Review

Benzodiazepines and Zolpidem for Chronic Insomnia

A Meta-analysis of Treatment Efficacy

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Objective.—To evaluate the efficacy of benzodiazepines and zolpidem tartrate in chronic insomnia based on a quantitative review of literature.

Data Sources.—Articles from 1966 to 1996 were identified using MEDLINE, by a manual review of relevant journals, and from bibliographies of identified articles.

Study Selection.—Studies using randomized, double-blind, placebo-controlled, parallel or crossover designs with benzodiazepines or zolpidem in adults younger than 65 years with chronic insomnia (modified *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for primary insomnia) were selected for review. Self-report and polysomnographic measures of sleep-onset latency, total sleep time, number of awakenings, and sleep quality were selected as outcomes.

Data Extraction.—Twenty-two studies met the selection criteria. A combined test of *P* values was performed, pooling broadly from the 22 studies to determine whether medication was superior to placebo. A combined test of effect sizes was performed on the subset of studies that reported effect size information to determine the magnitude of medication effect.

Data Synthesis.—A homogeneous sample of studies summarized 1894 patients treated for a median duration of 7 days. The combined test of *P* values demonstrated that medication was superior to placebo in all 4 outcome measures. Treatment response was moderate in magnitude by the combined test of effect sizes.

Conclusions.—Benzodiazepines and zolpidem produced reliable improvements in commonly measured parameters of sleep in patients with chronic insomnia. Relative to the chronic and recurring course of insomnia, both the limited duration of treatments studied and the lack of follow-up data from controlled trials represent challenges for developing evidence-based guidelines for the use of hypnotics in the management of chronic insomnia.

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THE PREVALENCE of chronic insomnia among adults in the United States is 10% by recent estimates, and the annual cost for its treatment is estimated at $10.9 billion.[1-4] Individuals with chronic insomnia report elevated levels of stress,[5] anxiety,[5,6] depression,[5,7] and medical illnesses[8-10] and demonstrate interpersonal and occupational impairments when compared with good sleepers.[11-14] Insomnia that extends over a 1-year period has been demonstrated to be a risk factor for the development of major depression,[15] and longitudinal studies indicate that untreated chronic insomnia does not remit with time.[16-18]

Relatively little is known about the origin or pathophysiological characteristics of chronic or primary insomnia, and as a result, interventions have focused mainly on symptom reduction.[19-22] Individuals with primary insomnia are most often seen in primary care settings, and medication treatments for insomnia predominate over behavioral ones.[1,23] The frequency of this treatment is reflected in the observation that prescription sleeping pills are used by 4% of the population in a given year and that 0.4% of the population use hypnotics for more than a year.[1,23,24]

Benzodiazepines are the most common class of medications for treating insomnia and have been considered the standard intervention in outcome studies.[25] While benzodiazepines are effective for the treatment of acute insomnia, their role in the management of chronic insomnia remains unclear. The adverse effect profile of benzodiazepines includes daytime sedation, motor incoordination, and cognitive impairments such as anterograde amnesia.[1] Long-term exposure carries the additional risks of physical dependence, withdrawal, and rebound insomnia.[26] To manage the persistent and recurring symptoms of insomnia, clinicians have decreased prescriptions of benzodiazepines by 30%, and increased prescriptions of antidepressants (eg, trazodone hydrochloride, amitriptyline hydrochloride, doxepine hydrochloride) by 100% from 1987 to 1991.[27] However, there are few outcome studies of antidepressants used as hypnotics, and these medications can have their own adverse effects such as orthostatic hypotension, cardiac dysrhythmias, and mortality associated with overdoses.[28-31]

