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THEORETICAL REVIEW

Placebo effects in primary insomnia

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Summary Placebo effects are commonly observed in insomnia clinical trials. With the advent of longer-term trials, such effects appear to be remarkably robust and durable. In this paper we review the classic factors that are believed to contribute to placebo effects and how these factors operate in insomnia randomized clinical trials. Beyond this we suggest that the episodic nature of insomnia may interact with patient preferences for intermittent dosing in such a way as to sustain placebo effects in the long term. An appreciation of the latter phenomenon may provide increased power to detect therapeutic outcomes and may be used to potentiate clinical gains.

Introduction

It is a common finding within insomnia randomized clinical trials (RCTs) that placebos produce significant changes on self reported sleep continuity measures.[1] In a recent meta-analysis of such effects,[1] McCall and colleagues estimated the magnitude of pre to post change on sleep latency and total sleep time measures to be approximately 20%. Longer-term trials (both intermittent and nightly dosing) show that such effects are not only stable but that clinical improvements continue to occur over time. A representation of placebo effects for several recent trials is contained in Fig. 1.

The purpose of the present article is to review - the traditional explanations for what the placebo effect is and to advance a hypothesis that placebo effects may be maintained over long periods of time as a result of a peculiar interaction between illness severity, pill taking behavior, and interval or contingent reinforcement.

What is a placebo?

The term placebo is most frequently used to refer to the ingestion of an inert substance. The concept,

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[1] The term sleep continuity is used to represent one of the two major classes of sleep variables (sleep continuity vs sleep architecture measures) and denotes the set of variables that are associated with sleep initiation and maintenance (sleep latency, number of awakenings, wake after sleep onset and total sleep time).

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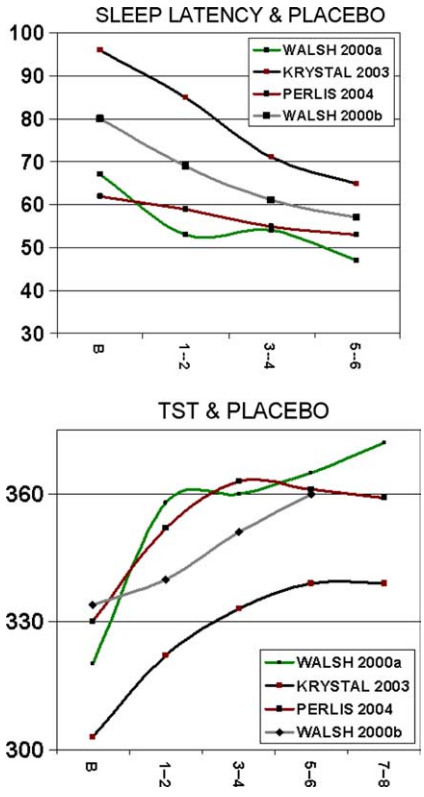

Figure 1 Placebo effects on sleep continuity (SL and TST). The data provided in this figure are 'schematic' representations of the self report values provided in each of the four given studies. All data are provided as biweekly averages and are smoothed. Data provided as weekly averages were recalculated to represent biweekly averages. Data provided as monthly averages were represented as biweekly averages by carrying the last observation forward. All the data in the schematic are truncated at 6 weeks to allow for all four studies to be represented across the four time points.

however, can be broadly applied to a variety of non-pill interventions such as sham medical procedures and simulated psychotherapies. All placebo conditions share at least three common features. First, the 'intervention' itself is thought to be inactive, i.e. incapable of producing therapeutic effects through the manipulation of the factors that produce disease or disease symptoms. Second, the deployment of a placebo condition allows one to control for the effect of observation and measurement. Third, the placebo manipulation is utilized to control for non-specific effects of interventions.

In what ways can placebos produce change?

Clinical improvement during placebo administration may be driven by any number of factors including: (1) regression to the mean, (2) the Hawthorne Effect, (3) Expectancy (4) Cognitive Dissonance, (5) the non-specific effects of participating in research, and (6) physiologic changes produced by placeboes.

These concepts are briefly described below and then, in the following section, are applied to the problem of placebo effects in insomnia studies that use placebo-pills as inert comparators during the conduct of randomized clinical trials.

