



CLINICAL REVIEW

The treatments of chronic insomnia: A review of benzodiazepine receptor agonists and psychological and behavioral therapies

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S U M M A R Y

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The present review provides an assessment of the efficacy and safety of benzodiazepine receptor agonists (BZRAs) and psychological and behavioral interventions for insomnia. These methods include relaxation techniques, sleep hygiene rules, stimulus control, sleep restriction and cognitive techniques, often also referred to as cognitive-behavioral therapy (CBT) when encompassing cognitive strategies and at least one kind of behavioral intervention.

In order to provide a comprehensive assessment of the literature regarding the efficacy and safety of these standard treatments for insomnia, an integrative synthesis of the existing meta-analytic studies for each of the various treatment modalities was conducted. Where meta-analytic studies were not available, data from double-blind placebo-controlled randomized controlled trials (RCTs) were included.

The summary findings from this review are (1) BZRAs and psychological and behavioral methods are effective to treat insomnia in the short-term and the latter have significantly more durable effects when active treatment is discontinued; and (2) there is only very limited evidence that BZRAs retain their efficacy during long-term treatment.

The present review underscores the need for further research regarding the comparative efficacy and safety of these treatments for insomnia, how this varies with age and comorbidity, and how the various treatment modalities impact (1) daytime functioning, (2) quality of life, (3) health care utilization; and (4) pharmacoconomics. Finally, it is particularly important that studies be conducted to determine if successful insomnia treatment influences the clinical course of the diseases that often occur co-morbidly with sleep continuity disturbance.

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Introduction

In June 2005 The National Institutes of Health (NIH) convened a State-of-the-Science (SOS) Conference¹ related to the topic of “manifestations and management of chronic insomnia in adults”. The panel members of this conference came to a series of conclusions including:

- there is sufficient evidence regarding the efficacy of sedative hypnotics and psychological and behavioral interventions for insomnia,

- that there is little to no data regarding the comparative efficacy of the established treatment modalities, and
- there is insufficient evidence to support the widespread practice of using antidepressants, low dose atypical neuroleptics, and OTC agents for the treatment of insomnia.

While these conclusions clearly established what can be considered as evidence-based practice and what clinical research is urgently needed, the published document did not provide a summary of the evidence which served as the platform for the consensus statement. The present review seeks to summarize the evidence from meta-analytic studies or randomized controlled trials underlying these statements.

Methodological considerations
What constitutes evidence?

In the last decade many publications about evidence-based medicine and grading of scientific evidence obtained from clinical

Abbreviations: AE, adverse event; BZRA, benzodiazepine receptor agonist; CBTI, cognitive behavioral treatment; IIT, intent to treat; NOA, number of awakenings; OTC, over the counter medication; PT, pharmacotherapy; RCT, randomized controlled trial; SAD, sedating antidepressant; SL, sleep latency; TST, total sleep time; WASO, wake after sleep onset.

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trials have been published. Basic information about this approach can be found in the publications of Sackett et al.² or Greenhalgh.³ In brief, medical evidence relating to therapeutic strategies is graded according to certain principles (e.g., whether there is random assignment, double blinding, placebo controls, adequate sample sizes, appropriate statistics, etc.). Given this approach, many authorities in the field agree that the highest form of evidence for a given treatment comes from the meta-analysis (MA) of randomized placebo-controlled studies, though this statement also has been met with considerable criticism. The second best evidence derives from single randomized controlled trials (RCTs). Less valuable evidence comes from any of the following: treatment studies without placebo controls, case series studies, quasi-experimental studies, and consensus reports based on expert opinion.

Data source

As noted above, the primary sources for this review are the meta-analytic studies pertaining to the efficacy of benzodiazepine receptor agonists (BZRAs) and psychological and behavioral treatments for insomnia. Additional sources of information include double-blind randomized placebo-controlled trials (when meta-analyses are not available), and the standards of practice statements from the American Academy of Sleep Medicine.

Data summaries

Each therapeutic domain will be assessed for efficacy and safety in terms of acute and long-term effects. Acute studies refer to investigations lasting between 1 and 4 weeks. Long-term studies refer to investigations lasting at least 6 months. The summary for each of the meta-analytic studies will include their core data with respect to search strategy, inclusion and exclusion criteria, number of studies and subjects included, and the report of the relevant outcome data in the form of effect sizes (ESs) and absolute and percent change data (when available). The latter allows one to judge the clinical meaningfulness of the treatment outcomes. The former allows for an assessment of treatment outcome that takes into account both mean and change and sample variability. Effect sizes (usually computed according to the formula of Cohen⁴) are classified as minor (0.2), medium (0.5) and large (>0.8).

Treatment outcomes

The majority of data summarized in this paper are primarily based on treatment effects as they occur with self-report sleep continuity measures based on sleep diaries. These measures commonly include sleep latency (SL), wake time after sleep onset (WASO), number of awakenings (NOA), total sleep time (TST), sleep efficiency (SE%) and overall subjective ratings of sleep quality (SQ). This approach is adopted so as to allow for a common mode of assessment across treatment modalities (i.e., pharmacotherapy vs. psychological treatments). The utility of this choice is further buttressed by the perspective that treatment efficacy is best assessed 1) using the same assessment strategy that is required to establish diagnosis (subjective complaint) and 2) relative to the patient's perception of illness severity.^c

^c The second of these claims may not appear valid given that many consider polysomnographic assessed sleep continuity to be the "gold standard" measure. The proposition that patient perception is essential is, however, borne out by the following. It is unlikely that a hypnotic would be considered efficacious if it produced moderate to robust changes on PSG, but little to no change, on self-report, measures.

Review

The acute effects of BZRAs

There are four meta-analyses which serve to establish the efficacy of BZRAs for the treatment of insomnia.

The first study, published by Nowell and colleagues⁵ searched the literature from 1966 to 1996 in the databases MEDLINE, Current Contents, SLEEP, Journal of Sleep Research and selected bibliographies. Selection criteria for inclusion were the diagnosis of primary insomnia in males and females ages 18–65 years who were studied under placebo-controlled or parallel group design conditions using a randomization or a double-blind approach. Substances included were classical benzodiazepine hypnotics (alprazolam, chlordiazepoxide, diazepam, estazolam, flurazepam, lorazepam, quazepam, temazepam, triazolam) and zolpidem. Outcome variables were SL, NOA, TST and an overall rating of SQ. Twenty-two studies (encompassing $n = 1894$ patients) fulfilled the inclusion and exclusion criteria. This subset of studies was analyzed to determine whether medication was superior to placebo during acute administration (for a median duration of use = 7 days). The effect sizes relative to placebo (as assessed between subjects) were SL = 0.56; NOA = 0.71; TST = 0.65; and SQ = 0.62.

