

# Combining Pharmacologic and Nonpharmacologic Therapies for Insomnia

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Although both clinical experience and formal studies confirm the efficacy of cognitive-behavioral therapy (CBT) and hypnotic medications as treatments for insomnia, the interaction of the 2 treatments when combined has not been fully clarified. In principle, they could potentiate each other, not interact at all (in which case the benefits would be the sum of the 2 treatments alone), or inhibit each other. In this review, I suggest that the weight of available evidence indicates that the 2 treatments have a beneficial interaction, but that the paucity of data should prevent excessive generalization. It would be desirable for future studies to employ newer hypnotics with a range of doses in both nightly and p.r.n. administration and to examine comorbid as well as primary insomnias. The manner in which the medication is presented to the patient and the caregiver's conviction regarding the effectiveness of therapy need to be carefully controlled. Studies that consider these issues will need to be performed before firmer conclusions can be reached.

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Both behavioral interventions and pharmacologic therapies have been utilized to improve sleep in patients with insomnia, and therapies of both modalities have established significant efficacy. It is not yet clear, though, whether there would be benefits to combining nonpharmacologic and pharmacologic treatments, whether such benefits would be additive or synergistic (or even antagonistic), and whether the order of treatment utilization (i.e., simultaneous or sequential) influences outcome.

Cognitive and behavioral therapies are the mainstay of nonpharmacologic treatments for insomnia. A recent consensus statement by the National Institutes of Health noted that cognitive-behavioral therapy (CBT) is as effective as hypnotic medications in the short-term treatment of chronic insomnia and, unlike medications, may have efficacy that lasts beyond the duration of treatment.<sup>1</sup> Cognitive-

behavioral therapy for insomnia varies between studies and practitioners but generally includes behavioral elements such as relaxation training (e.g., progressive muscle relaxation<sup>2</sup>), stimulus control, sleep restriction, and cognitive techniques developed to reduce anxiety-producing and erroneous beliefs about sleep and sleep loss.<sup>1</sup> Stimulus control techniques are designed to form an association between the physical space of the bedroom and the act of sleeping and to regularize the sleep/wake schedule. Sleep restriction therapy addresses a behavior that can perpetuate insomnia—spending unnecessarily long and inefficient periods of time in bed, which the patient employs in a vain effort to increase the amount of sleep.<sup>3</sup> Distraction techniques<sup>4</sup> and paradoxical intention may also be incorporated into CBT for insomnia.

Pharmacologic therapy for insomnia has traditionally involved use of hypnotic agents that act as indirect agonists at the  $\gamma$ -aminobutyric acid (GABA<sub>A</sub>) receptor complex. Starting in the 1970s, these agents were primarily the “diazepam-like” benzodiazepines. The 1990s saw the introduction of the newer nonbenzodiazepine GABA agonists, including zolpidem, zaleplon, and, more recently, eszopiclone. As we will see later, most of the studies of combined therapy have involved the older benzodiazepines, and there are few data available on combination approaches using the newer agents. In addition, a new medication, ramelteon, which acts as a high-affinity and specific melatonin receptor agonist, is now available; no studies have yet been published on its use in conjunction with CBT. In the following sections of this article, the studies available on combining therapies are examined.

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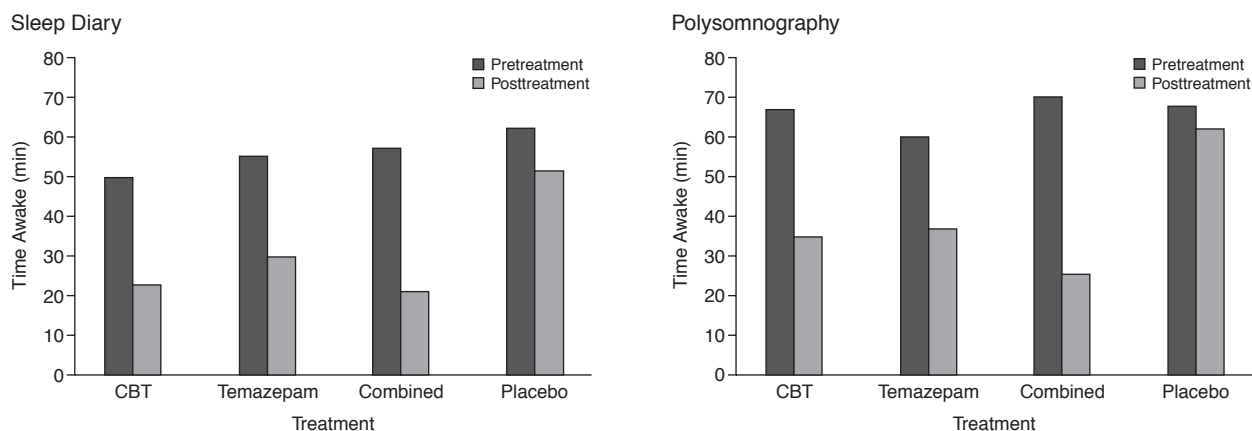
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Figure 1. Effect of CBT, Temazepam, Combined CBT and Temazepam, and Placebo on Waking After Sleep Onset, as Measured by Sleep Diary and Polysomnography<sup>a</sup>



