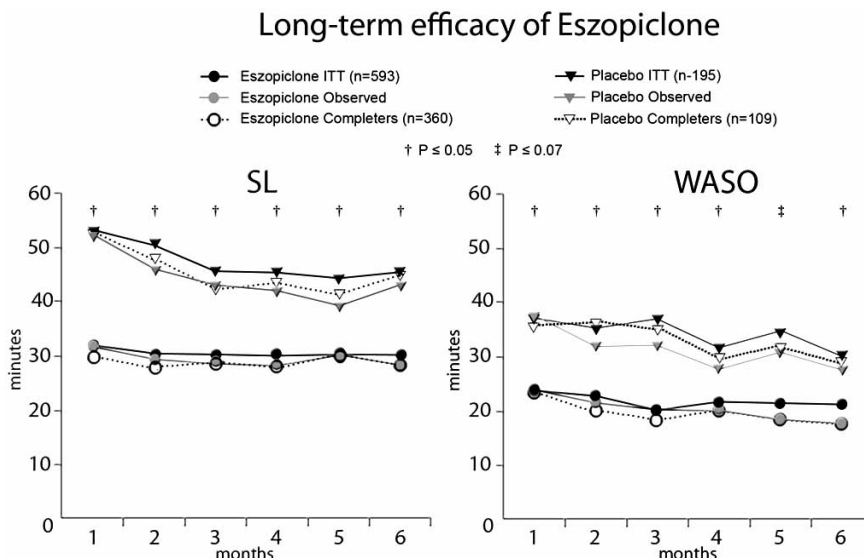


Fig. (1). Long term efficacy of Eszopiclone.

to 3.7 ± 2.5 doses/week during week 3. Pill utilization data are not provided for week 4. Global clinical improvement measures showed “moderate to very marked improvement for 90% of the patients”. The safety data revealed 143 adverse events in 133 people. Thus, 7% of sample exhibited AEs including headache, depression, nightmares, and anxiety. This rate of AEs (and type) was deemed consistent with the published safety data.

The primary limitations of this study are 1) the finding that pill use declined with time may be an artifact of the design, 2) the limited set of sleep continuity variables acquired (Just SL and TST), and 3) the lack of effectiveness analyses (overall and as a function of “+ pill” vs “- pill”. With respect to the first issue, it seems that the initial peak in medication use was necessarily followed by a reduction in use, given the limited supply of medication (21 doses for 28 days). A better assay of medication use would have been to allow this scenario to freely vary (provide an instruction to use “as needed” and a full compliment of medication). Under these conditions a downward trend in medication use might be more meaningful. With respect to the second issue, this is (frankly) a perennial problem with most insomnia research; the full compliment of sleep continuity variables is not obtained, or analyzed, or presented. By not presenting number of awakenings (NOA) or wakefulness after sleep onset (WASO) one cannot fully know how effective the medications were, especially given that ~47% of the sample presented with middle and late insomnia. Finally, while not the stated aim of the study, it is difficult to understand why the data were not arrayed in a manner which would allow a determination of how the effectiveness (real world) data compared to the prior efficacy data from the RCTs.

LONG-TERM USE OF SEDATIVE HYPNOTICS

To our knowledge, only two RCTs and two open label extension studies have been conducted evaluating the efficacy and safety of “long term” use of hypnotics. The lack of research is, in large measure, due to the general unwillingness to even entertain the idea of long-term and/or maintenance therapy for insomnia. The other contributing factor pertains to a fundamental lack of consensus about what chronic insomnia is (vs acute insomnia) and thus how it should be treated. The lack of consensus is best illustrated by the lack of standard definition for what constitutes “chronic”. Some define chronic as being symptomatic for 30 or more days; others use three or six month cutoffs [36]. While the difference between 1,3, and 6 months may seem relatively trivial, the distinction is important because it demarcates the point at which 1) the disorder can be expected (as a chronic disease) to persist unabated and 2) more than two week treatment interventions are required. The data to date [37-39] suggest that insomnia lasting a year or more is likely to continue for time periods of up to a decade. Given this context, the concept of “long term treatment” must be reconsidered in terms of regimens that can be applied for years or decades. Clearly, this is not in keeping with the current conceptualization of “long term treatment”. This said, the studies below provide the first and best data regarding the risk for adverse outcomes with extended treatment and the sustainability of treatment efficacy over the “long run” (6-12 months).