The National Institutes of Health Consensus Conference on Sleeping Pills and Insomnia in 1984 developed guidelines discouraging the use of sedative-hypnotics beyond 4 to 6 weeks because of concerns raised over drug misuse, dependency, withdrawal, and rebound insomnia.[32] The appropriateness of benzodiazepines in the management of chronic insomnia would be supported if the benefits of treatment outweighed the risks. Unfortunately, studies establishing the efficacy of sedative-hypnotics in treating chronic insomnia have suffered from several limitations. The symptoms of insomnia and insomnia disorders have been conceptualized differently over time and across existing diagnostic classifications, eg, the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) of the American Psychiatric Association,[33] the *International Classification of Sleep Disorders* (*ICSD*) of the American Sleep Disorders Association,[34] and the *International Classification of Diseases,*

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Ninth Revision (*ICD-9*) of the World Health Organization.[35] These evolving definitions of insomnia have led to differing inclusion and exclusion criteria in medication trials. This, in turn, has limited attempts to summarize the treatment effects of specific medications used across different studies. In a similar fashion, this diagnostic heterogeneity has made it difficult to summarize the differential effects of classes of medication based on the expression and course of insomnia symptoms over time.

In addition to differing inclusion and exclusion criteria, the outcome measures used to evaluate insomnia have also varied substantially between trials, and there has been little consensus on how these outcome measures represent or define patients who respond to treatment. Outcome measures range from quantitative measures of sleep, such as sleep-onset latency, to qualitative measures of sleep, such as perceived sleep quality, to measures of daytime well-being or daytime functioning.[19,36,37] Adding to this complexity, there continues to be considerable controversy over the meaning of the discrepancies that exist between subjective and objective (polysomnographic) measures of good and bad sleep, and over the interpretation of the effects of medication on the relationship between these 2 domains.[38,39]

One procedure developed to respond to this problem is the quantitative review or meta-analysis. This procedure draws on the quantitative rigor and the statistical standards used in primary data analysis, but is applied to integrate information derived from different studies.[40,41] To our knowledge, while several quantitative approaches have been applied to the literature that examines the effects of behavioral interventions on insomnia, similar efforts have not been made to examine the effects of medication on insomnia.[42,43] In an attempt to answer the larger questions of whether, and to what extent, commonly used medication treatments benefit patients with chronic insomnia, we report on a meta-analysis of outcome studies that used benzodiazepines or zolpidem tartrate to treat patients with a diagnosis consistent with the *DSM-IV* criteria of primary insomnia.

METHODS

Data Sources

Published studies were identified through searches of MEDLINE for the period 1966 to 1996, through searches of Current Contents, and from references cited in the reports obtained. The mid 1960s marked the introduction of benzodiazepines into clinical use. Various searches were evaluated to produce the strategy eventually used. The subject heading *insomnia* restricted to the subject subheading of *drug therapy* was combined with the subject heading *placebos* and the text word *placebos*. This formed the basic search strategy for MEDLINE. This emphasized sensitivity at the expense of specificity. The *Journal of Sleep Research*, from the first issue to volume 4, 1995, was searched by the subject *insomnia* in Current Contents and by manual review. The bibliographies of obtained articles were reviewed to identify additional studies. Articles were limited to those published in the English language. Studies in unpublished form, abstract form, dissertation or thesis form, and book chapters were not included.

Study Selection

We chose to examine patients with primary insomnia for several reasons. Primary insomnia represents the prototypical insomnia disorder, as opposed to insomnia that is secondary to psychiatric, general medical, or substance use disorders. Primary insomnia is a broader classification than the chronic insomnia subtypes in the *ICSD*, and the diagnostic criteria are more readily extracted from research reports. In clinical samples, primary insomnia is the second most frequent insomnia diagnosis after insomnia related to a mental disorder.[44] Finally, the treatments for primary insomnia are aimed at the insomnia itself, whereas treatments for secondary forms of insomnia, in general, are oriented toward the underlying disorder.[45]

Because the *DSM-IV* criteria have only recently been adopted, studies not using *DSM-IV* criteria were reviewed for patient descriptions that were compatible with the *DSM-IV* diagnostic criteria. Our goal was to use criteria that would be sensitive enough to allow as many studies as possible to be considered, but as specific as possible to be consistent with the current construct of primary insomnia.

