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# A meta-analysis of sleep changes associated with placebo in hypnotic clinical trials

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**Abstract**

**Objectives**: The effects associated with placebo (EAP) have been incompletely described in clinical trials of insomnia treatment. We conducted a meta-analysis of insomnia medication trials for the purpose of estimating the magnitude of sleep EAP.

**Method**: We reviewed Medline for 1966 through 2000 for the meta-analysis. The subject heading of *insomnia* restricted to the subheading of *drug therapy* was crossed against the results of a search on the subjects heading *placebo* and text word *placebo*. We selected only papers that examined primary insomnia, incorporating both placebo and active medication therapies in a randomized, double-blind, parallel-group design. We required that results be reported for 1, 2, 3, or 4 weeks of treatment, and that outcomes be reported in hours/minutes.

**Results**: Five papers satisfied our requirements for eligibility, comprising 213 patients receiving placebo for a 2-week interval. Subjective sleep latency demonstrated a significant reduction (mean ± S.E.) of 13.1 ± 2.0 min (95% confidence interval (CI) 9.2, 17.0) for the placebo group after combining the data across studies. Subjective total sleep time demonstrated a significant increase of 13.5 ± 5.4 min (95% CI 2.9, 24.0). Polysomnographic (PSG) sleep latency demonstrated a non-significant reduction of 2.5 ± 4.3 min (95% CI −5.9, 10.9).

**Conclusions**: The confirmation of EAP in insomnia clinical trials argues for the retention of a placebo control in future insomnia clinical trials.



*Keywords*: Placebo; Ethics; Hypnotics; Sleeping pills; Meta-analysis

## 1. Introduction

The symptoms of many different psychological disorders improve during administration of placebo in the context of controlled clinical trials of psychotropic medication. This phenomenon is commonly termed 'the placebo effect', but it is unclear to what extent the change in symptom severity is due to the expectant hopefulness in consumption of the placebo, or whether the change is attributable to the passage of time, or non-specific effects of participation in a research project. In the interest of linguistic precision, we will use the term 'placebo effect' only to refer to the patient's expectation associated with placebo ingestion, and will use the more general term 'effects associated with placebo' (EAP) to describe the sum of all factors leading to symptom change during placebo administration. Also, although the term placebo has been applied to non-pharmaceutical, psychological interventions such as quasi-desensitization, this paper will define placebo as an inert substance designed for ingestion unless otherwise specified.

Although EAP have been described for most psychiatric disorders, including even more severe disorders such as bipolar disorders and schizophrenia [1,2], there is surprisingly little information about EAP during insomnia treatment. If EAP exist at all, then it seems likely that EAP would occur during clinical trials for primary insomnia, given that the overall level of psychopathology is by definition less than that seen in psychiatric disorders [3], and less severe disorders might be more susceptible to EAP [4].

Conclusions are mixed regarding whether there are EAP associated with insomnia, with some authors deducing that EAP do exist, [5–8] and others take the opposing view [9–12]. Resolution to this issue is not trivial, as administration of placebo in clinical trials has both economic and ethical implications. We sought to address this question through combining the information provided in several clinical studies using meta-analytic techniques. Our goal is not to

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establish the clinical significance of placebo, but rather to establish whether there is any change associated with placebo that might serve to guide the design of future clinical trials.

## 2. Methods

### 2.1. Strategy

Inspection of recently published hypnotic clinical trials reveals that many study designs include up to 4 weeks of treatment, and that changes in key outcome variables are typically reported for the end of each week of treatment. The possible number of outcome variables is large including subjective sleep latency (SL), subjective wake after sleep onset (WASO), subjective number of awakenings, subjective total sleep time (TST), polysomnographic (PSG) SL, PSG WASO, PSG TST, PSG sleep stages, PSG microarousals, and others. We believed that subjective SL, subjective TST, PSG SL, and PSG TST would be among the most commonly reported outcome variables, and that their clinical relevance had face validity. Therefore, we began our meta-analysis with the intent of describing EAP for subjective SL, subjective TST, PSG SL, and PSG TST for the intervals concluding 1, 2, 3, and 4 weeks of placebo administration.

### 2.2. Data sources

Other groups have recently published meta-analyses examining hypnotic/placebo differences [13,14], and we elected to build our meta-analysis around the methods described in Nowell et al. [13]. We searched Medline for the period of 1966 through 2000 for papers in English. The subject heading of *insomnia* restricted to the subheading of *drug therapy* was crossed against the results of a search on the subjects heading *placebo* and text word *placebo*. We also crossed the terms *insomnia*, *hypnotic* and *clinical trials*.