The second study, published by Holbrook and colleagues⁶ searched the databases MEDLINE, the Cochrane Controlled Trials Register (from 1966 to 1998) and selected bibliographies. In addition these authors contacted pharmaceutical companies for further details about published and unpublished studies. Selection criteria were primary insomnia, age > 18 years both sexes, double-blind strategy, placebo or active control and randomization. Forty-five studies ($n = 2672$ patients) were retained for evaluation to determine whether benzodiazepine treatment was superior to placebo during acute administration (median duration of use ~7 days). Substances included were classical benzodiazepine hypnotics and one "non-benzodiazepine" (triazolam, flurazepam, temazepam, midazolam, nitrazepam, estazolam, lorazepam, diazepam, brotizolam, quazepam, lopraxolam, flunitrazepam and zopiclone). The self-report sleep continuity variables assessed were SL and TST. The authors did not provide effect size estimates but instead provided mean difference scores with confidence intervals. The mean difference (as assessed between subjects) for SL was 14.3 min and was 48.4 min for TST. With respect to side effects, BZRAs were found to result in more adverse events than placebo. The side effects noted include daytime drowsiness and dizziness or lightheadedness. Interestingly, the drop-out rates for BZRAs and placebo were, however, similar. Finally, when comparing zopiclone to the other hypnotics, no superiority for the former emerged. The authors conclude from these data that the benefits of therapy may not warrant the increase in the occurrence of side effects and adverse events.

The third study, published by Dundar and colleagues^{7,8} in 2004 (also referred to as the NICE study), compared the "newer" "non-benzodiazepine" hypnotics (i.e., "Z" – drugs: zopiclone, zolpidem or zaleplon) with classical benzodiazepine hypnotics (e.g., BZs: diazepam, lopraxolam, lorazepam, lormetazepam, nitrazepam, temazepam, etc.) not only with respect to short-term efficacy but also concerning side-effect profiles and pharmaco-economical aspects. A literature search was conducted in the databases MEDLINE, EMBASE, PsycInfo, SCI/Web of Science, the Cochrane Library, selected bibliographies and selected psychopharmacological journals from 1966 to 2003. Inclusion criteria were comparison of a Z-drug with a BZ or of a Z-drug to any other Z-drug, double-blind strategy, randomization, insomnia diagnosis, both sexes, no upper age limitation. For the final analysis 24 eligible studies were identified which met inclusion and exclusion criteria. Altogether, data from 3909 patients who took part in the

various trials were considered. Trial duration ranged from one night to 6 weeks. Statistical analysis was based on meta-analysis of studies which compared the same drugs. Data were then pooled using a fixed effect model with calculation of odds ratios and 95% confidence intervals. Outcome variables for sleep included subjective estimates of SL, TST, NOA, WASO and sleep quality.

The authors concluded that the two classes of drugs (BZs vs. Z-drugs) did not differ from one another with respect to safety or efficacy. Minor differences between the BZRAs were observed with respect to safety and efficacy. Zolpidem was found to produce shorter sleep latencies and less rebound insomnia upon discontinuation than zopiclone. Zaleplon was found to produce slightly shorter sleep latencies than zolpidem. Finally, BZs were found to be more economical than the Z-drugs. The authors conclude that the failure to detect differences between the medication classes may not necessarily represent a true “no difference” but may be ascribable to the methodological differences between the included studies. They also levy the criticism that the majority of the studies were funded by the pharmaceutical industry and thus may have been biased.

It should be noted that this report has been strongly criticized by several authors.^{9,10} The primary issue being that classifying medications solely by class (without taking into account the pharmacokinetics and pharmacodynamics of each medication within each class) can lead to “eccentric and potentially dangerous conclusions”.¹⁰ Put differently, one problem related to pharmacokinetics was that Dundar et al. “lumped” together short and long acting medications. This may have obscured class differences and lead to the erroneous conclusion that the two classes of drugs (BZs vs. Z-drugs) were not different with respect to safety or efficacy.

The fourth study published by Glass and colleagues¹¹ investigated the impact of sedative hypnotics using a meta-analytical strategy in a subgroup of elderly patients (>60 years) with insomnia. The data sources included MEDLINE, EMBASE, The Cochrane Clinical Trials Register, PubMed, PsycLit and selected bibliographies were searched from 1966 to 2003. As with the prior study, Glass and colleagues also asked the drug manufacturers of newer compounds to provide additional details from published and unpublished studies. Inclusion criteria were age > 60 years both sexes, randomized controlled trial, insomnia diagnosis, pharmacological treatment for at least five nights. Twenty-four studies including 2417 participants (>60 years of age) were identified who met stringent in-and-exclusion criteria. Substances included in the analysis were zopiclone, zolpidem, several benzodiazepines (e.g., temazepam and triazolam), and the antihistaminic diphenhydramine. Outcome parameters included subjective estimates of SL, TST, NOA, sleep quality and adverse events. Statistical analysis was based on the calculation of effect sizes (according to Cohen's d^4) or common odds ratios for adverse events. An overall analysis combining all medications against placebo revealed significant effects for NOA (mean reduction size: 0.63, $P < 0.001$), TST (mean difference 25.2 min, $P < 0.001$), and sleep quality (effect size 0.14, $P < 0.05$).

The data analysis also revealed an increased risk of adverse events, mostly reversible and not severe, with active medication compared to placebo. Odds ratios compared to placebo were 4.78 for adverse cognitive events, 2.61 for adverse psychomotor events and 3.82 for daytime fatigue with the sedative hypnotics. A heightened incidence of falls and motor vehicle crashes was reported with active drugs compared to placebo. The main conclusion from the study drawn by the authors was that in patients over the age of 60 years the benefits associated with the use of sedative hypnotics are marginal and outweighed by the risks.

Summary and comment

The data from these meta-analyses are not entirely consistent and each investigator reaches different conclusions. Considering the meta-analyses by Nowell et al.⁵ and Holbrook et al.,⁶ the data clearly suggest that BZRAs produce significant clinical gains (as compared to placebo) with moderate to large effect sizes with short-term use (usually between a few days and maximally 6 weeks in most of the studies analyzed). Looking more specifically at the differences between “older” benzodiazepine hypnotics and “newer” so-called Z-drugs (i.e., zolpidem, zopiclone and zaleplon), Dundar et al.^{7,8} challenge the widely assumed superiority of the latter, at least on the basis of the studies they analyzed. Reaching an even more critical conclusion, Glass et al.¹¹ express profound doubt that in the elderly, the benefit of pharmacological therapy with BZRAs outweighs the risks.

When considering the evidence provided by the above summarized meta-analyses, it becomes clear that issues like adverse events, rebound insomnia, development of tolerance, abuse or dependence from BZRA have not yet received comparable attention in meta-analytic reviews, though undoubtedly these issues are extremely important and deserve the utmost scrutiny for everyday clinical practice. As most of the relevant literature is solely focussed on insomnia outcome measures, it also remains unclear whether other relevant parameters, i.e., quality of life, daytime functioning, severity of comorbid conditions, long-term sequelae of insomnia are positively influenced by the short-term pharmacological treatment of insomnia.