Six Month RCT Studies

Krystal *et al.* 2004 [40]. This study was the first long duration trial ever conducted. It was a 6 month randomized, double-blind, multi-center, placebo-controlled trial of eszopiclone (3mg) in patients with DSM IV defined primary insomnia. Eligible subjects were between the ages of 21 to 65 years old and were required to report less than 6.5 hours of sleep per night, and/or a sleep latency of more than 30 minutes each night for at least 1 month. Sleep continuity was evaluated on a weekly basis using an interactive voice-response system. The parameters assessed included: sleep latency; total sleep time; number of awakenings; wake time after sleep onset; and quality of sleep. Monthly ratings were also obtained for ability to function, daytime alertness, and sense of physical well-being.

A total of 1194 patients were screened. Of these 791 met all eligibility criteria and 788 were randomized and received treatment (eszopiclone [n = 593]; placebo [n = 195]). Approximately 63% of the sample was female (mean age 43 ± 11 years). No data were provided regarding insomnia history (age of onset, duration of illness) or insomnia phenotype (initial, middle, or late insomnia). Study results were that eszopiclone (vs placebo) produced significant and sustained improvements in sleep latency (e.g., Week 1 30 vs 60 minutes; Week 24 30 vs 45 minutes), wake time after sleep onset (e.g., Week 1 20 vs 45 minutes; Week 24 21 vs 30 minutes), number of awakenings (e.g., Week 1 2.0 vs 2.0; Week 24 1.6 vs 2.0 minutes), total sleep time, (e.g., Week 1 375 vs 330 minutes; Week 24 382 vs 345 minutes), quality of sleep (e.g., Week 1 6.0 vs 4.4; Week 24 6.4 vs 5.5). Of particular note is that the initial sleep continuity gains were remarkably stable with time, and that this was true regardless of the analytic technique used to accommodate “right censorship” (i.e., subjects lost to follow up). For an illustration of this stability see Fig. (2). Monthly ratings of next-day function, alertness, and sense of physical well-being were also significantly better with the use of eszopiclone than with placebo. As can be seen from the data above and in Fig. (2), there was no evidence of tolerance. The most common adverse events were unpleasant taste (26% vs 5.6%), headache (19.6 vs 19.0) and infection (15.9% vs 6.7%).

The primary limitation of this otherwise landmark study was the use of weekly assessments for the sleep continuity variables. This form of retrospective reporting may have conferred an artificial level of stability to the data. On a more minor note, these investigators reported their data in medians (although means were available in the various tables). Use of median values makes the interpretation of the sleep continuity findings, relative to the established literature, more difficult.

Krystal *et al.* 2007 [41]. Like its predecessor, this study was also a 6 month randomized, double-blind, multicenter, placebo-controlled trial in patients with DSM IV defined primary insomnia. It was conducted over the course of 25 weeks with zolpidem extended-release (12.5mg). Unlike the prior study, this investigation allowed subjects to utilize medication in a manner akin to the intermittent dosing studies. Specifically, subjects were instructed to “take the medication on those nights when they judged it to be necessary,