Changes in wake after sleep onset from pretreatment to posttreatment as measured by sleep diaries and nocturnal polysomnography. Sleep diary data are based on 2 weeks of self-monitoring at baseline (before treatment) and the last 2 weeks of treatment. Polysomnographic data are based on nights 2 and 3 before and nights 5 and 6 after treatment.

<sup>a</sup>Adapted with permission from Morin et al.<sup>5</sup>

Abbreviation: CBT = cognitive-behavioral therapy.

### CBT AND PHARMACOTHERAPY FOR THE TREATMENT OF INSOMNIA

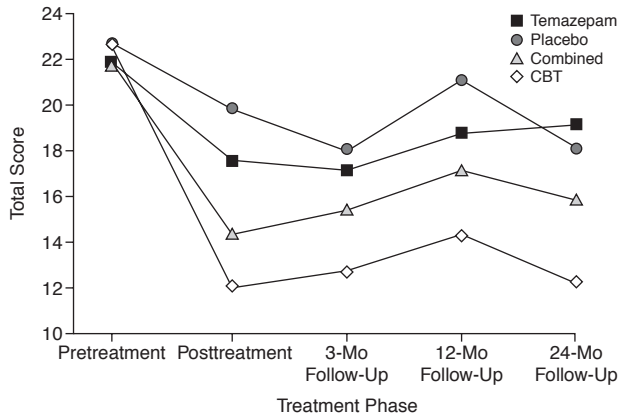
Morin et al.<sup>5</sup> examined combination therapy in 78 individuals aged 55 years or older with a history of sleep-onset or maintenance insomnia for at least 6 months. They were randomly assigned to receive CBT (8 weekly, 90-minute, small-group sessions), pharmacotherapy (temazepam 7.5–30 mg as needed, but at a minimum of 2–3 nights/week), CBT plus pharmacotherapy, or placebo. Sleep outcomes were assessed via sleep diaries, polysomnography, and clinical rating scales. All active treatments (CBT, temazepam, CBT plus temazepam) resulted in significant improvements in total wake time and sleep efficiency ( $p < .05$  for both), as well as wake after sleep onset ( $p < .01$ ), as reported in patient diaries (Figure 1). There were no significant differences among the treatment groups, but there was a trend for patients who received CBT plus temazepam to fare better than patients who received CBT or temazepam alone. All 3 treatments tended to decrease polygraphically measured wake time after sleep onset, but only the combined treatment reached statistical significance. In addition, only study participants who received CBT, with or without the addition of temazepam, considered their sleep to have improved significantly; these patients were also less distressed and experienced less interference when performing daytime tasks.<sup>5</sup>

There have been some data to suggest that CBT may be associated with long-term improvements not seen with acute use of pharmacotherapy. The participants in the above trial were followed up for 3, 12, and 24 months after

trial completion, although the placebo group was offered an active treatment after 3-month follow-up, and some patients resumed pharmacotherapy after trial cessation. Follow-up was conducted by means of a sleep diary. Patients who received CBT showed no significant change from posttreatment to follow-up in their total score on the Sleep Impairment Index, suggesting that the improvements in sleep obtained during the study were maintained. Those who received medication only did not experience continued benefit at follow-up; the clinical course of the combined therapy group was more variable (Figure 2).<sup>5</sup>