Insofar, more empirical work, especially research independent from the pharmacological industry, is needed regarding

- the relative efficacy and safety of hypnotics in general, and for interactions as they occur relative to pharmacokinetics, pharmacodynamics, the insomnia phenotypes (i.e., initial, middle, and late insomnia), and age and sex.
- whether the pharmacological treatment of insomnia reverses the risks which are conferred by untreated insomnia for new onset illnesses (e.g., depression, hypertension, glucose homeostasis dysregulation, etc.)
- whether reduced risk for new onset illness outweighs the risks for adverse events, and
- the economic impact of the pharmacological treatment of insomnia on job performance and/or health care utilization.

Long-term efficacy and safety with BZRA treatment

Very little is known about the long-term efficacy and safety of BZRA treatment in patients with chronic insomnia. There can be no doubt, given the chronic nature of insomnia, that this is an important issue which needs to be addressed. To our knowledge there are only two published investigations on this topic. One which is a 1-year open-label extension study from two randomized, double-blind, trials of zaleplon.¹² The other is a placebo-controlled trial lasting 6 months in patients treated with eszopiclone.¹³

In the study by Ancoli-Israel et al.¹² in a sample of 260 patients with primary insomnia, it was found that elderly subjects maintained statistically significant levels of improvement for SL, NOA, and for TST ($P < 0.001$ for each variable) for treatment durations of up to 12 months.

In the study by Krystal et al.¹³ in a sample of almost 800 patients with primary insomnia, it was found that adult subjects maintained statistically significant improvement (as compared to placebo) for SL, WASO, NOA and for TST ($P < 0.001$ for each variable) for the treatment period of 6 months. SOL was reduced by 43.6 min (48% change; placebo: 33 min; 34% change), WASO was reduced by

39 min (47% change; placebo: 22.5 min; 32% change), NOA was reduced by 1.3 (41% change; placebo: 0.9; 26% change) and TST was increased by 75.9 min (25% change; placebo: 35.7 min; 12% change). Of particular note is that the initial sleep continuity gains were remarkably stable with time, and that this was true regardless of the analytic technique used to accommodate “right censorship” (i.e., subjects lost to follow-up). For an illustration of this stability see Fig. 1.

With respect to safety, the analysis of clinical laboratory studies, vital signs, electrocardiograms, and findings on physical examination indicated that there was no evidence of significant drug-related safety issues for the 6-month treatment period with eszopiclone. The spontaneous report of adverse events for the 6-month trial was 81.1% for the eszopiclone group and 70.8% for the placebo group. The majority of adverse events (AE) in each group were mild or moderate in severity (placebo, 89.2%; eszopiclone, 87.7%), and the most common AEs were unpleasant taste, headache, infection, pain, nausea, and pharyngitis. Two of the most frequent side effects (unpleasant taste and pharyngitis), it should be noted, appear to be limited to eszopiclone and are not characteristic of the whole class of BZRAs. Finally, the authors note that after discontinuation of active medication there was no evidence of withdrawal symptoms or rebound insomnia (during a period of 5–7 days). Just recently, a secondary data analysis from this study¹⁴ reported also beneficial effects of long-term treatment with eszopiclone on quality of life and work limitation due to the insomnia.

Summary and comment

There is insufficient data at this time to conclude one way or another about the long-term efficacy of BZRA treatment. The results from the above mentioned studies are promising in that they provide for the first time data that suggest that nightly use of hypnotics may confer stable effects for periods of up to 12 months. This said, neither study provided AE or serious AE data by month, so it is not possible to determine if there was an escalation or de-escalation of side effects/medical symptoms with long term use of this particular BZRA. Such information, even in the absence of additional studies, would assist with the determination about whether or not BZRAs may be used to manage insomnia for long

periods of time. Furthermore, the crucial question of rebound effects upon discontinuation of medication after long-term treatment merits special attention. Future studies in this area need to encompass longer follow-up periods (ideally 6–12 months or longer) to clarify the clinical course of patients having been treated with BZRA for periods of 6 month. The question is whether these patients will be in remission or have to be put on medication again to maintain their improvements of sleep.

The acute and long-term effects of psychological and behavioral treatments

CBT for insomnia is a multimodal therapy which includes cognitive techniques (i.e., cognitive restructuring) and one or more of the following psychological/behavioral interventions: stimulus control, sleep restriction, relaxation methods, and sleep hygiene instructions. A detailed description of these techniques can be found in several published treatment manuals.^{15–18} There are now five published meta-analyses which serve to establish the efficacy of psychological and behavioral methods, respectively, multimodal CBT as defined above. Please note that these studies differ from those published for pharmacological interventions in at least one way: most of the psychological/behavioral studies evaluate pre-post change and thus have effect sizes which are calculated based on within subject (as opposed to between subject) variance.

It is also important to note that some of these treatments (e.g., sleep restriction and stimulus control) do not prolong sleep time but, on the contrary, result in a shortening of total sleep time during the acute treatment interval (4–8 weeks). This is the case because treatment includes reducing the amount of time spent in bed via 1) the prescription to phase delay bedtime and/or 2) the instruction that patients leave the bedroom when awake during the sleep period. Thus, it is usually the case that TST effects are smaller, compared to other sleep continuity parameters, in trials encompassing stimulus control or sleep restriction.

The first study published by Morin and colleagues¹⁹ searched the literature from 1974 to 1993 by “computer search”, and in reference lists of previous reviews. Inclusion criteria were target problem sleep onset, maintenance or mixed insomnia, non-pharmacological treatment, and group design. Outcome measures

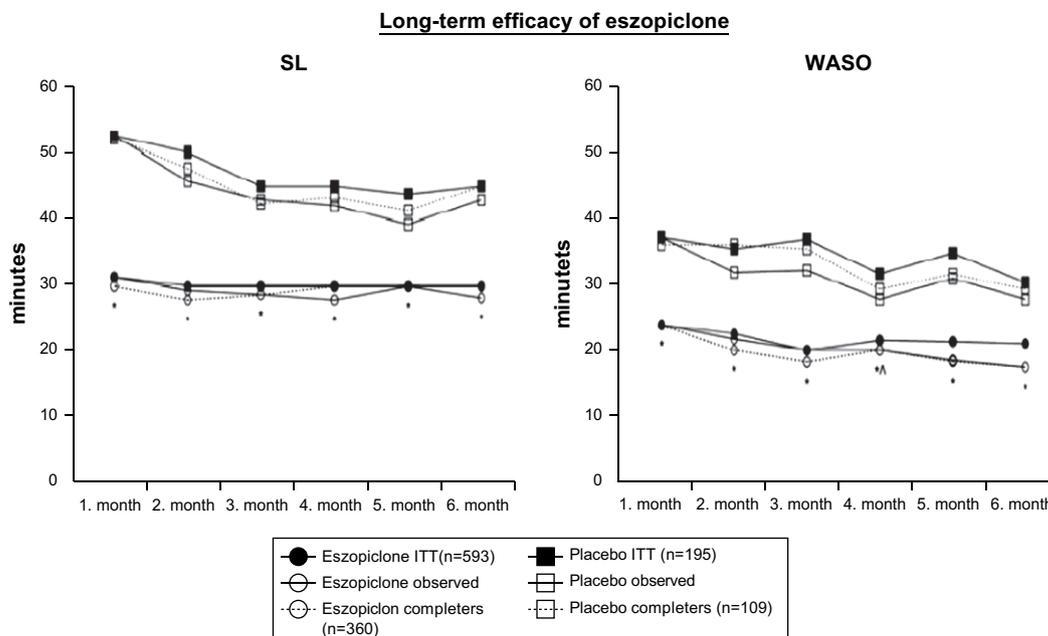


Fig. 1. Long-term efficacy of eszopiclone for sleep latency (SL) and wake after sleep onset (WASO) compared to placebo. Data taken from Krystal et al.¹³ ITT, intent to treat.

