Placebo for a Single Night Improves Sleep in Patients with Objective Insomnia

Eldor Rogev MD[1]* and Giora Pillar MD[1,2]

[1]Sleep Laboratory, Rambam Health Care Campus, Haifa, Israel
[2]Department of Pediatrics, Carmel Medical Center affiliated with Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

ABSTRACT: **Background:** Insomnia is the most common sleep disorder. Treatment options are improved sleep hygiene, relaxation, cognitive behavioral therapy, and medications. Studies examining the effect of hypnotics on insomnia reported that placebo had a substantial beneficial effect.

Objectives: To evaluate whether placebo is an effective treatment for insomnia.

Methods: We assessed 25 patients with insomnia who were enrolled in a hypnotic study but prior to the study were asked to undergo two full nights in laboratory polysomnography studies: with and without a placebo. Although they were not explicitly told that they were receiving a placebo, the participants knew that the results of these studies would determine whether they met the criteria to participate in the pharmaceutical study.

Results: Although the participants acknowledged that they were given a placebo, almost all measures of their sleep improved. With placebo, sleep latency was shortened from 55.8 ± 43.5 to 39.8 ± 58.5 minutes ($P < 0.05$); total sleep time was extended from 283 ± 72.5 to 362.9 ± 56.3 minutes, and sleep efficiency improved from 59.57 ± 14.78 to 75.5 ± 11.70% ($P < 0.05$). Interestingly, placebo had no effect on the relative sleep stage distribution (percentage of total sleep time), except for a trend toward increased percentage of REM sleep.

Conclusions: Our findings show a clear and significant beneficial effect of placebo on insomnia, despite participants' understanding that they were receiving placebo. These results emphasize the importance of the patients' perception and belief in insomnia treatment, and suggest that in some cases placebo may serve as a treatment.

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KEY WORDS: sleep, insomnia, placebo, polysomnography, rapid eye movements (REM)

Sleep disorders constitute one of the most important public health problems in the general population, with a prevalence of up to 50% of the population suffering from any disorder in their sleep [1]. Of the sleep disorders, the most common is insomnia, with an estimated prevalence of 7%–30% [2]. The high prevalence, disruption of daily function and insult to quality of life, along with the resultant strain on medical organizations, emphasize the need to maximize efforts to treat this disorder.

Insomnia comprises several complaints: difficulty falling asleep, frequent arousals and difficulty maintaining sleep, and early-morning awakening. The duration of symptoms affects the diagnosis and treatment. Transient insomnia describes symptoms lasting several days. Insomnia symptoms that last longer than a few days but less than 3 weeks are termed short-term insomnia. Chronic, or long-term, insomnia by definition lasts more than 1 month [1]. The following criteria are needed to diagnose insomnia: a) a complaint of difficulty initiating sleep, maintaining sleep or early arousal, or a complaint of non-refreshing sleep or poor sleep quality; b) disruption of sleep despite adequate conditions and opportunities needed for normal sleep; and c) the presence of clinically significant distress or impairment of daily function as a result of the sleep disorder [3].

The etiology of chronic insomnia is variable and complex, consisting of numerous medical and mental factors. Psychophysiological insomnia is a condition where the fear of the inability to sleep is the major stress factor causing insomnia. Also, chronic insomnia may be comorbid with psychological disorders (such as depression) or neurological diseases (e.g., Parkinson's disease), or it may result from other medical conditions (such as asthma) or may be a side effect of medications, recreational drugs or alcohol [1]. Other causes of insomnia include inadequate sleep hygiene and idiopathic insomnia [3-5]. Importantly, it has been shown that treating insomnia may aid in alleviating a comorbid state [6].

There are several approaches to the treatment of insomnia [7]. These include improving sleep hygiene, stimulus control therapy, relaxation techniques before sleep, cognitive behavioral therapy and more. Despite these therapeutic options, most insomnia patients eventually use sleeping pills. There is a wide variety of medications for the treatment of insomnia, such as benzodiazepines, melatonin agonists, anti-psychotics,

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antidepressants, barbiturates and non-benzodiazepine sleep medication (such as zolpidem and eszopiclone) [8].