Jacobs et al.<sup>6</sup> studied the combination of zolpidem and CBT on 63 younger (aged 25–64 years) primary insomniacs, with a main complaint of difficulty going to sleep. Patients were randomly assigned to receive either CBT (4 30-minute individual sessions and 1 telephone treatment session), pharmacotherapy (zolpidem 10 mg nightly for 28 days, then 5 mg nightly for 7 days, then 5 mg every other night for 7 days), CBT plus pharmacotherapy, or placebo. The primary outcome measure was sleep-onset latency, as assessed by sleep diary; secondary measures included sleep diary measures of sleep efficiency and total sleep time and nightcap measures of sleep-onset latency, sleep efficiency, and total sleep time. Assessment from the sleep diary indicated that CBT had the most potent effect on reducing sleep latency. All treatments, including placebo, increased total sleep, with a nonsignificant trend for the greatest increase with zolpidem. There was no increased benefit in the combined therapy group. At 12-month follow-up, all CBT groups showed continued benefits; no data were available on the zolpidem-only group.<sup>6</sup>

Figure 2. Long-Term Effects of CBT, Temazepam, Combined CBT and Temazepam, and Placebo on Sleep Impairment Index<sup>a</sup>



Pretreatment, posttreatment, and follow-up changes in total scores for the Sleep Impairment Index (patient version).

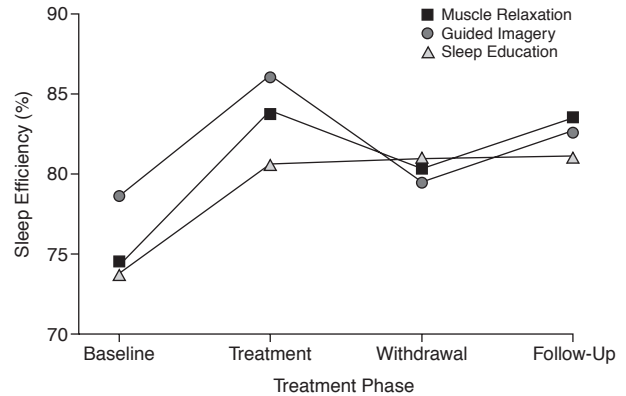
<sup>a</sup>Adapted with permission from Morin et al.<sup>5</sup>  
Abbreviation: CBT = cognitive-behavioral therapy.

## RELAXATION THERAPY AND PHARMACOTHERAPY FOR THE TREATMENT OF INSOMNIA

Rosen et al.<sup>7</sup> reported that relaxation therapy combined with pharmacotherapy had a greater effect on sleep than pharmacotherapy combined with sleep education. Patients aged 21 to 65 years with chronic insomnia (N = 41; final N = 32) were randomly assigned to receive estazolam (1 mg h.s.) and seven 1-hour small-group sessions of either sleep education or progressive muscle- or imagery-based relaxation training. Patients who received relaxation training were asked to engage in 2 additional 15-minute independent practice sessions a day, which were monitored by means of a relaxation log. Total sleep time lengthened significantly in all 3 groups: by 65 minutes in the muscle relaxation group, 40 minutes in the guided imagery group, and 34 minutes in the sleep education group. Patients engaged in both types of relaxation experiments experienced a significant increase in sleep efficiency (Figure 3) and decrease in waking after sleep onset relative to baseline, but patients in the education group did not.<sup>7</sup>

In a study that is actually a comparison, rather than a combination treatment protocol, Waters et al.<sup>8</sup> found that patients who received flurazepam alone fared better on all sleep measures than patients who were trained in a combination of relaxation and distraction methods or individuals who practiced sleep restriction and stimulus control. Adults with chronic insomnia (N = 53) were randomly assigned to receive progressive muscle relaxation and cognitive distraction, sleep restriction and stimulus control, flurazepam (15 mg at bedtime), or sleep hygiene education. Outcome

Figure 3. Effects of Muscle Relaxation, Guided Imagery, and Sleep Education in Combination With Estazolam 1 mg on Sleep Efficiency<sup>a</sup>



Effects of muscle relaxation, guided imagery, and sleep education in combination with estazolam 1 mg on sleep efficiency.