included SL, WASO, NOA or TST. From a pool of over 100 reports, 59 studies ($n = 2102$ patients) were evaluated to determine the magnitude of pre-post change as it occurs with psychological and behavioral interventions. (Statistical methods included calculation of effect sizes based on Cohen's d^4 or similar methods²⁰). In this analysis of within subject variance, the effect sizes were SL = 0.88; WASO = 0.65, NOA = 0.53, and TST = 0.42. Only the effects for SL and WASO were found to be significant. These effects were also rendered in terms of mean differences and percent change (pre to post). The values for the four parameters were as follows: SL = -27.7 min (43.1% change; placebo: -8 min; 12.6% change), WASO = -32.7 (46.4% change; placebo: -10.2 min; 15.3% change), NOA = -0.6 (29.8% change; placebo: -0.2; 9.5% change) and TST = +28.5 min (8.2% change; placebo: +4.2 min; 1.2% change). These clinical gains were maintained following the discontinuation of therapy for periods of time averaging 6 months.

The second study published by Murtagh and colleagues in 1995²¹ searched the databases PsycLit and MEDLINE, reference lists of relevant review articles in books and unpublished studies (dissertations) for the time period of 1973–1993. Inclusion criteria were involvement of a psychological treatment or a combination of psychological treatment, at least $n = 5$ subjects with primary insomnia, and the exclusion of comorbid insomnia. With this method 66 studies ($n = 1538$ patients) were evaluated to determine the magnitude of pre-post change compared to the control group as it occurs with psychological/behavioral interventions. For statistical analysis effect sizes were calculated according to the formula of Glass et al.¹⁸ Three sleep continuity variables were assessed including SL, NOA and TST. In this analysis of within subject variance, the effect sizes were SL = 0.87; NOA = 0.63 and TST = 0.49. These effects were also rendered in terms of mean differences and percent change (pre to post). The values for the three parameters were as follows: SL -24 min (39.5% change), NOA = -1.2 (73% change) and TST = +32 min (9.4% change). Significance values were not provided, but the effect size estimates for SL and NOA are clearly moderate to large. As with the prior study, the authors provide data which suggest that these clinical gains were maintained following the discontinuation of therapy.

Fig. 2 provides a representation of the sleep continuity effects for both the meta-analyses. Table 1 compares the effect sizes described in the two studies^{19,21} for the specific treatment modalities.

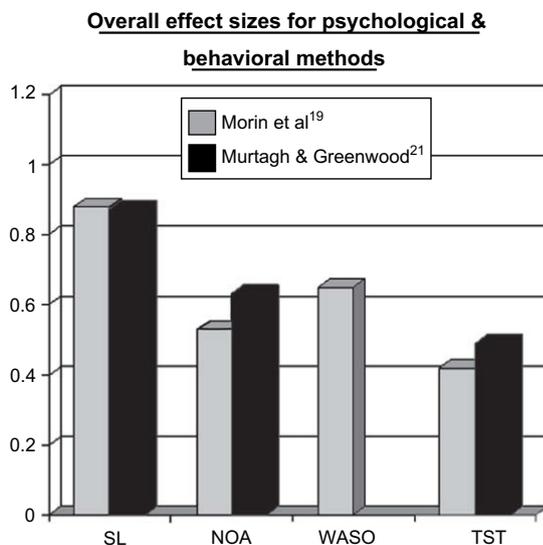


Fig. 2. Effect sizes pre-to-post treatment with psychological/behavioural treatments for different outcome variables. Effect sizes include various strategies. Data taken from Morin et al.¹⁹ and Murtagh and Greenwood.²¹ NOA, number of awakenings; SL, sleep latency; TST, total sleep time; WASO, wake after sleep onset.

When evaluating the data in Table 1, it should be borne in mind that there is a substantial overlap between the meta-analyses of psychological treatments with respect to the trials they analyzed and hence it is not surprising that the results are substantially convergent. The table also provides comparative data for single psychological or behavioral therapies. While these data suggest that 1) each monotherapy may preferentially effect one or more sleep continuity parameters and 2) combined therapy produces large effects for most of sleep continuity parameters, these conclusions must be held tentatively owing to the small number of studies contributing to several of the assessments.

Finally, both meta-analyses provided effect size estimates for the follow-up period (mean duration ca. 6 months). These data clearly illustrate that acute gains with this type of treatment are not only maintained following treatment but appear even to be augmented with time, especially with respect to sleep latency and total sleep time (see Fig. 3 for the data presented in the Morin et al.¹⁹ study). This is truly remarkable for brief interventions consisting of 6–8 therapy sessions.

The third study published by Pallesen and colleagues²² evaluated behavioral and psychological interventions in an elderly insomniac patient population (mean age > 60 years). For data analysis, a computer search in the databases PsycLit and MEDLINE from 1966 to 1998 was performed. Inclusion criteria were behavioral or psychological treatment, sleep onset, maintenance, or mixed insomnia, and a mean age > 60 years. Outcome variables including SL, WASO, and TST were subjected to statistical meta-analysis. A total of 13 studies ($n = 388$ patients) were retained for analysis. Significant effects for psychological/behavioral treatments were found for SL, NOA, WASO and TST. Effect sizes of acute treatment were SL 0.41; WASO 0.61; NOA 0.25; TST 0.15. These results were found to be stable at follow-up (average length of follow-up was 6 months; effect sizes: SL 0.64; WASO 0.59; NOA 0.66; TST 0.37). The authors concluded that behavioral treatments produced significant and long-lasting improvements in older patients with insomnia.

The fourth study published by Montgomery and Dennis²³ provided a systematic review of psychological/behavioral and other non-pharmacological strategies for sleep problems in the same patient population (age > 60 years), analyzing the effects of psychological and behavioral therapies, bright light and physical exercise in this patient population. The literature sources included MEDLINE, EMBASE, CINHALL, PsycInfo, the Cochrane Controlled Trials Register, the National Research Register and the sleep bibliography of www.websciences.org for a period from 1966 to 2002. Inclusion criteria were randomized control trials, age over 60 years, and the complaint/diagnosis of insomnia. Exclusion criteria were severe and/or unstable medical and psychiatric illnesses (e.g., dementia or depression), secondary sleep disorders, and/or failure to meet a checklist of methodological issues to ensure the quality of the studies. For statistical analysis mean differences relative to placebo and 95% confidence intervals were calculated. For psychological and behavioral treatments, six studies ($n = 274$ patients) were identified who met in- and exclusion criteria. Outcome measures included sleep diary assessed SL, WASO and TST. These treatments were associated with minimal changes in SL (mean decrease: 3 min) and modest effects on WASO (mean decrease: 22 min) and TST (mean increase: 14.6 min). For bright light and physical exercise, the database was still too small to draw clear-cut conclusions, but the data were considered promising by the authors. The authors concluded that psychological and behavioral strategies are best used for elderly patients with sleep maintenance problems. Furthermore, it was suggested that bright light treatment and physical exercise programs might be useful adjuvants.