Regression to the mean refers to the likelihood that an outcome variable will show a significant change based on the severity of the initial baseline values.[2-5] The more severe the initial value, the more likely it is that subsequent measures will be less severe. Regression to the mean is especially likely to occur in clinical trials as (1) severe forms of illness are often required for inclusion into such studies and (2) subjects are most likely to volunteer for research studies when their illness is at its most severe. The result is that improvements are likely to occur with the simple passage of time (especially for diseases that are episodic or have a waxing and waning course). Alternatively, initial severity may set the stage for 'regression' while other factors account for the change towards more modal values.

The Hawthorne Effect pertains to the effects of observation and measurement. Specifically, the Hawthorne effect (e.g.[6-9] refers to the possibility that individual behaviors may be altered because the subjects under observation know they are being studied. Thus, subjects may alter their behavior, or their subjective reports, given the knowledge that they are being observed and do so in a way that is thought to comply with the known, or perceived, intent of the observers.

Expectancy refers to, as the name implies, the belief that clinical improvement will occur (e.g.[10-12]). That is, participation in a clinical trial may cause the patient to be more hopeful about their condition and the possibility of change and lead them to 'expect' that they will improve with time. While expectancy may exert its effects simply by biasing self report measures, it is equally plausible that effects may occur via increased tolerance for discomfort or through an alteration to the disease process through physiologic mechanisms.

Cognitive dissonance is a form of expectancy, but in this case refers to the issue of how subjects manage perceptions and thoughts that promote distress. Specifically, dissonance occurs when ones thoughts or behaviors are inconsistent with ones attitudes, beliefs, or self-concept. The disconnect leads to distress and the individual manages the distress by changing the related attitudes,

cognitions, or behaviors.[13] In the present case, in order to avoid or diminish cognitive dissonance that arises from the thought that one is wasting his/her time participating in research, a new thought or belief such as 'I am getting better, so this is not a waste of time,' is engaged. Interestingly, some of the classic studies in cognitive dissonance were related to participation in experimental studies.[14]

Non-specific effects of participation in a clinical trial There are a whole host of behaviors that are fundamentally altered by participating in clinical research including regular monitoring, self monitoring, changes in behavioral that are required by the protocol, etc. Any one, or all of these, factors may mediate either the perception of illness severity or the severity of the illness itself.

Physiologic change refers to the possibility that placebos may initiate change through the physical consequences of increased optimism or altered expectation. For example, placebo use has been associated with changes in brain neurochemistry in patients with chronic pain syndromes[15,16] and Parkinson's Disease[17–19] and with alterations in limbic activity in patients with major depression.[20] Taken together such data suggests that there may be a physiologic basis for placebo effects, but that this occurs primarily with diseases of the central nervous system.[17,21]

Placebo effects and insomnia

Regression to the mean It certainly stands to reason that this kind of placebo effect may be operational in insomnia clinical trials. In fact, the data presented in Fig. 1, pattern over time in a way that is consistent with regression to the mean effects. That is, the largest changes in sleep continuity tend to be associated with the highest initial severity values. When considering the literature as a whole,[22–24] it can be said that the average baseline values for most insomnia trials do indeed reach a level of sleep disturbance severity which is likely to be permissive of regression to the mean effects. For example, in a meta-analysis undertaken by Smith and colleagues,[24] the average baseline sleep continuity values were: Sleep Latency 48.8 ± 29.7, Wake after sleep onset 55.1 ± 32.8, and total sleep time 332.1 ± 55.3. Such values, while not as extreme as those seen in the more recent long term trials (e.g.[25–28]), clearly allow for the change towards more modal values.

The hawthorne effect There are very few treatment regimens that are as rigorously monitored as what occurs during a RCT. This is likely to be doubly true of the Insomnia RCT as this kind of trial requires daily observations as well as regular contact (weekly or bi-weekly) with research staff. As a result, this level of scrutiny can be expected to contribute to the report bias which occurs in association with the subjects' desire to demonstrate positive clinical effects.