The placebo effect, known for its medical impact since the 18th century, is the effect of a certain medical therapy resulting from the patient's belief in the therapy [9]. Since the 1930s, comparing treatments, medication and equipment to placebo is the standard in medical research, while attempting to keep all parts of the study, including the data collection, as similar as possible between the two groups – those receiving the tested therapy and those receiving placebo. This method enables scientists to isolate the measured effect, while eliminating the influence of the placebo effect. Several therapies that have been compared to placebo, such as the use of citronella in the treatment of head lice [10,11], showed an advantage over the "mock" treatment. Other cases, on the other hand, such as prophylactic use of low dose heparin in the prevention of pancreatitis after endoscopic retrograde cholangiopancreatography [12], have failed to show a statistically significant advantage over the placebo. Due to the obvious psychological component of insomnia, it is reasonable to assume that this effect is especially prominent in the treatment of these disorders. Indeed, many previous studies on insomnia have reported a positive placebo effect [13-15]. However, in most of these studies the patients did not know whether they received a medication or a placebo. We sought to study the effect of placebo on patients with insomnia who knew they were receiving placebo. Identifying a significant placebo element in the treatment of insomnia in this regimen may provide a better understanding of the disorder, and perhaps (in the long run and within ethical limitations) raise the possibility of integrating placebo in the treatment of people suffering from insomnia.

PATIENTS AND METHODS

This comparative retrospective study was based on data collected from prospective studies conducted at the sleep lab of Rambam Health Care Campus, Haifa. The protocols of the study were approved by the Rambam Health Care Campus institutional review board, and consisted of a single-blind placebo treatment for enrolled patients to determine whether they meet inclusion criteria for another double-blind hypnotic medication study. This paper relates only to these pre-study protocols. The data were collected from studies attempting to objectively determine the diagnosis of insomnia in various volunteers who were to participate in future insomnia medication studies.

PATIENTS

The study group comprised all 25 patients suffering from insomnia who underwent an all-night complete polysomnographic study in the sleep lab with and without placebo. All these patients had been clinically diagnosed with insomnia prior to the polysomnography. Their mean age and body mass index were 49.6 ± 9.6 years and 23.7 ± 2.8 kg/m^2, respectively. Each of the patients, as a part of the evaluation for eligibility for the aforementioned studies, underwent two full-night in-lab PSG studies: the first night with placebo and the second without. The patients were not explicitly told that the pill they were given contained inactive components, but it is a reasonable assumption that they understood they had not received any active medicine since they were told that their participation in the clinical trials relied on the results of these PSG studies. Furthermore, on the morning following the placebo night they stated they assumed they were given a placebo and not an active medication. The PSG studies were performed at the Rambam Health Care Campus, Haifa, Israel. In addition, they underwent a prior PSG study to exclude sleep-disordered breathing and periodic leg movements in sleep. The inclusion criteria were as follows: a) an objective diagnosis of insomnia, defined by a previous polysomnographic study showing the following three conditions: sleep latency of more than 20 minutes, more than 30 minutes of wake after sleep onset (WASO), and a total sleep time of less than 6.5 hours out of at least 8 hours of time in bed; and b) age 18 or above. Exclusion criteria were: a) hypnotic usage during the previous month prior to the study, b) any unstable medical condition, c) any mental comorbidity (especially anxiety or depression), and d) any medication usage that can affect sleep.

PROTOCOL

All participants underwent two studies in the sleep lab, the second was performed after they were given a placebo pill. In each study they were required to arrive at the sleep lab at 20:00, at which time they were asked to complete an evening questionnaire. At least one hour prior to bedtime the participants were hooked up to electrodes for the PSG study. On nights when placebo was administered, the pill was given to the patients 30 minutes before they were told to go to bed. Lights-off was set at 22:00 in all studies, and lights-on at 06:00.