The fifth study published by Irwin and colleagues²⁴ evaluated treatment efficacy in older adults (>55 years old). Data analysis was

Table 1
Effect sizes of different psychological and behavioral methods for insomnia.

	SL		TST		WASO	NOA		SQ
	MOR ^a	M/G ^b	MOR	M/G	MOR	MOR	M/G	M/G
Stimulus control	0.81 (15) ^c	1.16 (20)	0.41 (7)	0.38 (6)	0.70 (5)	0.59 (11)	0.61 (12)	1.30 (6)
Sleep restriction	0.98 (1)	0.85 (4)	−1.06 (1)	0.37 (4)	0.76(1)	–	–	–
Relaxation somatic	0.83 (32)	0.81 (36)	0.25 (10)	0.52 (16)	0.06 (1)	0.56 (13)	0.57 (15)	0.97 (15)
Relaxation cognitive	1.20 (7)	0.93 (13)	0.28 (1)	0.57 (5)	0.28 (2)	0.56 (3)	0.37 (5)	1.08 (1)
Bio-feedback	1.00 (7)	–	0.38 (4)	–	0.70 (2)	0.97 (2)	–	–
Paradoxical intention	0.63 (9)	0.73 (12)	0.46 (5)	0.10 (6)	0.81 (1)	0.73 (4)	1.00 (6)	0.77 (8)
Sleep hygiene	0.71 (2)	–	1.16 (2)	–	–	−0.12 (1)	–	–
Combination therapy	1.05 (15)	1.00 (18)	0.75 (6)	0.78 (18)	0.92 (3)	−0.05 (4)	0.84 (10)	1.12 (17)
All combined	0.88 (91)	0.87 (116)	0.42 (36)	0.49 (60)	0.65 (15)	0.53 (38)	0.63 (55)	0.94 (53)

NOA, number of awakenings; SL, sleep latency; SQ, sleep quality; TST, total sleep time; WASO, wake after sleep onset.

^a Morin et al.¹⁹

^b Murtagh and Greenwood.²¹

^c Figures in brackets: number of comparisons.

based on a literature search in the databases Cochrane Controlled Trials Register, PsycInfo, PubMed, Scientific Citation Index (SSCI) for the years from 1966 to 2004 and reference lists from the included studies. Inclusion criteria were the diagnosis of primary insomnia, randomized controlled trial including at least one cognitive-behavioral intervention, and having relevant outcome criteria (SL, WASO, TST SE% and SQ). Statistical analysis was based on calculation of effect sizes and 95% confidence intervals. The authors identified 23 randomized controlled trials without indicating the exact number of patients included. Significant effects for psychological and behavioral treatments were found for SL, WASO, SE% and SQ. Mean effect sizes (random effects model) of acute treatment (overall) were SL 0.50; WASO 0.69; TST 0.17, SE% 0.74 and SQ 0.79. No differential effects of treatment type (relaxation vs. behavioral intervention vs. combined treatments) were found.

Summary and comment

The data from these meta-analyses provide convergent evidence that psychological and behavioral treatments produce robust improvements in sleep continuity and that these gains are stable

following treatment for periods of up to a year. These effects appear to be achievable for both adults and older adults, although there is some suggestion that older patients may benefit less. The average clinical outcomes (averaged across studies and in order of magnitude) are as follows: SQ (0.84); WASO (0.65); SL (0.67); NOA (0.47); TST (0.31) where the SL and TST effects are the most variable across the analyses. These outcomes are summarized in Table 1. These summary results appear to provide a clear picture regarding the efficacy of behavioral and psychological treatments for insomnia. This said, several considerations need to be taken into account.

First, the number of meta-analytic studies in a given field, unlike standard empirical studies, does not represent a growing evidence base, but rather only repeated analyses of existing data. That is, most of the meta-analyses presented above draw from a common pool of studies (same decades, same sources to identify studies, etc.). Thus, multiple studies (using the same, or nearly the same, inclusion/exclusion criteria) only serve to enhance our confidence in the replicability of the analyses as opposed to the replicability of the findings. The exception to this rule is when the meta-analyses are conducted focusing on (or comparing) specific interventions, divergent populations, or specific or alternative clinical outcomes. This exception applies to the current situation; two of the meta-analysis provided outcome data (and an assessment of the effects of specific interventions) for the majority of the adult spectrum and three focused on outcomes as they occurred in elderly subjects.

Second, the meta-analyses on psychological or behavioral or combined interventions are not, by and large, composed of randomized placebo-controlled studies. This fact prompted the American Academy of Sleep Medicine (AASM) in its first practice report^{25,26} to reach a less optimistic conclusion about the effects of psychological interventions in insomnia. By grading the evidence according to standard methodology none of the behavioral/psychological strategies (stimulus control, sleep restriction, relaxation training, paradoxical intention, biofeedback sleep hygiene, combination therapies) were ranked as “Grade A” (=highest grade) and only stimulus control was given a Grade B recommendation. These estimates were mainly reached based on the strict criterion of Level A methodology that requires an intervention control for placebo effects (i.e., have a placebo control). Since the majority of studies within the behavioral sleep medicine arena have used only wait-list control groups and/or pre-post comparisons, the AASM’s initial conclusion was that there is not enough evidence to state that psychological treatments fulfill the strictest criteria for scientific evidence.

Recently, the AASM²⁷ published an update on their former report. This systematic review was conducted on 37 treatment studies published between 1998 and 2004 which were identified through PsycInfo and MEDLINE searches. The 37 identified studies

Effect sizes for psychological & behavioral methods at follow-up

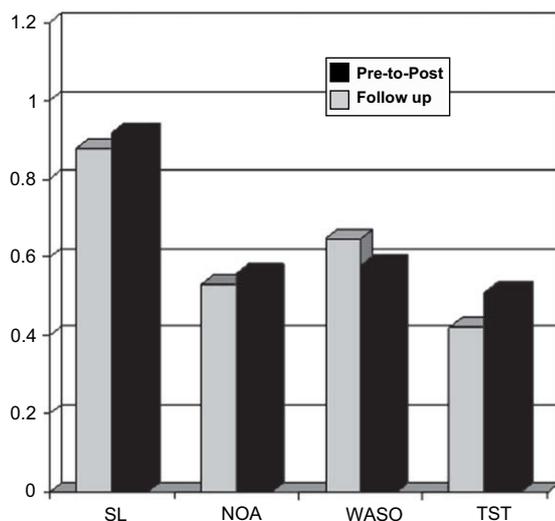


Fig. 3. Effect sizes pre-to-post treatment and at follow-up for CBT. Data taken from Morin et al.¹⁹ NOA, number of awakenings; SL, sleep latency; TST, total sleep time; WASO, wake after sleep onset.

included 2246 subjects/patients. Criteria for inclusion were diagnosis of insomnia, at least one treatment condition with psychological or behavioral treatment, randomized controlled trial or a non-randomized group design or a clinical series or a single subject experimental design with a minimum of 10 subjects and had as outcome variables at least one of the following: SL, WASO, NOA, TST, sleep efficiency or SQ. From this analysis the authors concluded that five treatments now met the criteria for empirically supported psychological treatments (corresponding to a Grade B recommendation) for insomnia, i.e., stimulus control therapy, relaxation, paradoxical intention, sleep restriction and combination CBT-I. It needs to be stressed at this point that this conclusion is mainly based on the absence of “real” placebo-controlled studies in the psychotherapeutic field of insomnia treatment.