Expectancy when subjects report improvement, they may do so because they expect to improve and in fact experience improvement based on the strength of their expectation. This phenomena may, within the context of insomnia trials, occur for psychological reasons. That is, the use of placebos may contribute to a reduction in worry and/or cognitive arousal. Diminished worry and/or cognitive arousal when using placebos may contribute to sleep continuity improvement which in turn may reinforce the expectation that the placebo can, and does, produce positive change.

Cognitive dissonance as with expectancy, this factor may also be inordinately operative in insomnia RCTs. In this case, the level of subject burden may be directly related to the magnitude of clinical gains. The increased 'work load' involved with prospective monitoring (daily sleep and wake diaries) may serve to fuel the search for, recognition of, and/or confabulation of positive gains so that one can ward of the distress that might otherwise occur with participation in research where the subject suspects that he/she may not be getting active treatment.

Non-specific factors There are variety of non-specific factors that may contribute to real or perceived change including the effects of: self monitoring, attending to sleep wake scheduling, pre-bed rituals, and the ceding of control 'to a higher authority'. In the case of self-monitoring, the regular measurement of symptoms may directly alter how the patient views the frequency and severity of their sleep complaints. When assessed retrospectively (e.g. as part of a clinical interview) the subjects' characterization of their average symptom profile is likely to be based on memory heuristics like primacy, recency, and saliency. Arguably the last of these heuristics most informs the subject regarding illness severity and makes it likely that this form of measurement will lend itself to more extreme values. When assessed prospectively with sleep diaries, the subject is more likely to form an opinion regarding symptom frequency and severity on the basis of the sampled data. As result, this form of measurement will lend itself to less extreme values. To the patient, this may be perceived as positive clinical change. Clinically, patients often express this very

sentiment 'keeping these diaries has really helped to improve my sleep'.

As with self monitoring, attending to sleep wake scheduling may also produce positive change. That is, if the patient is encouraged to 'take the pill' at bedtime, then the he/she may be more cognizant about scheduling when bed time occurs so that medication use does not interfere with their evening activities. To the extent that this corresponds to the regularizing and/or delay of bedtime, one can expect positive clinical effects. In the case of regularizing bedtime, this may produce a more stable circadian pattern which, in turn, promotes an improved capacity to initiate sleep. In the case of delaying bedtime, to avoid sedation effects, this may result in the patient's staying awake longer which, in turn, promotes better sleep continuity via the priming of the sleep homeostat.

The engagement of a pre-bed ritual (preparing to take 'medication' and the ingestion of 'medication') may serve as a sign or stimulus for the response of sleep and may also promote good sleep continuity via the enforcement of a quiescent period prior to the attempt to initiate sleep.

Finally, regarding the 'ceding of control to a higher authority', participation in a clinical trial sets up a scenario whereby the subject in the RCT, to one extent or another, abandons self regulation in favor of following the protocol. This can be expected to positively affect sleep continuity in two ways. First, the subject may abandon the practices, which have, thus far proved to be unsuccessful at ameliorating their sleep disturbance (in favor of the rules as they are set out by the RCT). Second, the very act of 'ceding control' may make it less likely that the subject will 'try to sleep'. Less effort in this regard may have the paradoxical effect of providing for improved sleep continuity.[29–32]

Physiologic changes produced by placeboes Both acute and chronic changes may occur with the regular use of placebos. Acutely, reduced sleep related worry may have a direct impact on the physiology of insomnia. That is, insomnia is thought to occur in association with hyperarousal as evidenced by increased metabolic rate and sleep period-related increases adrenergic tone and cortisol output. Reduced worry may serve to attenuate these phenomena and be permissive of good sleep continuity. Chronically, the use of placebos may become unconditioned stimuli for 'down regulation' or sleep itself. That is, the act of taking a placebo may elicit classically conditioned responses (e.g.[33]).

Insomnia severity and periodicity

Each of the above factors, alone or in combination, may account for the occurrence of the 'placebo effect' in insomnia RCTs. Less clear is why the effect appears to be sustained. What factor or factors account for this aspect of the placebo phenomenon?