With the exception of criterion (C), which is the exclusion of other primary sleep disorders from the *DSM-IV* definition of primary insomnia, we applied the remaining diagnostic criteria for primary insomnia to identify relevant studies to be reviewed. We required that studies state explicitly that patients had difficulty initiating or maintaining sleep or experienced nonrestorative sleep for at least 1 month (A). Clinically significant distress was inferred from patients seeking treatment for insomnia or symptomatic volunteers (B). Investigators needed to state explicitly that psychiatric (D) and general medical conditions (E) were assessed and ruled out as the cause of the insomnia. In reviewing studies, it became apparent that clinical trials of patients with exclusively acute insomnia were rare and relied on experimental manipulations to simulate acute insomnia.[46] Therefore, in terms of the meta-analysis, we considered it reasonable to include studies whose investigators failed to report the duration of symptoms, since subjects more than likely experienced persistent insomnia symptoms based on this pattern represented by the larger pool of studies.

While uniform assessment procedures would improve the homogeneity of study populations, there has been no agreed-on procedure for establishing the absence of psychiatric or general medical conditions. Furthermore, structured interviews were not available until the mid to late 1970s. In an effort to balance sensitivity and specificity, we chose to accept the investigator's report that psychiatric and general medical conditions were evaluated and believed not to be responsible for the chronic insomnia condition to fulfill criteria D and E in the *DSM-IV*.

We limited our meta-analysis to studies that used a placebo-control group, parallel-group design, randomized patient assignment, and double-blind assessment of outcomes. We also included crossover designs, but to minimize the impact of carryover and order effects, we extracted data for only the first treatment period, when available. Open studies, active-control equivalence studies, Latin-square designs, and preference studies were not included. While these designs contribute to the accumulated evidence concerning hypnotic effects in insomnia, our goal was to generate the most conservative estimate of treatment effects attributable specifically to the medication intervention.

We limited our review to specific study designs for several additional reasons. Because previous research has shown large night-to-night variability in sleep measures in patients with insomnia, patients selected for extremes of sleep disturbances at one point in time (ie, baseline severity criteria) may demonstrate subsequent improvement over the course of observation that reflects regression toward the mean rather than the effects of treatment.[47,48] Symptomatic improvements over time within the structure of a clinical study can result from self-monitoring, sleep hygiene instruction, and the demand characteristics that accompany the experimental protocol.[49-51] These effects are reflected in within-subject analyses and can be seen in analyses of waiting-list groups, sham treatment groups, and placebo groups.[36] These factors taken together suggest that an appropriate control group and between-group comparisons are needed to isolate the specific effects of medication from other factors.

We excluded from further review studies that were restricted to patients older than 65 years. Age-related declines in sleep quality and continuity, increases in secondary forms of insomnia, increases in comorbid medical conditions (and concurrent medication treatments), and hypnotic dosage modifications were the reasons for this restriction.[52,53] We have reviewed pharmacologic studies of primary insomnia later in life elsewhere.[52]

We also chose to focus our review on studies examining zolpidem and the benzodiazepines used clinically in the United States. These medications represent a class of medications whose effects are believed to be mediated by GABAergic action.[54] The following is a list of eligible benzodiazepines: alprazolam, chlordiazepoxide hydrochloride, diazepam, estazolam, flurazepam hydrochloride, lorazepam, quazepam, temazepam, and triazolam. For studies that evaluated the effects of more than 1 eligible medication, eg, triazolam vs temazepam vs placebo, we calculated combined probabilities and effect sizes for 1 medication vs placebo to avoid problems introduced by calculating multiple probabilities and effect sizes from the same sample.[43,55] If flurazepam was 1 of the 2 active agents, then it was selected to calculate effect sizes. Otherwise, the representative medication for a single study with more than 1 active agent was chosen randomly. We chose to "oversample" flurazepam because it was included in many studies as the "gold standard" for hypnotic treatment and was used to evaluate the efficacy of the other medications. Establishing its efficacy lends support to interpreting active control equivalence studies where newer benzodiazepines were tested against flurazepam as the typical control agent and no placebo group was used.