In sum, it is clear that patients derive clear-cut benefits from single components of psychological/behavioral treatment or from combined multidimensional CBT in the short- and long-term. Further rigorous research is needed, however, that tries to incorporate appropriate placebo controls, monitor only conditions, or active comparators to assure that psychological and behavioral interventions or their combination a) is efficacious for reasons above and beyond, e.g., expectancy, the effects of self-monitoring, and/or the simple passage of time, b) exerts effects that are comparable or superior to those obtained with standard pharmacotherapeutic interventions.

The comparative efficacy of BZRAs and psychological/behavioral treatments

Five larger-scale studies^{28–32} and one comparative meta-analysis³³ have been conducted on this topic. In the four investigational studies, psychological/behavioral interventions were compared to triazolam, temazepam, zolpidem and zopiclone, respectively.

The first study, conducted by McClusky and colleagues²⁸ assessed the acute effects of triazolam and behavioral strategies over the course of a 4 week intervention and at a follow-up period of 9 weeks. Two sleep continuity variables were assessed including SL and TST. Only triazolam affected sleep latency and total sleep time during the first 2 weeks of treatment. By the fourth week the effects were comparable with both interventions producing about a 50% decrease in SL and 15% increase in TST. At follow-up (where both treatment modalities were discontinued at 4 weeks) only the subjects treated with behavioral interventions maintained their gains.

In the second study, conducted by Morin and colleagues²⁹ multimodal CBT was compared to temazepam alone and temazepam in combination with CBT. Of relevance to the present review is the comparison between CBT and temazepam. Two sleep continuity variables (WASO and TST) were assessed pre-to-post treatment and for three follow-up intervals over a 2-year period (3, 12 and 24 months). As might be expected from the McClusky et al. study, 1) the pre-to-post changes were comparable (the CBT and temazepam groups exhibited about a 50% reduction in symptom severity for WASO and about a 10% increase in TST) and 2) on follow up, only the CBT patients maintained their gains. In fact, it would appear that the CBT subjects exhibited a steady improvement from pre-treatment to the 24 month follow-up assessment for TST. This improvement was not paralleled by a continued decline in WASO (these effects were relatively stable). This implies that either there was a steady improvement in SL (while not reported – this would be consistent with the meta-analytic data) or that SL and WASO remained stable while sleep opportunity was progressively increased over time.

In order to provide a representation of the effects of the two mono-therapies, the TST data are presented in Fig. 4. Please note that these averages are not based on intent-to-treat statistics. This

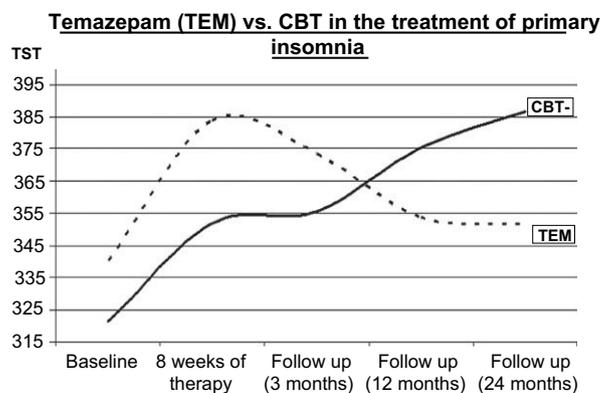


Fig. 4. Temazepam vs. cognitive-behavioral therapy (CBT) in the treatment of primary insomnia: total sleep time (TST). Data taken from Morin et al.²⁹

said both groups had an equal number of subjects lost to follow-up.

In the third study, conducted by Jacobs and colleagues³⁰ CBT alone was compared to zolpidem monotherapy, combined CBT + zolpidem, and to placebo. Two sleep continuity variables (SL and TST) were assessed pre-to-post treatment and for four follow-up intervals over a 1-year period (1, 3, 6 and 12 months).

The major finding from this study was that the pre-to-post changes for SL were not comparable. This was due to a 50% loss of effect for zolpidem monotherapy mid-treatment (after 4 weeks). This loss of effect evidently persisted until the end of active therapy and throughout the 1 month follow-up period (see Fig. 5). In contrast, the effect for total sleep time was comparable for acute treatment. The investigators concluded that their results indicate that CBT administered alone is superior to pharmacotherapy.

The fourth study, conducted by Sivertsen and colleagues³¹ compared multimodal CBT with zopiclone monotherapy (7.5 mg) and a placebo control condition in a sample of 46 older adult subjects (mean age, 60.8) with primary insomnia. The study utilized a randomized double-blinded placebo-controlled approach and included both self-report measures (based on sleep diaries) and PSG data. The active treatment phase of the trial lasted for 6 weeks and was followed by a 6 months follow-up. Sleep diary outcomes included WASO, TST and SE%.

The acute effects were that CBT and zopiclone a) reduced WASO (34% and 16%, respectively), b) increased TST (5% and 11%, respectively) and c) increased SE% (17% and 13%, respectively). None

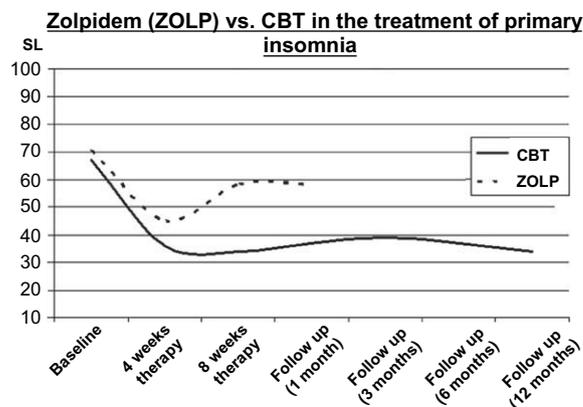


Fig. 5. Zolpidem vs. cognitive-behavioral therapy (CBT) in the treatment of primary insomnia: effects on sleep latency (SL). Data taken from Jacobs et al.³⁰

of these effects were found to differ by condition. At follow-up, the CBT effects for WASO were found to be superior to both placebo and zopiclone. Interestingly, polysomnographic data indicated an even stronger effect for CBT compared to zopiclone treatment.