At the heart of this issue is that insomnia symptoms exhibit a pattern that may be more episodic than chronic. That is, when the patient is actively ill, insomnia symptoms may occur on a regular basis, but not unremittingly so. This is commonly observed clinically, and tacitly acknowledged within research circles. With respect to the latter, most clinical trials require that subjects exhibit symptoms on more than 3 nights per week. Implicit in this inclusion criteria is that subjects exhibit either subsyndromal symptoms or no symptoms at all on up 4 nights per week. Finally, there are two preliminary studies that provide direct evidence that insomnia is a periodic phenomena.[34,35] One the two studies clearly illustrates that patients with chronic insomnia exhibit significantly improved sleep once every 2–3 days[34,35] This patterning, while potentially attributable to a variety of mediating variables, is likely due to factors related to the homeostatic regulation of sleep. That is, after several days of poor sleep, it is likely that there is a sufficient build up in 'sleep pressure' to produce a good night's sleep or at least a better than average night's sleep.

Whether such episodes pattern in a non-random way within individuals, or within the patient population as a whole, remains to be assessed. Such an evaluation would require that subjects be monitored (with sleep diaries and/or actigraphs) for an extended interval and that the data be analyzed for the relative occurrence of 'good' and 'bad' nights of sleep. Once the pattern data are obtained, a frequency distribution for the measured interval could be constructed. If the data are non-random, the idiographic distributions would exhibit peak frequencies for each individual. Averaging of the idiographic distributions, in turn, would allow for the detection of peak frequencies for the sample as a whole.

In the absence of such an analysis, the inclusion criteria of 3 or more nights of insomnia per week may serve as a guide. That is, patients' may be expected to exhibit either a good night's sleep (or at least a better than average night's sleep) once every 1–6 days. The possible within week patterns (1 week) are represented in Table 1. Longer intervals are, of course possible, and the ability to

Table 1 Sleep patterns during a 1-week period.

Pattern	Nights: number of nights of insomnia/ week	Ratio: bad to good nights	Interval: bad nights prior to a good night
BGGBGGB	3	1/2	0.5
BGBGBGB	4	1/1	1
BBGBBGB	5	2/1	2
BBBGBBB	6	3/1	3

B, bad night's sleep and G, good night's sleep.

detect such rhythms will depend on the duration of the sampling window. Assuming the sampling window is two weeks, it is possible that the individual may experience a good night of sleep only once every 13 days.

In Fig. 2, a theoretical frequency spectrum is provided, with a peak frequency at the 2–3 night intervals. (Please note: resolving whether such rhythms are stable will depend on the number of sampling windows obtained per individual). While such a frequency spectrum is, at this time, only hypothetical, the important point illustrated is that the periodic occurrence of good sleep may serve to reinforce the placebo effect and account for the persistence of such effects in patients with insomnia.

Periodicity of symptoms and their potential association with placebo effects

Most of the clinical trials that have been conducted with placebo conditions fall into one of three categories: nightly use, intermittent use, and PRN use. The definition of these medication schedules (conditions) varies from study to study.

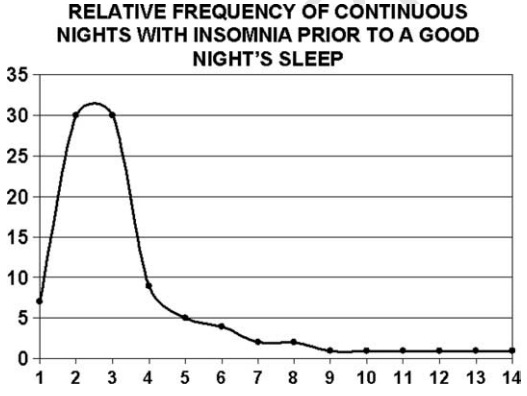

Figure 2

This is so much the case, that even nightly use studies allow subjects some degree variability with respect to pill use. For example, subjects in nightly use studies-while instructed to use the 'medication' nightly-are typically allowed to continue in the trial when 'medication' is only taken on as few as 5 nights per week. Thus, nightly use might be best construed as 5–7 nights per week; intermittent use as 3–5 nights per week and PRN use as 1–3 nights per week.