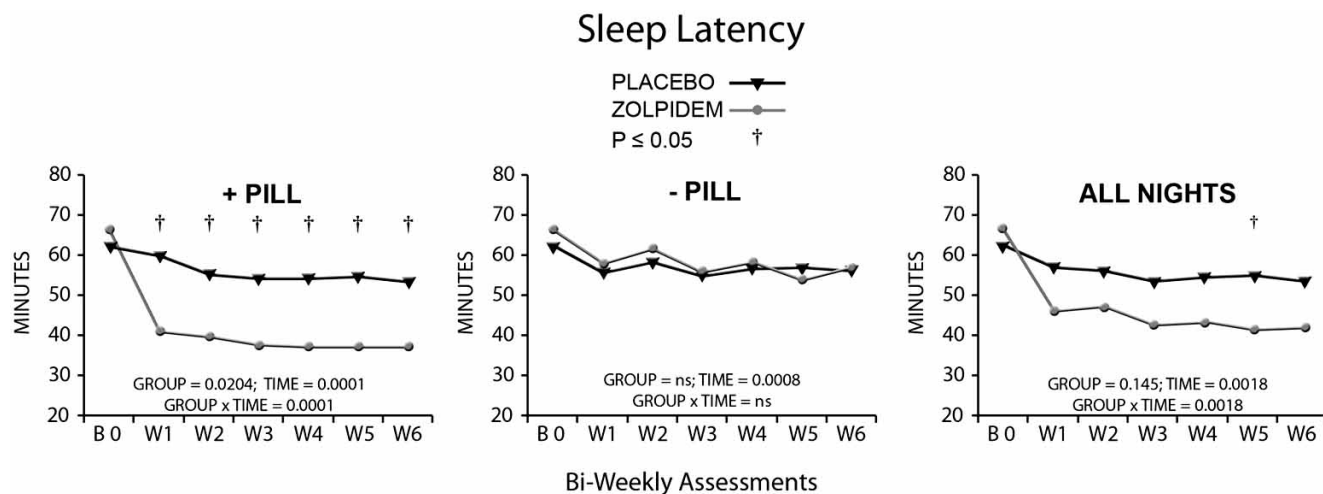


Fig. (2). Sleep latency.

with the caveat that they were required to self-administer study medication at least 3 nights per week". Eligible subjects were between the ages of 18 and 65 years old and who reported at least 3 months of difficulty falling asleep, difficulty maintaining sleep, or difficulties with non-restorative sleep where at least 1 hour of wakefulness occurred during the sleep period (SL and/or WASO) on 4 or more nights per week. Sleep continuity was evaluated on a daily basis using an interactive voice-response system. The parameters assessed included: sleep latency; total sleep time; number of awakenings; wake time after sleep onset; and quality of sleep. Monthly ratings were also obtained for ability to function, daytime alertness, and sense of physical well-being.

A total of 1701 patients were screened and 1025 met all eligibility criteria and were randomized. 1018 subjects received treatment (zolpidem extended-release [$n = 669$]; placebo [$n = 349$]). Approximately 61% of the sample was female (mean age 45 ± 11 years). As with the prior study, no data were provided regarding insomnia history (age of onset) or insomnia phenotype (initial, middle, or late insomnia). Data were provided regarding duration of illness. 4.1% of the sample had for ≤ 1 year; 36.0% for 2 to 5 years; 25.6% (261) for 5 to 10 years; and 34.2% of the patients had had insomnia for ≥ 10 years. Study results were that zolpidem extended-release significantly differed from placebo at every time point for all the sleep continuity variables (SL, WASO, NOA, TST), daytime function (morning sleepiness and ability to concentrate), and for the global PGI and CGI measures. The most frequent adverse events for zolpidem extended-release were headache, anxiety and somnolence. No rebound effect was observed during the first 3 nights of discontinuation. Finally, the authors noted that the patients in the active medication condition reported, on average for the

6 months, taking slightly more medication (111 vs 86 of 180 nights). The month to month utilization was dubbed as "stable" within each of the treatment groups.

The primary limitations of this study were 1) the lack of mean sleep continuity values (weekly or monthly or pre-to-post values) so as to allow for the resolution of treatment effects as they might compare to the established literature, 2) 1) the lack of mean sleep continuity values (weekly or monthly or pre-to-post values) so as to allow for the resolution changes in efficacy over time; 3) the absence of a "+pill" and "-pill" analysis, 3) the lack of a statistical analysis of medication use over time which took into account the trends of both groups.

Extension Studies

Ancoli-Israel *et al.* 2005 [42]. This investigation was a 1-year open-label extension study of two randomized, double-blind trials of zaleplon conducted in the United States (36 centers; $n = 551$) and in Europe (50 centers; $n = 437$). Patients (ages 59-95) self-administered zaleplon nightly (flexible dosing with 5 or 10 mg) for 6 to 12 months. The study was concluded with a 7-day single-blind placebo-controlled run-out period. Inclusion criteria were that subjects complete the double-blind phase of the parent study and a run-out period of 7 days followed by 7-28 treatment-free days. During the treatment free period subjects were reassessed to determine if subjects continued to be symptomatic. Subjects who reported a median sleep latency of 30 min or more and sleep-associated daytime complaints were eligible for the extension study. Subjects were initially assessed for 7-15 days to determine the study dose and then were followed monthly using sleep diaries that profiled the week prior to the in-lab safety assessments. Overall, the diary based sleep continuity

data showed significant improvement in time to sleep onset (~30% decrease), number of nocturnal awakenings (~30% decrease), and total sleep time (~12% increase). These gains were stable over time and were associated with an adverse event rate that was comparable to the antecedent short-term trial. The single blind discontinuation was associated with worsening of insomnia symptoms, but as can be seen in Fig. (3), the loss of clinical gains did not constitute rebound insomnia.

The limitation of this study, although understandable given its length, is the lack of the use of daily sleep diaries. As with prior studies, monthly retrospective estimates may have conferred an artificial level of stability to the data.