The fifth study conducted by Wu et al.³² compared temazepam treatment to CBT, a combination of both and placebo in a sample of 71 chronic insomniacs for an intervention period of 8 weeks and follow-ups after 3 and 8 month after treatment discontinuation. Acute treatment effects were superior for all three active conditions compared to administration of placebo with respect to standard self-rated sleep continuity measures. Initially, temazepam effects were superior to CBT, however, at follow-up, CBT proved to be clearly more effective than pharmacotherapy, for both self-rated and polysomnographic parameters. CBT was also found to affect pre-sleep arousal and dysfunctional beliefs about sleep. These changes did not occur with pharmacotherapy.

Finally, there is one comparative meta-analysis³³ assessing treatment outcomes with psychological/behavioral studies and pharmacotherapy with BZRAs. From an initial pool of 190 treatment outcome studies of primary insomnia 14 cognitive-behavioral studies involving 250 subjects and eight pharmacotherapy studies involving 286 subjects met the inclusion/exclusion criteria. The two groups did not differ with respect to gender or age. The average number of psychotherapy sessions was 4.9 ± 2 over an average period of 5.3 ± 2.1 weeks. The average length of pharmacotherapy (PT) was 2.0 ± 2 weeks. Table 2 presents the pre-post treatment means and weighted effect sizes for the following four sleep continuity variables: sleep latency (SL), number of awakenings (NOA), wake after sleep onset time (WASO), and total sleep time (TST). The table also includes a weighted effect size for a measure of sleep quality. Fig. 6 provides a graphical representation of the effect size data.

The major findings from this analysis was (when evaluating the treatment modalities pre-post and without respect to placebo controls) a) the over all mean effect size averaged over all sleep continuity variables was comparable for psychological/behavioral treatments and pharmacotherapy (0.79 vs. 0.80) and b) the two treatment modalities had similar sleep continuity effects for all but one variable, sleep latency. In this case, SL was more reliably reduced with psychological/behavioral interventions as compared to PT (CBT-I = 1.05 and PT 0.45, $t = -2.85$, $P < 0.05$). It was concluded that cognitive-behavioral treatments for primary insomnia appear to yield results that are comparable to pharmacotherapy and may be superior for sleep initiation problems.

Table 2

Comparison of pharmacological therapies and psychological/behavioral methods (from Smith et al.³³).

Subjective sleep outcome measure (sleep diary)	Pre-treatment value (M, SD)	Post-treatment value (M, SD)	Pre-to-post treatment change (difference)		Number of studies	Number of subjects	Weighted effect size ^a (M, SD)
			Value	%			
<i>Sleep latency (min)</i>							
Pharmacotherapy	48.85 (29.73)	34.36 (26.26)	-14.49	30	6	129	0.45 (0.28)
Behavioral therapy	54.24 (28.52)	30.93 (16.03)	-23.31	43	12	225	1.05 (0.76)
<i>Number of awakenings</i>							
Pharmacotherapy	3.00 (1.99)	1.83 (0.137)	-1.17	39	4	108	0.97 (1.0)
Behavioral therapy	2.44 (1.84)	1.67 (1.59)	-0.76	27	4	58	0.83 (1.3)
<i>Wake after sleep onset time (min)</i>							
Pharmacotherapy	55.09 (37.8)	29.49 (19.5)	-25.60	46	1	17	0.89 (29)
Behavioral therapy	68.60 (40.27)	30.22 (23.98)	-38.38	56	5	81	1.03 (0.19)
<i>Total sleep time (min)</i>							
Pharmacotherapy	332.08 (55.3)	372.59 (48.97)	+40.51	12	6	130	0.84 (0.76)
Behavioral Therapy	333.28 (63.6)	352.89 (44.22)	+19.61	6	8	146	0.46 (0.62)
<i>Sleep quality rating</i>							
Pharmacotherapy	3.10 (0.59)	3.08 (0.55)	0.62	20	4	109	1.20 (1.3)
Behavioral therapy	3.38 (0.68)	3.39 (0.67)	0.96	28	5	82	1.44 (1.2)

* $P = 0.01$, $t = 2.85$ (unequal n , $df = 20.59$).

^a Overall weighted effect size = $[\text{sum}(di \times n)]/\text{sum}(n)$.

Effects sizes for a comparison of CBT and pharmacotherapy

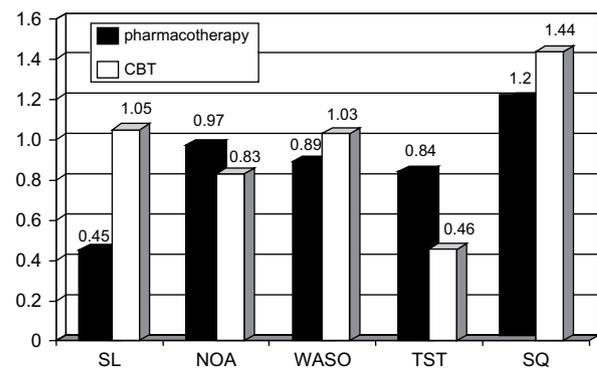


Fig. 6. Comparative meta-analysis of pharmacotherapy and psychological/behavioral strategies for persistent insomnia. Data taken from Smith et al.³³ NOA, number of awakenings; SL, sleep latency; SQ, sleep quality; TST, total sleep time; WASO, wake after sleep onset.

Summary and comment

The most conservative interpretation of these comparative data is that psychological/behavioral interventions (and their combination) and BZRAs, during acute treatment of 4–8 weeks, produce comparable outcomes and that psychotherapy has better durability as manifested by stable gains at follow-ups. Up to now, a stability of treatment gains beyond active administration of medication has not been demonstrated for BZRA.

As a possible methodological caveat it should be taken into consideration that the “comparability” findings may not reflect the comparable efficacy of the *active treatments* but instead occur partly, or wholly, owing to other nonspecific factors. It is not clear in the empirical studies cited above whether contact time with a therapist or physician or other research staff was controlled for. Thus, when receiving psychological/behavioral interventions, subjects quantitatively might have had more exposure to a health professional than in the pharmacotherapy groups. This factor needs to be more strictly controlled in future studies to confirm that the effects of psychological/behavioral interventions are specific and not only a result of intensive communication with the patients. Espie¹⁸ has already shown that such a type of analysis is feasible and their results suggest that the effect of psychological behavioral

Table 3
Summary of effect sizes for BZRAs and psychological/behavioral methods.