Measures

As with 2 previous meta-analyses of behavioral treatments in insomnia,[42,43] we found that only 4 variables were measured frequently enough to be considered central outcomes in a quantitative review. These variables, usually measured from questionnaires and from sleep diaries, are sleep-onset latency, total sleep time, and the number of awakenings. Sleep quality, when evaluated, was generally represented on an ordinal scale with descriptors such as fair, good, excellent, etc. We conducted separate meta-analyses for each of these 4 dependent measures.[43,55,56] We used the outcome measure reported for the end of the clinical trial to represent the findings of the study. If a series of summary measures were reported, such as weekly averages, then these were combined into a single summary for the study. Polysomnographic evaluations, less commonly performed in longitudinal, between-group designs, were also included. Wake after sleep onset was reported in less than a quarter of the studies we identified. Thus, only number of awakenings was considered in the meta-analysis.

In determining whether medications were superior to placebo and to use the maximum amount of information, we used a broad, inclusive approach and combined studies at the level of *P* values because effect sizes could not be extracted for a majority of studies obtained. However, in an effort to quantify the magnitude of response, a subset of studies with self-reported outcomes and with adequate reporting of data to calculate effect sizes was also selected. We performed meta-analyses for posttreatment, between-group comparisons from this pool of studies. Because of limited reporting of baseline information, we did not perform before and after between-group comparison of outcomes.

Estimation of Combined *P* Values and Effect Sizes

The approach described by Rosenthal[41] was used to combine studies. One-tailed *P* values for each outcome were converted to *z* scores, summed, and divided by the square root of the number of combined tests to obtain an unweighted summary estimate of the combined *P* values. The summary *z* score was weighted for sample size according to the formula: $z(w) = (\Sigma df^* z)/(\Sigma df^2)^{1/2}$, where *df* represents the degrees of freedom associated with each statistical test and *w* represents weighted. The heterogeneity of *P* values was determined by summing the square of the difference between the *z* of each study and the mean *z* across all studies. This summary measure of heterogeneity was compared with a χ^2 distribution with the degrees of freedom equal to 1 less than the number of studies combined.

The value of Cohen *d*, the standardized mean difference, was used in the present analyses to quantify the magnitude of treatment effects.[57] For example, the posttreatment value for the mean of the experimental group was subtracted from that of the control group and the difference was divided by the pooled SD of the 2 groups, $d_i = (\text{mean}_{ei} - \text{mean}_{ci})/\text{SD}_{pi}$, where *i* represents individual study; *e*, experimental group; *c*, control group; and *p*, pooled. The calculations were performed such that a positive effect size reflected a beneficial medication effect. Sleep-onset latency tends to have a skewed distribution, but most of the studies identified reported sleep-onset latency as a mean (rather than a median or other summary for skewed data) and parametric tests predominated. Transformation of variables was seldom reported.

To account for different sizes of groups for the summary estimate d_s, the formula by Hedges (1982) was used: $d_s = \text{sum}(w_i \times d_i)/\text{sum}(w_i)$, where w_i is $\text{weight}_i = 2N_i/(8 + d_i^2)$ and N_i is the total sample size from the individual study.[41,58] All effect sizes in the current analyses represent reported data and not estimates from test statistics.

These effect sizes represent standardized *z* scores that can be interpreted as the magnitude of the difference between treated and control patients in units of SD. From individual effect sizes and variances, a weighted summary effect size and its confidence interval were calculated and a test of the heterogeneity of effect sizes was performed.[59,60] In behavioral science research, *d* of 0.2 is considered small, 0.5 is medium, and 0.8 is large.[57] In addition, the effect size *d* can also be meaningfully represented by the relative percent improvement of the treatment group compared with the control group.[43] The *z* score for the effect size is determined directly from the cumulative distribution function of a standard normal curve.