<sup>a</sup>Adapted with permission from Rosen et al.<sup>7</sup>

variables included sleep-onset latency, number of awakenings, difficulty falling asleep, restfulness of sleep, and sleep quality. Significant differences were found between the treatment groups in terms of difficulty falling asleep, sleep restfulness, and sleep quality. Patients who received flurazepam had the least difficulty falling asleep, and patients who received only sleep hygiene education, the most; similarly, patients who received flurazepam experienced the most restful and best-quality sleep (Figure 4).<sup>8</sup>

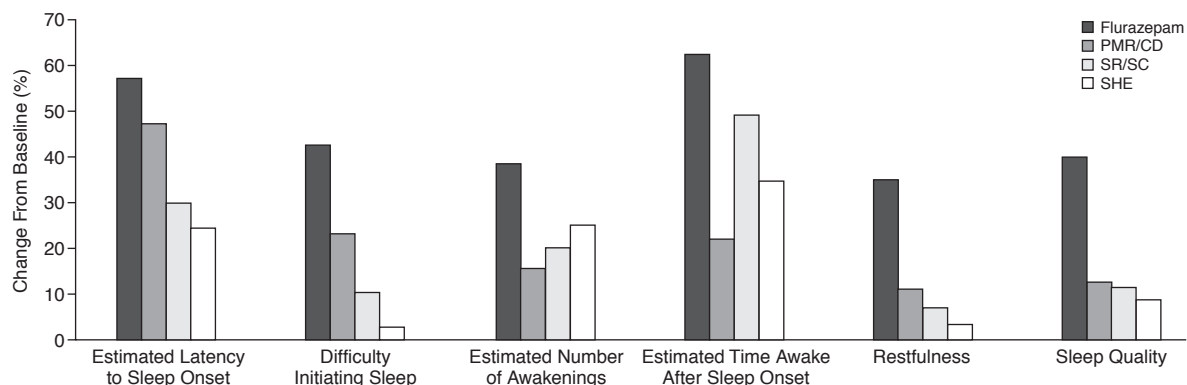
## CBT AND MODAFINIL FOR THE TREATMENT OF SLEEPINESS COMPLAINT IN INSOMNIACS

Daytime sleepiness and fatigue can be a complaint in insomniacs and potentially can increase during some aspects of CBT, such as sleep restriction. Modafinil, a stimulant with a mechanism of action different than that of amphetamine or methylphenidate,<sup>9</sup> was studied by Perlis et al.<sup>10</sup> in insomniacs. Thirty patients were randomly assigned to receive CBT and placebo, CBT and modafinil (100 mg), or a contact control and modafinil for 10 weeks. Modafinil alone did not improve any sleep continuity measures, but the patients who received both modafinil and CBT were more adherent to the CBT and experienced reduced daytime sleepiness.<sup>10</sup>

## TREATMENT SEQUENCE AND SLEEP OUTCOMES

Vallieres et al.<sup>11</sup> explored the possibility that treatment sequence may have an effect on outcome. Seventeen patients with insomnia of 6 months' duration or longer were randomly assigned to receive 5 weeks of zopiclone 3.75 to 7.5 mg followed by 5 weeks of zopiclone and CBT,

Figure 4. Effect of Flurazepam 15 mg, Progressive Muscle Relaxation With Cognitive Distraction, Sleep Restriction With Stimulus Control, and Sleep Hygiene Education on Subjective Sleep Measures<sup>a</sup>



Effect of flurazepam 15 mg, progressive muscle relaxation with cognitive distraction, sleep restriction with stimulus control, and sleep hygiene education on subjective sleep measures.

<sup>a</sup>Based on Waters et al.<sup>8</sup>

Abbreviations: PMR/CD = progressive muscle relaxation plus cognitive distraction, SHE = sleep hygiene education, SR/SC = sleep restriction and stimulus control.

5 weeks of zopiclone and CBT followed by 5 weeks of zopiclone only, or CBT alone for 10 weeks, after a 3-, 5-, or 7-week baseline. At the midpoint of the 10-week study—the point at which patients who initially received zopiclone alone were transitioning to a combination of zopiclone and CBT, and patients who initiated on the combined therapy were transitioning to zopiclone alone—patients who had received CBT or combined therapy, but not medication alone, experienced improvement over baseline in total wake time and sleep efficiency ( $p < .05$ ), while no groups experienced a significant change in sleep time. Patients who received the combined therapy for the first 5 weeks tended to have less time awake (24.02 minutes) than patients who received CBT (50.60 minutes) and had significantly less awake time than those who received medication alone (55.95 minutes). Patients initiated on combined therapy experienced the highest sleep efficiency at that point.<sup>11</sup>

At the conclusion of the 10-week study, patients who received combined treatment/CBT had a significantly lower wake time (20.48 minutes) than did patients who received CBT/CBT (34.17 minutes) or medication/combined treatment (40.6 minutes); there were no significant differences among the groups in terms of total sleep time. Patients who received combined treatment/CBT had the greatest sleep efficiency at study end (95.45%), followed by patients who received CBT/CBT (90.97%) and patients who received medication/combined treatment (88.70%).<sup>11</sup>