Roth et al. 2005 [43]. This study was a 6-month open-label extension phase of the Krystal et al. (2003) study

summarized above. Eligible subjects were adults (ages 21 to 64) with DSM-IV defined primary insomnia who completed the parent study. Subjects who were initially randomized to eszopiclone continued with active medication (n=360). Subjects who were initially randomized to double-blind placebo were crossed over to eszopiclone (n=111). Both groups continued in the follow up study for 6 months during which they completed sleep diaries on a weekly basis using an interactive voice-response system. The parameters assessed included: sleep latency; total sleep time; number of awakenings; wake time after sleep onset; and quality of sleep. Monthly ratings were also obtained for ability to function, daytime alertness, and sense of physical well-being. Safety and compliance were assessed at monthly clinic visits.

Subjects who were initially randomized to eszopiclone and then were continued on active medication reported, as

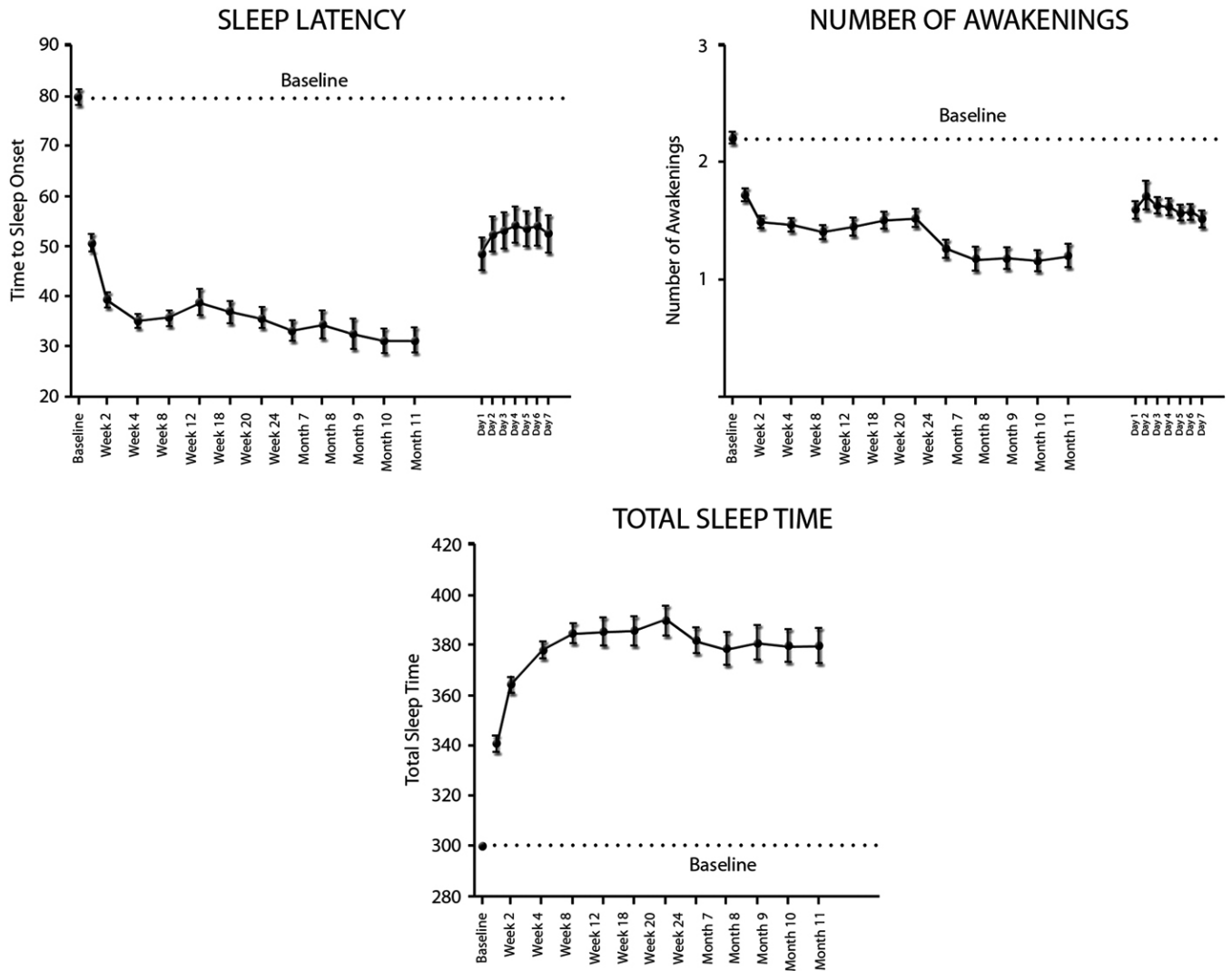


Fig. (3). The dotted line in each graphic represents the baseline (pre-Tx) values for SL, NOA and TST. The Day 1-7 at the right side of each graph represents the initial 7 day discontinuation from medication. The discrepancy between the baseline and the 7 day values represent not only a lack of rebound insomnia but suggest that clinical gains are sustainable in the absence of treatment.