Data Extraction

All coding criteria of hard measures such as age, sleep measures, and treatment duration were coded by 1 investigator (P.D.N.). Study selection was performed after 2 separate reviews to code for each study's eligibility. The retrieval of study outcomes data, which involved more subjective judgment, was completed by consensus between 2 of the investigators (P.D.N. and S.M.) and then reviewed by members of the team (M.A.D., D.J.B., and C.F.R.). Thus, the data to be retrieved and summarized were sample statistics reported in the literature from primary studies.

RESULTS

Excluded Studies

A total of 198 studies were identified from all sources (if multiple studies reported data from the same sample, only the study whose main aim was the question of efficacy was selected). Eleven studies were not in the English language. Seventy-four studies did not present data regarding efficacy of benzodiazepines or zolpidem in patients with primary insomnia. Thirty-one studies were excluded for duration and diagnostic criteria. Of these 31, 15 studies were conducted with psychiatric patients, 7 were with general medical patients, 2 were with patients with other primary sleep disorders, and 7 for combined duration and diagnostic reasons. Twenty-one studies were ex-

Table 1.—Study Characteristics of Benzodiazepines and Zolpidem in Chronic Insomnia*

Source, y	Hypnotic†	No. of Subjects	Attrition No.	Age, Mean (Range), y‡	% Male	% Prior Hypnotic Use	Illness, t§	Symptoms‖	Diagnostic Criteria¶
Kajak et al,[37] 1994	T 0.25	1507	192	51 (18-71)	86	43	Chronic	NR	NR
Monti et al,[77] 1994	Z10, T 0.5	24	1	(20-65)	13	NR	MNR	NR	NR
Scharf et al,[78] 1994	Z15, Z10	75	8	38 (22-60)	36	NR	>3 mo	NR	NR
Hermann et al,[70] 1993	Z10, L2	25	4	(25-65)	57	48	>2 mo	NR	*DSM-III-R*
Declerck et al,[64] 1992	Z10	18	0	(20-50)	0	100	NR	NR	NR
John et al,[61] 1991	F30, E2, E1	223	...	(18-65)	NR	NR	>3 mo	NR	NR
Lie et al,[67] 1990	F30	36	0	38 (20-59)	33	NR	>12 mo	SO>M>O	NR
Kripke et al,[36] 1990	F30, F15	107	8	38 (26-57)	41	100	0.65-46 y	M	*DCSAD*
Nair et al,[75] 1990	F30	60	4	47 (19-65)	53	NR	118 mo	NR	NR
Fonciano et al,[76] 1990	F30	26	2	30 (18-60)	54	NR	NR	NR	NR
Scharf et al,[77] 1990	F30, E2	244	14	41 (21-65)	NR	NR	>3 mo	NR	NR
Dominguez et al,[66] 1986	F30, E2	74	9	47 (21-65)	54	NR	>3 mo	NR	NR
John,[6] 1984	T 0.5, L2	41	11	41 (18-61)	40	20	>6 mo	NR	*DCSAD*
Melo de Paula,[68] 1984	F30	60	5	30 (19-55)	28	NR	2-120 mo	M	NR
Walsh et al,[79] 1984	E2, E1	379	35	41 (21-65)	24	NR	>3 mo	M>SM>SO	NR
Iden et al,[60] 1983	Q30	57	7	47 (23-59)	42	NR	Chronic	NR	NR
Hernandez-Lara et al,[71] 1983	Q15	36	5	(22-65)	33	NR	Chronic	NR	NR
Mendels et al,[73] 1983	Q15	80	20	46 (20-60)	66	NR	Chronic	NR	NR
Kuanang et al,[65] 1982	TE20, TE10	60	0	(16-59)	NR	NR	3-8 mo	M>SO>O	NR
Tinnola et al,[72] 1980	F30	10	0	(21-36)	40	NR	NR	NR	NR
Tillingim,[69] 1979	TE30	75	1	(18-59)	23	100	5-7 y	M	NR
Fabre et al,[58] 1978	T 0.5	277	93	45 (18-60)	48	NR	MNR	NR	NR