Given that there is a periodicity to both insomnia symptoms and medication/placebo use, the question that must be addressed is 'how do the two line up'? That is, how does the incidence of 'good' nights occur in association with pill use? If one accepts that the incidence of a good nights sleep occurs at 2–3 day intervals, then within a nightly use schedule subjects will experience significant improvement in their sleep continuity 20–40% of the time that placebos are used. With intermittent dosing and PRN use of placebos, subjects will experience significant improvement in their sleep continuity between 40–100% of the time that placebos are used. In the case of the former, this represents an interval reinforcement schedule. In the case of the latter (when the association occurs 100% of the time), this represents contingent reinforcement schedule. Both schedules are highly reinforcing. Fig. 3 represents a schematic representation of this phenomenon.

In sum, with each occurrence of a poor nights sleep there is an increasing probability that the subject will experience (due to an increase in the homeostatic pressure for sleep) a good nights sleep. To the extent that pill-taking behavior is aligned with the natural occurrence of good sleep, one can expect that the placebo effect will be reinforced. Such regular and reliable reinforcement may, in turn, account for the ability of an insert substance to produce stable effects over time.

Can interval or contingent reinforcement account for increased clinical gains over time with the use of placebos?

While interval and contingent reinforcement may explain how placebo effects can be maintained over long periods of time, they are, however, unlikely to account for the kind of continuous clinical improvement that is evident in Fig. 1. Instead, it seems more likely that the acute gains and their maintenance with time sets the stage for 'secondary gains' which owe to other factors. This may include the counter conditioning of one or several forms of

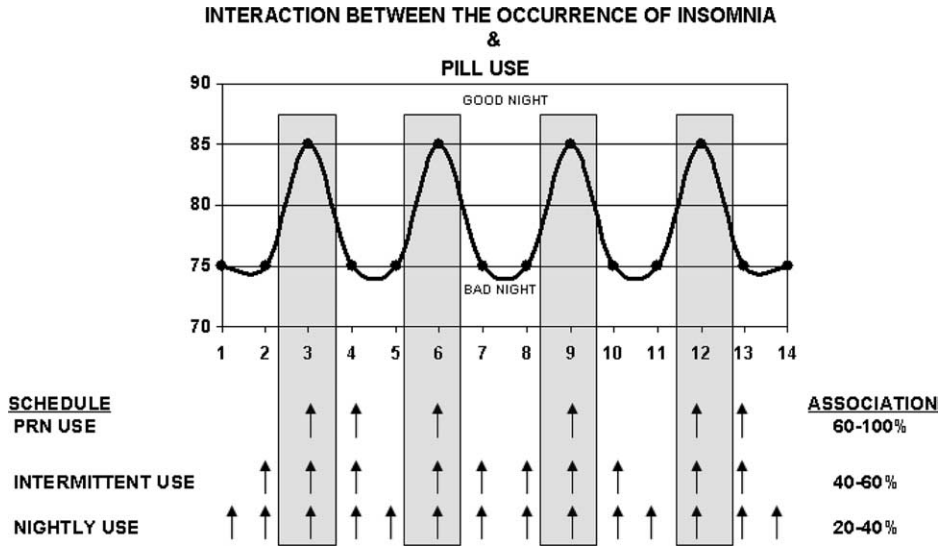

Figure 3 Interaction between the occurrence of insomnia and pill use. In this figure, the ordinate represents sleep efficiency. Thus the occurrence of 'good' sleep is represented by the 'peaks' and the 'troughs' or baseline represent the occurrence of bad sleep. The arrows represent when pills are taken and the gray boxes indicate when there is a correspondence between pill use and the occurrence of good sleep.

arousal (i.e. cognitive, cortical and/or somatic arousal),[36,37] and/or cognitive changes (e.g. less sleep related worry and catastrophization)[38] and/or neuroendocrine alterations (e.g. less cortisol secretion and augmented melatonin secretion) that come with, and are permissive of, reliably improved sleep.

Do patient preferences interact with the reinforcement phenomena?

While little is known about patient preferences with regard to placebo/medication use when medications are used ad libitum, preliminary data from our group[39] suggest that patients with chronic insomnia tend to use medication conservatively and on an intermittent basis. With respect to the latter, the more patients gravitate toward non-nightly dosing, the more likely it is that pill use will align with the natural periodicity or occurrence of good sleep. That is, if patients wait until they really need a 'sleeping pill', then it is increasingly likely that pill use will occur on precisely the nights where there is enough homeostatic pressure to produce improved sleep.