compared to the pre-study baseline: decreased sleep latency (e.g., Baseline 90 min, Month-7 44 min Month-12 45 min.); wake time after sleep onset (e.g., Baseline 83 min, Month-7 35 min, Month-12 40 min.); number of awakenings (e.g., Baseline 3.2, Month-7 1.7 Month-12 1.6.); and increased total sleep time (e.g., Baseline 302 min, Month-7 389 min Month-12 382 min.). Sleep quality, ratings of daytime function, alertness and sense of physical well-being were also significantly improved. Of note, while formal analysis of temporal patterns (time effects or group*time effects) do not appear to have been undertaken, the sleep continuity outcomes were represented graphically and it appeared that 1) eszopiclone yielded very stable effects over time and 2) placebo showed the typical “drift” that occurs in insomnia RCTs [52].

Subjects who were initially randomized to double-blind placebo and then switched to open-label eszopiclone reported, as compared to the prior month of placebo treatment: decreased sleep latency (e.g., Baseline 63 min, Month-7 35 min, Month-12 44 min.); wake time after sleep onset (e.g., Baseline 70 min, Month-7 48 min, Month-12 27 min.); and number of awakenings (e.g., Baseline 2.6, Month-7 1.6, Month-12 1.8.); and increased total sleep time (e.g., Baseline 339 min, Month-7 400 min, Month-12 381 min.). Sleep quality, ratings of daytime function, alertness and sense of physical well-being were also significantly improved. Finally, although also not formally analyzed, it appears that (if initial the initial group differences were accounted for), the effects of eszopiclone may have been potentiated by the prior exposure to placebo (at least for SL and TST).

The limitations of this study, were the same as those that occurred with the parent study including: the use of weekly assessments for the sleep continuity variables.

SUMMARY

At present there is only limited evidence for the durability of the medical treatment of insomnia over time. Only one RCT has been conducted over the course of 6 months for nightly dosing [40], although the results of this study are supported by two extension studies [42,43]. Several studies have been conducted on the issue of intermittent dosing [21,26,31-33]. All of these studies have been conducted with zolpidem or extended release zolpidem. Only two of these studies were conducted with a nightly dosing comparator [26,32] and only one was conducted as a long term investigation (6 months) [41]. In general, the results from these studies suggest, assuming equipotency³ (non-inferiority amongst the various benzodiazepine receptor agonist compounds), that 1) BZRAs can be used effectively and safely on a nightly basis for periods of up to 6 months⁴, 2) nightly

use of BZRAs does not result in a loss of efficacy over time, 3) intermittent dosing is effective and safe for periods of between three and six months, 4) rebound insomnia (a worsening of insomnia symptoms as compared to pre-treatment) does not occur on non-medication nights, irrespective of whether placebos are substituted for active medication.

FUTURE PROSPECTS

Intermittent Dosing. The concept of intermittent or non-nightly dosing clearly came about in relation to both clinician and patient desire to use sleep medication more sparingly and by so doing reduce the chances of habituation, tolerance, dose escalation, and abuse. While it is unclear whether these issues were of concern with BZRA therapy in the first place, there has yet to be a direct test of efficacy and safety of this strategy. That is, there has not been a single trial that provides evidence that safety and/or efficacy is enhanced by intermittent dosing as compared to nightly dosing. All that is known is that the approach works on “+pill nights”, that there is no rebound insomnia on “-pill nights”, and that (over all) patients are better off than their baseline profiles or as compared to patients treated intermittently with placebo. Thus, at this juncture, it is critical that we not accept intermittent dosing as a legitimate regimen until such a time as a formal, large scale, long term study is conducted which shows that the strategy confers some advantage over nightly dosing.