*NR indicates not reported; MNR, measured but not reported; and ellipses, could not be determined.
†E indicates estazolam; F, flurazepam hydrochloride; L, lorazepam; Q, quazepam; TE, temazepam; T, triazolam; and Z, zolpidem tartrate.
‡For those entries not listing a mean, the original manuscripts reported only ranges.
§Responses with > represent a minimal duration criterion; otherwise a range of time, an average, or the specifier "chronic" is reported.
‖SO indicates sleep onset; SM, sleep maintenance; M, mixed; and O, other.
¶*DSM-III-R* indicates *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*; *DCSAD*, *Diagnostic Classification of Sleep and Arousal Disorders*.

luded by age criteria, 20 of these for geiatric subjects and 1 for childhood ages. Thirty-nine studies were excluded by design criteria, primarily 2-phase designs where the first phase was a placebo washn. A pool of 22 studies met inclusion and exclusion criteria; their characteristics are presented in Tables 1 and 2.[30,37,60-79] The ist of 198 studies is available on request rom the authors.

Study Characteristics

The final pool of 22 studies span the ears 1978 to 1996 and reported on 1894 predominately middle-aged patients with hronic insomnia, who were entered into andomized, placebo-controlled, double-lind trials with a selected benzodiazpine or zolpidem intervention. These tudies included approximately 60% vomen. Treatment duration was at most 5 days (median of 7 days). In these 22 tudies, 32 groups were treated with a enzodiazepine or zolpidem (several studes had 3 or more groups). Ten groups sed flurazepam; 6 used estazolam; 5 used olpidem; 4 used triazolam; 3 used quaepam; 3 used temazepam; and 1 used lorepam. Studies with alprazolam, chlorliazepoxide, or diazepam were unable o be identified or did not meet inclusion riteria.[80,81]

Among potential moderators of treatnent effect (Tables 1 and 2), the distriution of patients with a history of hypotic treatment was reported in only 6 of 2 studies and the symptom profile (sleep onset, sleep maintenance, early morning awakening) was reported in only 3 studies. The duration of symptoms was difficult to summarize as studies varied in their method and detail of reporting.

Only 3 studies reported using diagnostic criteria to establish cases, and only 1 study reported diagnostic criteria to assess the presence of psychiatric syndromes. Most studies reported that psychiatric illness were ruled out, but it remains unclear how this was done and whether this would include, for example, anxiety disorders in addition to mood disorders. One study specifically assessed and included patients with personality disorders, thereby clarifying the scope of results.[82]

Eleven studies used a placebo washin or lead-in as a baseline measure whereas the other studies did not use a placebo baseline. Only 7 studies reported whether aspects of sleep hygiene such as structuring the regularity and duration of bedtime, restricting napping, or modifying caffeine intake were used. Compliance, whether for drug or for sleep hygiene, was reported in only 9 studies. The adequacy of the double-blind was not reported in any of the 22 studies.[83]

Outcome Characteristics

Sixteen of 22 studies examined only self-reported sleep measures, mostly recorded from daily diaries or logs. One study reported only polysomnographic findings, and 5 reported both. Sixteen reported outcome measures in units of time, (eg, minutes or hours). Five reported outcome measures as numbers of responders. One reported dimensions on an index specific to the study. Table 3 summarizes these findings in terms of whether a study measured the given outcome, whether the measured outcome results were reported, and the 2-tailed P value associated with the outcome. To avoid calculating multiple probabilities from the 5 studies that included both a self-report measure and a polysomnographic measure, the self-report measure was selected for the meta-analysis of P values. The P values reported for the results of the studies by Declerck[64] and Monti[77] were from polysomnographic variables, as no self-report measure was available.