### 2.3. Study selection

We selected only papers that exclusively or predominantly included primary insomnia to reduce the additional expected variability in measurements taken over time in clinical trials of persons with insomnia secondary to mental disorders or medical disorders. For example, placebo is typically paired with an antidepressant medication in studies of depressed insomniacs; therefore the participants in such trials might expect a mood-effect as opposed to a sleep-inducing effect of their medications. Indeed, the severity of insomnia secondary to depression varies with improvement in mood, which would complicate the attribution of placebo as being related to changes in sleep, as opposed to changes in mood [15–17]. In contrast, sleep complaints per se are the focus of clinical trials of primary insomnia, and the participants of such trials would expect a sleep-inducing effect to result from consumption of study medication.

The term primary insomnia is found in the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) of the American Psychiatric Association [3]. Papers that predated the DSM-IV, or used an alternative nosology, such as the International Classification of Sleep Disorders of the American Sleep Disorders Association, were retained if sufficient information about the sample was provided to ascertain a sample of primary insomnia [18].

We further limited our selection to studies incorporating both placebo and active medication therapies in a randomized, double-blind, parallel-group design with continuous nightly dosing of study medication. We required randomized and double-blind techniques to reduce patient and observer bias. We required a parallel-group design to address order effects. There was no limitation on the type of active medication used. Studies using a cross-over design could be included, but data were extracted only for the first treatment period to minimize carryover and order effects. The appropriateness of papers for inclusion was on the consensus of WVM and RD.

### 2.4. Measures

Eligible papers reported baseline and treatment results for subjective SL, subjective TST, PSG SL, or PSG TST. We required that treatment results be reported for 1, 2, 3, or 4 weeks of treatment, and that the outcome variables be reported in hours/minutes. Outcome variables had to be reported with both a mean and with a measure of variance (S.D. or S.E.) at each time point, including baseline. Means and measures of variance were not extrapolated from figures. Subjective SL and TST were taken from sleep diaries, and were acceptable as either the results of a single night's sleep at the end of each week of treatment, or as an average of the entire week of treatment. Studies employing PSG outcomes were required to specify the use of standard sleep staging criteria [19].

### 2.5. Statistics

We implemented meta-analytic techniques described by Hedges and Olkin [20] to combine data across those studies chosen based upon the above criteria. The goal of these analyses was to combine the estimates of the EAP across studies. We first tested for homogeneity of EAP across studies to determine whether a fixed or random effects approach should be implemented. A fixed effects approach considers the set of chosen studies as homogenous and representing all potential studies of interest, while the random effects approach allows the studies to be more heterogeneous and considers them to be a sample from a population of comparable studies. In general, the random effects approach is more conservative since it usually produces confidence intervals for the estimated effects that are wider than those constructed using the fixed effects

approach. In this study we found significant evidence for heterogeneity of EAP effects across studies; therefore we only used the random effects approach when presenting the results.

Since the goal of these analyses is to combine estimates in the change in outcome measurements from baseline values across studies, we needed to obtain estimates of the correlation between pre-treatment and post-treatment values of each outcome variable. Information on this topic is not readily available in the literature pertaining to insomnia treatment, but relevant unpublished data was derived from the data set of a recently completed investigation of primary insomniacs randomized to either behavior therapy or a psychotherapy 'placebo' (quasi-desensitization) [21]. In that study, the correlations between baseline values and 2 weeks of 'placebo' treatment for subjective SL, subjective TST, PSG SL, or PSG TST were, respectively, 0.91, 0.87, 0.97, and 0.26 (J. Edinger, personal communication). These correlation values were used in the first iterations of our meta-analyses.

The results of the meta-analysis are reported as a change score for each outcome variable, along with 95% confidence intervals (CI), and *d* statistics for effects sizes. This approach is superior to separately presenting the combined baseline and treatment data for studies that may have different methods of calculating sleep latency, etc. Assuming that the methodology for scoring sleep parameters is internally consistent within each study, then combining pre/post difference scores of different studies should be valid.

## 3. Results

Our combined search strategy produced 402 candidate papers, and the abstract of each paper was read to ascertain qualification for the meta-analysis. The full paper was inspected if the abstract did not clarify the qualifications for analysis. Many studies prior to 1990 were eliminated on the basis of reporting only qualitative outcomes (i.e. changes in SL reported as 'better', 'worse', or 'no change') or failure to use a parallel group design. Papers from 1990 through 2000 were more likely to measure the outcomes variables in hours/minutes and to employ a parallel design, but the data for both baseline and follow-up were often either not reported at all, or represented only in a figure.