POLYSOMNOGRAPHIC STUDY

The overnight study was initially performed according to standard protocol using electroencephalogram, electrooculogram, submental and bilateral anterior tibialis electromyogram, electrocardiogram, nasal-oral airflow (thermistors and nasal pressure), chest and abdominal wall motion (piezo or impedance belts), body position and arterial oxygen saturation utilizing the Embla™ system (Embla, Broomfield, CO, USA). After excluding sleep-disordered breathing and periodic leg movements during sleep, in the subsequent study the channels consisted of EEG (3 channels), EOG, EMG, ECG and move-

PSG = polysomnography
EEG = electroencephalogram
EOG = electrooculogram
EMG = electromyogram
ECG = electrocardiogram

ments, with no respiratory recordings. The PSG studies were then scored by experienced technicians in the sleep lab.

DATA ANALYSES

The data analyses consisted of comparing the PSG results with and without placebo, utilizing a two-tailed paired Students *t*-test. $P < 0.05$ was considered statistically significant.

RESULTS

Data were available for all 25 patients. The mean age of the 6 males and 19 females was 49.6 ± 9.6 years (average ± SD, range 19–63), and mean BMI was 23.7 ± 2.8 kg/m^2 (range 21.5–28.8).

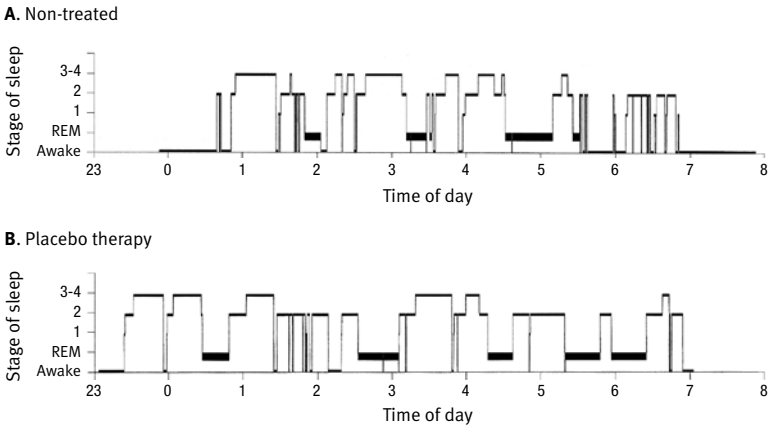
BMI = body mass index

Table 1. The effects of placebo on various sleep parameters

Sleep parameter	Baseline (mean ± SD)	Placebo (mean ± SD)	*P* value
Sleep latency (min)	55.88 ± 44.41	39.8 ± 59.74	0.05
Total sleep time (hr)	4.71 ± 1.23	6.04 ± 0.95	< 0.001
Sleep efficiency (%)	59.57 ± 15.08	75.5 ± 11.94	< 0.001
WASO (min)	136 ± 71.9	77.96 ± 45.97	< 0.001
% stages 1-2	51.76 ± 10.53	50.5 ± 13.47	NS
% stage 3	28.7 ± 9.67	27.93 ± 12.05	NS
% REM sleep	19.55 ± 5.08	21.57 ± 6.68	0.09
REM latency (min)	110.64 ± 51.89	93.84 ± 39.04	0.09
No. of brief awakenings (< 1 min)	20.04 ± 7.36	10.9 ± 7.49	0.06
No. of intermediate awakenings (1–3 min)	4.72 ± 3.7	4.52 ± 2.94	NS
No. of long awakenings (> 3 min)	4.88 ± 2.89	3.48 ± 2.89	0.01

WASO = wake after sleep onset, REM = rapid eye movements

Figure 1. A typical example of the hypnogram of one patient at baseline **[A]** and with placebo **[B]**. As can be seen, there is substantially less wakefulness and more sleep with placebo



None of them had apnea or periodic limb movements. The effects of placebo on the various sleep parameters are presented in Table 1. A typical example of one patient with (bottom) and without (baseline, top) placebo is shown in Figure 1.

On average, with placebo the participants slept better and longer. On average, sleep latency was shorter by 16.4 minutes, total sleep time was increased by 86.2 minutes, sleep efficiency was increased by 17%, and WASO was decreased by 76 minutes ($P < 0.05$ for all) [Table 1].