Author and year	No. of studies	No. of patients	Intervention	Effect size (<i>d</i>)				
				SL	TST	WASO	NOA	SQ
Nowell et al. ⁵	22	1894	BZ + ZOLP	0.56	0.71	0.65	–	0.62
Holbrook et al. ⁶	45	2672	BZ + ZOP1	–	–	–	–	–
Glass et al. ¹¹	24	2417	BZ + ZOLP/ZOP1 DIPH	–	–	–	–	0.14
Morin et al. ¹⁹	59	2102	BT + CBT	0.88	0.42	0.65	0.53	–
Murtagh and Greenwood ²¹	66	1538	BT + CBT	0.87	0.49	–	0.63	0.94
Pallesen et al. ²²	13	388	BT + CBT	0.41	0.15	0.61	0.25	–
Montgomery and Dennis ²³	6	294	BT + CBT	–	–	–	–	–
Irwin et al. ²⁴	23	–	BT + CBT	0.50	0.17	0.69	–	0.79

BT, behavioral therapy (single technique); BZ, benzodiazepines; CBT-I, multimodal cognitive-behavioral therapy; DIPH, diphenhydramine; NOA, number of awakenings; SL, sleep latency; SQ, Sleep quality; TST, total sleep time; WASO, wake after sleep onset; ZOLP, zolpidem; ZOP1, zopiclone.

interventions is a specific one independent of a mere “supportive” effect of psychotherapy.

Discussion

In this paper we have reviewed the meta-analytic evidence, along with data from a few RCTs, regarding the efficacy and safety of BZRAs and psychological and behavioral treatments. Table 3 summarizes the effect sizes from the relevant studies for both of these treatment approaches.

From this table it can be concluded that there is enough evidence to support the short time use (ca. 4 weeks) of BZRAs in the treatment of insomnia and the use of psychological interventions. As indicated elsewhere in this text, one must be careful when reviewing such summary data because the studies use different sources of variance to assess effects and only pharmacotherapy trials (as a rule) parse out non-specific effects via the use of placebo controls (which might not be fully possible in trials with psychological interventions). A limitation of the pharmacotherapy comparison meta-analyses is, as noted previously, that these studies tend to compare medications without accounting for pharmacokinetic and pharmacodynamic differences.

Another obstacle regarding relying on meta-analyses as one's evidence source is that many investigations are eliminated from such reviews because they do not use standardized definitions, measures, outcome variables and/or report the requisite mean and standard deviation data required for the conduct of meta-analyses. In the future, this obstacle may be surmounted to the extent that individual studies follow the recent recommendations for the use of research diagnostic criteria³⁴ and the use of the use of formal research standards for insomnia research.³⁵

The reviewed evidence strongly suggests a comparable effectiveness of BZRAs and psychological/behavioral interventions during periods of active treatment, which usually last maximally for 4 weeks with respect to BZRAs and encompass up to 8 weeks with the psychological treatments (4–8 weekly sessions with a therapist).

For both types of treatment the issue of adverse events and other problems has not yet been subjected to a quantitative meta-analysis. With respect to BZRAs, the already existing literature on adverse events, issues of rebound insomnia, development of tolerance, abuse and dependence should allow for a thorough analysis and should include unpublished data from pharmacological trials. This type of analysis may help the clinician to base treatment decisions not only on possible benefits of a given drug but also on its risk profile.

The question of adverse events has not been properly addressed up to now in research on psychological/behavioral methods, possibly taken it for granted that no such risks exist. However, when considering for example techniques like stimulus control or sleep restriction, which exert their positive benefits at least initially

through partial sleep deprivation, clinicians should be aware of the risk of increased tiredness/sleepiness which may have an impact for example on driving ability. Insofar, research on adverse events for psychological treatments needs to be intensified.

With respect to long-term effects of the different treatments beyond their active administration, a clear picture emerges favoring psychological/behavioral methods over BZRAs. The reviewed evidence doubtlessly allows the conclusion that the psychological/behavioral methods remain active beyond the initial 4–8 weeks of therapist contacts and stable gains, even further improvements, occur over a period of the next 6–8 months, even years. No such effects have ever been shown for BZRAs.

Generally, insomnia-oriented psychotherapeutic or pharmacological research could also profit from recent advances in the field of therapy research in mental disorders. Not only should studies give mean differences of variables of interest for pre- to posttreatment comparisons but also more detailed data-analyses on responders/non-responders or remitters/non-remitters including survival analyses after acute treatment should be planned and conducted.

These recommendations and suggestions are further explicated and summarized below in the practice points and research agenda as boxes.

Practice points

1. Psychological/behavioral treatments administered over a period of 4–8 weeks with weekly sessions produce robust and stable improvements in sleep continuity for periods of up to 2 years. Thus, these treatments should be considered as first-line treatment for insomnia. Adverse events like increased tiredness/sleepiness due to partial sleep deprivation inherent in some strategies (i.e., stimulus control, sleep restriction) need to be kept in mind and evaluated carefully in each patient.
2. BZRAs produce significant clinical gains (as compared to placebo) with moderate to large effect sizes (short-term treatment of maximally 4 weeks). Issues relating to adverse events, rebound insomnia, development of tolerance, abuse and dependency need to be carefully monitored in each individual patient. Clinical relevant effects of pharmacological treatment with BZRA beyond the active treatment period have not been demonstrated.
3. There is insufficient data to assess the long-term efficacy of BZRA treatment although there is initial evidence that their nightly use may confer stable effects for periods of up to 1 year.
4. When compared to BZRAs, psychological/behavioral strategies produce comparable outcomes during active treatment and have better durability beyond the active administration of treatment (see 1).

Research agenda

1. Large scale randomized clinical trials (RCTs) need to be conducted wherein the relative efficacy and safety (incidence of side effects) of BZRAs and psychological/behavioral treatments can be assessed concurrently and for an extended period of time during and following treatment. As part of these evaluations it will be critical to evaluate the full complement of sleep continuity variables (both via self-report and PSG) using standardized methods and definitions and additional non-sleep variables such as objective and subjective measures of daytime function, quality of life, and medical and psychiatric symptomatology.
2. RCTs need to be conducted that comparatively measure the costs and cost-effectiveness of different insomnia treatments.
3. When conducting RCTs for the evaluation of new compounds, the pharmaceutical industry should provide the full compliment of sleep continuity variables (both via self-report and PSG) using standardized methods and definitions and compare the target medication with not only placebo but also with other effective treatments, including behavioral and psychological treatments.
4. The safety and efficacy of insomnia treatment should be evaluated in important population subgroups, including children, nursing home residents, postmenopausal women, and in patients with insomnia associated with medical and psychiatric conditions.
5. RCTs for pharmacological and psychological/behavioral methods should be conducted in a manner where all trials are registered and the outcome data are open to scrutiny, regardless of whether the medication receives an indication from the FDA and/or the RCT results are published in peer reviewed journals.
6. Secondary analyses or post hoc analyses should be undertaken on existing data sets which:
 - Re-evaluate outcome, not in terms of average response, but as a function of positive treatment response.
 - Re-evaluate existing data, not in terms of average response, but in terms of night-to-night variability.
 - Assess acute treatment and withdrawal effects.
 - Assess the extent to which subjects continue to engage in psychological/behavioral practices (specifically, sleep restriction and/or stimulus control) following active treatment and whether this predicts long-term gains.
 - Assess the factors that predict treatment response (acute and long term) taking into account the initial intake profiles (e.g., type, severity, and chronicity of insomnia; age and sex; education status, med and alcohol use; etc.).

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