## DISCUSSION AND CONCLUSIONS

In summary, this author's reading of the literature suggests that 2 studies report a benefit of combining hypnotic

medication with nonpharmacologic treatment: Morin et al.<sup>5</sup> with CBT and temazepam and Rosen et al.<sup>7</sup> with estazolam and relaxation techniques. In contrast, Jacobs et al.<sup>6</sup> found no added benefit to combining zolpidem and CBT. It is difficult to compare these studies because they were conducted in different groups, had different primary endpoints, and utilized different hypnotic regimens. Morin et al.,<sup>5</sup> for example, studied older patients, focusing on waking after sleep onset and sleep efficiency, and utilized a p.r.n. administration schedule, whereas Jacobs et al.<sup>6</sup> emphasized sleep-onset latency in middle-aged subjects who took hypnotic medications nightly.

In addition to the difficulty in comparing individual studies, several other features of these studies as a group should be considered. First, all of them have examined patients with primary insomnia, who are probably a minority of patients seen clinically in medical practice. Although psychological and behavioral studies have been compared against placebo conditions in comorbid insomnias, little has been done systematically with combination therapies.

The nature of the medications used also needs to be considered. Most combination therapy studies employed older benzodiazepines (temazepam, estazolam, flurazepam); only 1 combined therapy study (Jacobs et al.<sup>6</sup>) used a newer nonbenzodiazepine (zolpidem). The Vallieres et al.<sup>11</sup> study of sequence effects employed zopiclone. Two studies also used relatively low doses (estazolam 1 mg in the Rosen et al. study,<sup>7</sup> flurazepam 15 mg in the Waters et al. comparison study<sup>8</sup>). In pharmacologic studies, comparisons between treatments usually involve multiple doses of each treatment unless there are substantial preexisting data showing equipotency. The combined therapy

studies to date have not employed a dose-response approach. There are, of course, some practical considerations in terms of the size of the study that would be required, but traditionally this would be needed before one could conclude that a treatment is or is not effective, alone or in combination.

It should also be noted that with 1 exception (Morin et al.<sup>5</sup>), these studies have administered medications on a nightly fixed schedule. The potential benefits of using hypnotics p.r.n. during either the acute treatment phase or the follow-up period have not yet been fully explored.

Another consideration in assessing the benefits of these 2 forms of therapy is to explore the context in which the patient is given the medication. Is the drug given by one caregiver, while the CBT is administered by another? If so, how are the relative roles of these 2 persons explained to the patient? Do both caregivers express the same degree of enthusiasm or conviction about the effectiveness of their treatment approaches? Does the manner in which the genesis of insomnia is explained to the patient alter the relative benefits of the 2 types of treatments? (The latter has been reported to have a significant effect on the clinical course in patients with idiopathic symptoms.<sup>12</sup>) It seems likely that a definitive study of combined therapies will need to consider these issues more fully.

Another area that has not been explored is integrating the fact that the patient is taking medication into the non-pharmacologic therapy. In therapy, for instance, the caregiver might be exploring cues in the patient's life that lead to anxiety about sleeping on a given night. If a patient is receiving a hypnotic p.r.n., it could be potentially useful to ask which days in the past week he or she took medication. Then one could explore what it was about those particular days that led the patient to worry that he or she might not sleep on that given night. To this writer's knowledge, this approach has not yet been systematically studied, but it is presented here as an example of how the concept of combination therapy could encompass integrating the 2 types of therapy to interact, rather than just administering them in parallel.

In conclusion, the data at this point are mixed but tend to suggest that combined therapies can be advantageous over monotherapy. More complete answers will require studies that consider issues of dose and timing, and the setting and manner in which a medication is given.

*Drug names:* diazepam (Valium), estazolam (Prosom and others), eszopiclone (Lunesta), flurazepam (Dalmane and others), methylphenidate (Ritalin, Metadate, and others), modafinil (Provigil), ramelteon (Rozerem), temazepam (Restoril and others), zaleplon (Sonata), zolpidem (Ambien), zopiclone (Lunesta).

*Disclosure of off-label usage:* The author has determined that, to the best of his knowledge, modafinil and methylphenidate are not approved by the U.S. Food and Drug Administration for the treatment of insomnia.

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