Final comment

The hypothesis advanced in the present paper is one that may not be limited to placebo use in patients with chronic insomnia. In fact, it seems likely that any disorder that is episodic (i.e. has symptoms that significantly vary in intensity over a period of days to weeks) may exhibit sustained placebo effects owing to the interaction of preferred pill use patterns, natural variation in symptom intensity, and the phenomena of interval and contingent reinforcement. A first step in evaluating whether such associations exist (for insomnia or any episodic disorder) will be empirical efforts to document (1) how symptom intensity varies in time and (2) what the preferred pill use strategies are for the populations that are known to exhibit sustained placebo effects.

Limitations regarding the proposed hypotheses

The ideas presented in this paper are proffered within a very narrow context: the effects of placebo use in patients with Primary Insomnia who are participating in pharmacologic RCTs. Accordingly, it is not clear to what extent similar effects may exist in clinical samples and/or in patients whose insomnia occurs in association with medical and psychiatric illness. While these caveats may viewed as 'limitations' they may also be viewed as appropriate targets for future research.

Practice points

Implications for clinical treatment

The observation that insomnia symptoms vary with time, if confirmed empirically, is of and in itself clinically useful. It allows the clinician working with insomnia patients to say with assurance that a good nights (or at least a better than average night's sleep) sleep is generally only 1–2 nights away. This may not only serve to prevent the patient from engaging in the compensatory practices that are thought to perpetuate insomnia (e.g. extending sleep opportunity), it also may serve to reduce sleep related anxiety and worry to a level that may also allow for positive clinical effects.The observation that placebo effects may (1) be maintained for extended periods and (2) result in continued improvement with time may also be clinically useful. Capitalizing on these effects may provide the clinician a way to withdraw patients from active medication which is likely to minimize the occurrence of rebound insomnia or withdraw effects.Finally, taking into account that concept of reinforcement may lead to the development and validation of dosing strategies that require less medication exposure to maintain clinical effects. For example, it has recently been proposed that partial reinforcement paradigms (continuous pill taking where some percentage of the pills are active drug and some percentage are placebos) may be used to manage chronic illnesses with results that are comparable to standard pharmacotherapy.[40,41] The application of partial reinforcement approach to the management of chronic insomnia may well lead to a resolution of the problem that is now all too evident: Insomnia is considered a chronic disorder for which there is no rational pharmacologic approach to its management in the long term. The value of the partial reinforcement approach, if it proved to be successful, is that it will provide a means by which the

- effects of pharmacotherapy can be extended (i.e. increase resistance to extinction);
- amount of drug required for the treatment is reduced, thereby maximizing benefits and reducing risks;
- side effects that occur with the use of hypnotics can be minimized, thereby potentially increasing adherence to treatment
- costs of long-term therapy with hypnotics can be reduced.

Research agenda

Implications for clinical trials

If it is the case that placebo effects are maintained owing to interval and/or contingent reinforcement and that clinical gains may continue to accrue with time owing to other factors that occur in association with acute gains, this poses an interesting problem for long term placebo controlled clinical trials in patients with insomnia. That is, with time, there will be a failure to distinguish between placebo and active medication effects and that this occurs, not as a result of the loss of drug efficacy, but owning to the continued improvement that is evident with long term use of placebos. Such a scenario requires that a whole host of issues be reconsidered vis-à-vis the conduct of hypnotic clinical trials.

- What is the proper way to define sustained efficacy viz. the use of hypnotics?
- What experimental design best allows for the resolution of long term effects-both for active medication and placebo effects? Should monitor only conditions be a standard condition for insomnia RCTs?
- Is it the case that continued clinical gains occur with both the use of active medications and placebos, and if not-why not?
- If the phenomena of continued clinical gains is limited to placebo use, is there a way to extend the initial gains that occur with active medication use so that they parallel the longer term clinical gains that occur with placebo use?
- Is there a point in time, given a long enough period of observation with patients using placebos, where a reversal of clinical gains is evident?

Each of these issues constitutes important avenues for future research.

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