Only five papers satisfied our requirements for eligibility (Table 1) [22–26]. The other studies were excluded for failure to report in minutes the mean value and spread for placebo at both baseline and a follow-up time point. Among the eligible papers, five provided data for subjective SL, and four provided data for subjective TST and PSG SL, with $> 90\%$ retention of subjects at the follow-up. Only two papers provided data regarding PSG TST; therefore we elected not to pursue a meta-analysis for PSG TST. Two hundred and thirteen patients were reported in the five papers, predominantly comprised by young and middle aged women. Four of the papers had severity eligibility requirements for their subjects' entry into randomization.

The eligible papers all provide data regarding baseline values and at least one follow-up time point. However, the papers differed on which time points were reported. Only the 2-week follow-up time point was uniformly available. Therefore, we elected to include only the 2-week follow-up time point in the meta-analysis.

Ultimately, modeling was only performed for the difference between baseline and the 2-week time point for subjective SL and TST, and PSG SL. We tested for homogeneity of the variances among studies and found significant evidence for lack of homogeneity for each variable tested. Therefore, only the more conservative and more appropriate random effects models were fit.

The mean $\pm$ S.E. for the change in subjective SL demonstrated a significant reduction of $13.1 \pm 2.0$ min (95% CI 9.2, 17.0), corresponding to a random effects size of 1.61. Likewise, the mean $\pm$ S.E. for the change in subjective TST demonstrated a significant increase of $13.5 \pm 5.4$ min (95% CI 2.9, 24.0), corresponding to a random effects size of 0.78. The mean $\pm$ S.E. for the change in PSG SL indicated a non-significant reduction of $2.5 \pm 4.3$ min (95% CI $-5.9$, 10.9), corresponding to a random effects size of 0.41. We tested the robustness of our findings by relaxing our assumptions regarding the pre-post correlations to 0.75 for each variable, but this did not alter the inference from our findings (Table 2).

## 4. Discussion

Our selection strategy identified only a small number of eligible papers. Many candidate papers with otherwise excellent designs were excluded because the data of interest were not reported, or were reported only in figures. The small number of eligible papers had a profound effect on our original ambition of examining EAP for four variables at four follow-up time points. Instead, we presented findings for only three variables at one time point.

Our results found statistically significant EAP for two variables, subjective SL and TST, but not for PSG SL. The changes were in the direction of improvement, and consistent with the common notion of a 'placebo effect'. The degree of numerical change in subjective SL and TST was only modest as measured in minutes, but the effects sizes were moderate to large.

The evidence for a placebo effect has implications for the design of clinical trials of hypnotic medication. For example, assume that there was no change in subjective sleep latency after 2 weeks of placebo administration, and an investigator wanted to test a new hypnotic for its efficacy in reducing subjective sleep latency by 20 min, with a Type I error of 0.05 and a power of 80%. In this instance only four subjects each would be required in the placebo and active treatment groups. However, we found that placebo is associated with a reduction in subjective sleep latency of 13 min,

Table 1
Studies included in meta-analysis

| Authors [Ref.] | Total no. | Active treatment comparison | Duration of complaint | Severity criteria for study entry | Placebo group no. | Placebo group mean age ± S.D. (range) | % Women in placebo group | % With primary insomnia | Duration of medication washout | Single blind placebo during baseline |
|---|---|---|---|---|---|---|---|---|---|---|
| Herrman et al. [26] | 21 | Zolpidem | > 2 months | Yes | 10 | (25–65) | 42.9 | 100 | N/S | Yes |
| Kripke et al. [22] | 99 | Flurazepam, midazolam | > 2 years | No | 25 | 37.4 ± 9.4 (25–57) | 64 | 82 | 20 days | N/S |
| Scharfet al. [23] | 75 | Zolpidem | > 3 months | Yes | 24 | 38 (22–60) | 64 | 100 | > 12 h | Yes |
| Walsh et al. [24] | 306 | Zolpidem, trazodone | > 1 month | Yes | 97 | (21–65) | 63 | 100 | > 7 days | Yes |
| Walsh et al. [25] | 112 | Zaleplon | N/S | Yes | 57 | 42.4 ± 11.1 | 77.2 | 100 | N/S | Yes |