Sleep stage distribution was not affected by placebo. REM latency tended to be shorter with placebo (17.2 min), but this was not statistically significant ($P = 0.09$). Similarly, REM percentage tended to increase from 20.2% to 21.6%, nearly a 7% rise, but was not statistically significant ($P = 0.09$). The relative proportion of sleep stages 1-2 and slow-wave sleep remained unchanged with the placebo.

Arousals from sleep were also affected by placebo [Table 1]. On average, brief arousals (less than 1 min each) decreased with placebo from 20.0 (totaling 12.6 minutes of wakefulness) to 10.9 arousals (totaling 4.7 minutes of wakefulness). Intermediate length arousals, between 1 and 3 minute duration each, were not significantly affected by placebo. Time spent awake during these arousals with and without placebo was 9.63 and 9.16 respectively. Long arousals (over 3 minutes each) were significantly reduced with placebo, from 4.9 (totaling 77.9 minutes of wakefulness) to 3.5 (totaling 40.9 minutes of wakefulness).

DISCUSSION

This study examined the effects of placebo treatment on the sleep of patients with known insomnia. Improvements were noted in sleep latency, total sleep time and sleep efficiency. Results show an average 16.4 minute reduction in sleep latency, and an increase of 86.2 minutes in total sleep time. Sleep efficiency rose by an average of 17%. The amount of time patients were awake during the night, after initially falling asleep, abated by 76 minutes on average. Interestingly, placebo affected all sleep stages similarly, leaving the relative sleep architecture unchanged. Unfortunately, because the study included only 6 men and 19 women, these small numbers made it under-powered for drawing conclusions regarding differential gender-related placebo effects. The trend of improvement with placebo seemed similar for both genders. It is well established that emotional and psychological stress has a negative effect on sleep quality. It is therefore not surprising that studies show beneficial effects of non-pharmaceutical therapies on somnopathies. The influence of "sleep hygiene" on quality of sleep is also well documented (i.e., controlling all behavioral and environmental factors

WASO = wake after sleep time
REM = rapid eye movements

that precede sleep and may interfere with sleep) [16] and is a basic part of the conventional treatment of insomnia. In their study Edinger et al. [17] show a significant and lasting improvement in the sleep of primary insomnia patients who were treated with cognitive behavioral therapy. It has also been shown that the addition of behavioral therapy to common treatment practices for insomnia improves the overall outcome of treatment [18]. Taking into consideration that the placebo effect is derived from its influence on the patient's psyche, it is not surprising that sleep quality is influenced in a manner similar to those of other psychological and behavioral therapies.

The placebo effect has been proven in several studies, in a variety of medical fields. Patients suffering from rheumatoid arthritis showed a positive response to placebo to such a degree that in 82% of patients the continuation of placebo therapy was considered justified [19]. A positive influence from the placebo effect on patients suffering from angina pectoris was also shown. Boissel and co-authors [20] demonstrated a 48% reduction in the number of angina attacks per week. Perhaps not surprisingly, psychological disorders have also been shown to be influenced by placebo. In their study, Coryell and Noyes [21] demonstrated a significant improvement in 25% of patients diagnosed with panic disorder who received placebo therapy. Parkinson patients are another population shown to be beneficially affected by placebo treatment, possibly mediated through activation of the damaged nigrostriatal dopamine system [22]. Other disorders where placebo has shown beneficial effects include depression [23], addiction [24], irritable-bowel syndrome [25], and others.

In the field of pharmaceutical therapy for insomnia, placebo treatment, used as a control, positively affected participants' sleep in several studies [17-19]. In addition to examining the effect of sham treatment itself, and not as a control, our study adds a unique perspective in that the participants were most likely aware of the fact that they were given placebo.