The research on intermittent dosing has also provided something truly novel that may, ultimately, be more useful than “+pill and -pill” approach. Both Cluydts *et al.* and Hajak’s and colleagues utilized placebos on “-Pill” nights. Cluydts’ provided medication and placebos using a single blind fixed schedule approach (5 nights active med and 2 nights placebo). Hajak “randomly” distributed the placebos throughout each 7 day block and in such a manner that all the zolpidem-placebo sequences were initiated with 2 days of active medication. The use of placebos in this context was, no doubt, undertaken in an effort to prevent the loss of expectancy effects due to non-pill use during intermittent dosing. Future studies should be undertaken to test this approach. Such studies should have, as part of their design, intermittent dosing with and without placebos and planned analyses that take into account “+ med”, “- med” and overall med effects on sleep continuity.

Cluydts’ *et al.* and Hajak’s and colleagues use of placebo also serves to open the door on the application of technique which may serve to allow placebos to do more than maintain expectancy effects; their efforts, combined with current partial reinforcement approaches, may serve to allow placebos to carry the full clinical effect of active medication during “intermittent dosing”.

The concept behind partial reinforcement [46,47] is that placebos may become conditioned stimuli for desired physiologic effects given the appropriate conditions. In brief, the appropriate conditions are as follows: 1) the active medication modulates physiologic responses (i.e., is not replacement therapy for substances the body cannot produce); 2) the active medication can be provided for a period of time without loss of its clinical effects; 3) placebo formulations of the medication delivery system are possible; and 4) placebos

³ Apart from the issues of dosing strategy or duration of treatment, there is the issue of the relative efficacy of BZs and BZRAs. While not addressed in this review, there are now at least three such studies. One by Dundar and Colleagues [44]. One by Buscemi *et al.* [45] and one by Riemann and Perlis (The Treatment of Insomnia: State of the Science. In Press – Sleep Medicine Reviews).

⁴ As noted previously, the FDA came to a similar conclusion but handled the conundrum of “what is long term therapy” by simply removing the short term indication for the two most recently evaluated BZRAs (eszopiclone and zolpidem-cr). Neither of these compounds, however, have been approved for the “long term” treatment of insomnia.

which are identical with the active medication may be interspersed with active medication on a random basis.

In the present application, partial reinforcement might amount to having subjects use a full dose formulation of a hypnotic for 1 month (nightly dosing) and then having the subjects cross over to intermittent dosing where all the non-med nights are placebos. As an intermittent dosing strategy one might expect that placebos would be delivered on between 2 and 4 occasions per week. In this paradigm, the provision of active meds on between 3 and 5 nights per week would be expected to reinforce the conditioning effects that were acquired during the month long initial exposure (hence the term partial reinforcement). The application of this strategy is current under evaluation.

Long Term Treatment. While intermittent dosing, with or without the use of placebos, represents a potentially viable approach for long term (or longer term) therapy with hypnotics, it is also useful to reconsider from first principles what constitutes a rationale approach to the medical management of chronic insomnia. The assumption underlying the need for the long term treatment of insomnia is that insomnia is a chronic condition. That is, untreated the disorder will not abate⁵ and medical treatment is only palliative. While the former is likely to be true, the latter has yet to be truly put to the test. The traditional approach to chronic insomnia might be best likened to aspirin therapy for headache. What if, however, headache is not the appropriate analogy. What if chronic insomnia is more analogous to infection. If true, then what might be expected to be the clinical outcome if insomnia (as an infectious process) is treated on an “as needed” basis (or *via* an intermittent dosing). One would expect that what could be cured will not be cured. Put differently, it may be the case that hypnotics have curative potential, but not as used within current treatment regimens. What remains to be researched is this fundamental question: “can sedative hypnotics provide a cure when dosed frequently enough for long enough”. To embrace this possibility, dose-response studies (where does equals duration of therapy) will need to be undertaken where such protocols will likely require nightly dosing, an end of treatment titration regime, and (potentially) a minor behavioral intervention for relapse prevention. Only with the results from this kind of study will we then be in a position to know how to proceed with the effort to develop a rationale approach to the medical management of chronic insomnia.

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⁵ While most agree with the tautological statement that “insomnia, when chronic, is chronic” (i.e., will not resolve of its own accord), there is a growing interest in the possibilities that insomnia may 1) have a waxing and waning course [48], and 2) significantly and systematically vary in severity over the course of days [49, 50]. The former suggests that chronic insomnia may be more of an episodic disease (like recurrent Major Depression). The latter suggests that insomnia may occur, in part, in relation to sleep homeostasis dysregulation [51] and that this kind of symptom variability may underlie the strong placebo effects that occur in insomnia RCTs [52].

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