Table 2
Baseline and 2-week values for placebo treatment of insomnia (minutes, mean ± S.D.)[a]

| Authors [Ref.] | Placebo group no. | Baseline subjective SL | 2-Week subjective SL | Baseline subjective TST | 2-Week subjective TST | Baseline PSG SL | 2-Week PSG SL |
|---|---|---|---|---|---|---|---|
| Herrman et al. [26] | 10 | 89.8 ± 44.3 | 72.8 ± 31.6 | 311.2 ± 76.0 | 327.4 ± 69.6 | 28.0 ± 19.0 | 41.7 ± 47.4 |
| Kripke et al. [22] | 25 | 43.4 ± 29.9 | 37.7 ± 30.0 | 370.8 ± 64.2 | 371.4 ± 63.6 | 29.6 ± 23.2 | 26.5 ± 28.6 |
| Scharf et al. [23] | 24 | 74.4 ± 47.3 | 63.2 ± 50.0 | 325.0 ± 54.0 | 351.0 ± 63.0 | 54.9 ± 28.5 | 51.1 ± 50.0 |
| Walsh et al. [24] | 97 | 82.4 ± 50.7 | 64.7 ± 46.7 | | | | |
| Walsh et al. [25] | 57 | 80.9 ± 47.6 | 65.6 ± 40.3 | 334.9 ± 71.5 | 347.2 ± 74.3 | 57.2 ± 28.9 | 49.8 ± 33.6 |

[a] SL, sleep latency; TST, total sleep time; PSG, polysomnography.

and now 22 subjects are required per group: a 5-fold increase.

The lack of significant change in PSG SL is consistent with everything known about insomnia. Insomnia is first and foremost a psychological phenomenon. Although insomniacs have poorer PSG sleep than non-complaining sleepers, the subjective aspects of insomnia are uniformly more impressive than the PSG aspects [27,28].

This meta-analysis cannot parcel out the sources contributing to the observed EAP. The authors of a recent meta-analysis compared placebo versus 'no treatment' in a variety of disorders, and found that, in general, placebo did not differ from 'no treatment' [29]. The authors concluded that any changes observed during administration of placebo was due to underlying fluctuations in the disorder, regression to the mean, or non-specific improvement associated with participating in a clinical trial. In short, these authors discounted the possibility that ingestion of placebo was associated with improvement in disease states through the psychological mechanism of encouraging hopeful expectations. The sole exception to their claim was regarding pain syndromes, for which placebo was superior to 'no treatment'. Perhaps insomnia is another exception. Two older studies found that a quasi-desensitization placebo was associated with improved subjective sleep only when the participants were told that it was beneficial [30,31]. A more recent study compared zolpidem and placebo in an intermittent dosing design over a period of 8 weeks [32]. This study found that intermittent ingestion of placebo was associated with a beneficial effect on sleep, weeks into the protocol, and long after regression to the mean should be complete. Together, these studies support the idea of a true (i.e. psychological) placebo effect.

The present meta-analysis cannot rule out the influence of non-psychological factors. For example, four of the five eligible studies had severity of illness requirements in their selection of patients (Table 1). This process produces a selection bias in favor of initiating the study at the time when patients are experiencing their worst insomnia, and encouraging a regression to the mean [5].

Our present findings have practical and perhaps ethical ramifications. If we had found no EAP, then it could be argued that an 'equivalence design' could be employed for testing the efficacy of new medications against a proven standard treatment in primary insomnia, without a placebo control. Instead, the presence of EAP in primary insomnia supports the idea that new medications be contrasted against placebo. Food and Drug Administration guidelines describe placebo controls in hypnotic medication trials, and our findings are consistent with these guidelines [33]. Those methodologists who recommend equivalence studies without placebo controls ignore the possibility that an investigational medication, active comparator, and placebo could all improve to the same degree in a susceptible sample. Only by including the placebo arm would the investigator realize that the investigational compound was not different from placebo.

This project found a modest EAP for subjective sleep variables in hypnotic clinical trials in samples of primary insomnia. This project has a number of limitations. First, the number of eligible studies was small, and may not reflect the broader experience. Many studies that appeared relevant to the question at hand had to be omitted for failure to explicitly report the numerical values of sleep variables in the placebo group. Second, the small number of studies may have allowed a Type II error suggesting no significant EAP for PSG SL when such an effect actually does exist. Third, we did not succeed in providing estimates of EAP at any time points other than at 2 weeks. It is unknown whether EAP appear earlier than 2 weeks, or are sustained or continue to accrue beyond 2 weeks. Fourth, the magnitude of EAP in primary insomnia may not apply to secondary forms of insomnia. Insomnia secondary to a mental disorder (especially depressive disorders) is the leading diagnoses associated with hypnotic medication prescription [34]. For example, it is unknown whether the greater global severity of illness in depressed insomniacs would be associated with a weaker or stronger EAP than that seen in primary insomnia [4]. Fifth, the subjects were primarily young women, and our results may not apply to older persons or men.

Our findings support the existence of EAP in insomnia medication trials. These findings, coupled with other literature suggesting that placebo is different from 'no treatment' in insomnia clinical trials, argues for the retention of placebo controls in insomnia clinical trials.

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