The concept of intentional placebo treatment as a viable long-term therapy for insomnia is debatable. Insomnia is a complicated and prolonged affliction, and its treatment usually requires adherence to long-term therapy, a good patient-doctor relationship, and perhaps most importantly a highly motivated patient. Although our study showed that placebo treatment had a positive effect on insomniac patients, this response was measured during a single night. The sustainability of these improvements remains unknown, requiring further investigation. Another consideration is the ethical implication of treating patients with placebo. Ethically condoning placebo treatment is beyond the scope of this article. The deceptive element in sham treatment may harm the patient-doctor relationship and the patient's trust in his or her physician. On the other hand, a wisely constructed therapy may help show patients the extent to which they can control their condition, thereby obviating other more costly and potentially harmful treatments. Furthermore, if patients are aware of their placebo treatment, the deceptive aspect of this treatment does not exist.

The study has several limitations. First, our participants were not told unequivocally that they were getting placebo. Second, because we evaluated the effects of placebo in a single night, the results of this study cannot be generalized or clinically applicable to patients suffering from insomnia. A larger scale work, with a greater number of patients, more than 2 night sleep studies per patient, and more than a single night study after administration of placebo, would yield more accurate and reliable results. Also, it is reasonable to assume that some patients will sleep better on the second night in a sleep lab due to the first-night effect in the lab. On the other hand, specifically in insomniacs, a reversed first-night effect has been observed. Since our study was based only on a single-night comparison we did not have a habituation night and it remains possible that some of the improvement is attributed to the first-night effect. Studies for several nights may shed light on this possibility. Finally, testing the effect of placebo in the home is necessary to better understand how placebo functions in patients' sleep.

CONCLUSIONS

Despite the above mentioned limitations, our findings demonstrate that placebo has a clear and significant beneficial effect on sleep in insomniac patients. Although the patients did understand they were receiving placebo and not a hypnotic medication, their sleep was still significantly improved compared to the baseline sleep without placebo. These results emphasize the importance of the patients' perception and belief in insomnia, and suggest that in some cases placebo may serve as a treatment.

Corresponding author:
E. Rogev
17 Nachalat Itzchak St., Tel Aviv 6744211, Israel
email: eldorrogev@gmail.com

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Capsule

Tumor epigenetics

That human tumors display both genetic mutations and epigenetic alterations – for example, in DNA methylation – has been known for many years. With the completion of cancer genome sequencing projects, possible causal links between the two have come into sharper focus. The discovery of recurrent tumor-associated mutations in genes that encode chromatin-modifying enzymes or DNA methyltransferases represents a clear link between tumor genotype and "epi-genotype." Emerging evidence suggests that a link can be subtle, as illustrated by two studies describing consistent epigenetic alterations in tumors with mutations in the gene encoding the metabolic enzyme succinate dehydrogenase (SDH). Killian et al. (*Cancer Discov* 2013; 3: 648) found that gastrointestinal stromal tumors harboring SDH mutations are characterized by dramatic and widespread DNA hypermethylation, whereas Letouzé et al. (*Cancer Cell* 2013; 23: 739) report that SDH-mutant paragangliomas display DNA hypermethylation that is associated with the silencing of genes involved in neuroendocrine cell differentiation. Both groups hypothesize that the hypermethylation phenotype is due to the aberrant accumulation of an oncometabolite that inhibits DNA-demethylating enzymes, with succinate being a strong candidate.

Eitan Israeli

Capsule

Inflammasome-derived IL-1β production induces nitric oxide-mediated resistance to Leishmania

Parasites of the Leishmania genus are the causative agents of leishmaniasis in humans, a disease that affects more than 12 million people worldwide. These parasites replicate intracellularly in macrophages, and the primary mechanisms underlying host resistance involve the production of nitric oxide (NO). In this study Lima-Junior et al. show that the Nlrp3 inflammasome is activated in response to Leishmania infection and is important for the restriction of parasite replication both in macrophages and in vivo as demonstrated through the infection of inflammasome-deficient mice with *Leishmania amazonensis*, *Leishmania braziliensis* and *Leishmania infantum chagasi*. Inflammasome-driven interleukin-1β (IL-1β) production facilitated host resistance to infection, as signaling through IL-1 receptor (IL-1R) and MyD88 was necessary and sufficient to trigger inducible nitric oxide synthase (NOS2)-mediated production of NO.

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Eitan Israeli