Combined Treatment Effects

To summarize these data while accounting for the magnitude of the treatment effect as well as the influence of sample size, a meta-analysis was performed from the available 22 studies. Tables 1 and 2 present the 22 studies. Table 3 presents the P value data for these 22 studies and the number of P values that were able to be combined for each outcome. Table 4 presents the data for the effect sizes that were combinable. Table 5 summarizes the combined results for the P values in the top portion and the combined effect sizes in the bottom por-

Table 2.—Study Characteristics of Benzodiazepines and Zolpidem in Chronic Insomnia*

Source, y	Criteria†	Design‡	Placebo Wash-In	Treatment Duration§	Sleep Hygiene	Compliance Checked	Outcome: Self-report‖	Outcome: Polysomnography (PSG)‖	Outcome: Dimension¶
Hajak et al,[37] 1994	Y	P	NR	28	NR	NR	Y	N	N
Monti et al,[74] 1994	Y	P	Y	27	Y	NR	Y	Y	T
Scharf et al,[78] 1994	Y (PSG)	P	Y	35	NR	Y	Y	Y	T
Herrmann, et al[79] 1993	Y (PSG)	P	Y	14	NR	NR	Y	Y	T
Declerck et al,[64] 1992	Y	X	NR	1	NR	NR	N	Y	T
Cohn et al,[61] 1991	Y	X	NR	4	NR	NR	Y	N	N
Elie et al,[67] 1990	Y	P	Y	28	NR	Y	Y	N	T
Kripke et al,[36] 1990	Y	P	Y	14	Y	Y	Y	Y	T
Nair et al,[75] 1990	Y	P	Y	7	NR	Y	Y	N	T
Ponciano et al,[76] 1990	Y	P	Y	21	NR	NR	Y	N	O
Scharf et al,[77] 1990	Y	P	NR	7	Y	Y	Y	N	T
Dominguez et al,[66] 1986	Y	P	NR	7	Y	Y	Y	N	T
Cohn,[62] 1984	Y	P	NR	7	Y	NR	Y	N	T
Melo de Paula,[65] 1984	Y	P	Y	14	NR	Y	Y	N	T
Walsh et al,[79] 1984	Y	P	NR	7	Y	Y	Y	N	T
Aden et al,[60] 1983	Y	P	Y	5	Y	NR	Y	N	N
Hernandez-Lara et al,[71] 1983	Y	P	Y	5	NR	NR	Y	N	N
Mendels et al,[73] 1983	...	P	Y	5	NR	NR	Y	N	T
Cuanang et al,[63] 1982	NR	P	NR	5	NR	NR	Y	Y	T
Linnoila et al,[72] 1980	NR	X	NR	14	NR	Y	Y	N	T
Fillingim,[69] 1979	Y	P	NR	4	NR	NR	Y	N	T
Fabre et al,[68] 1978	Y	P	NR	14	NR	NR	Y	N	N

*NR indicates not reported; ellipses, could not be determined.
†Insomnia symptom baseline severity inclusion criteria; Y indicates yes severity criteria were used to screen patients; Y (PSG), yes severity criteria were used, and they were based on PSG.
‡P indicates parallel groups; X, cross-over study.
§Days of medication exposure between baseline and final outcome measure.
‖Y indicates yes if under self-report or PSG columns; N, not collected as an outcome in these 2 columns.
¶T indicates time; N, number of patients; and O, other.

Table 3.—Significance Levels of Between-Group Statistical Tests in Original Studies*

Source, y	Sleep-Onset Latency	Total Sleep Time	No. of Awakenings	Sleep Quality
Hajak et al,[37] 1994	.01	.05	M	.002
Monti et al,[74] 1994	M	.05	M	NM
Scharf et al,[78] 1994	.02	.44	M	.8
Herrmann et al,[79] 1993	.03	.079	.39	.23
Declerck et al,[64] 1992	.05	.67	NM	NM
Cohn et al,[61] 1991	.1	.1	.1	.1
Elie et al,[67] 1990	.32	.15	M	NM
Kripke et al,[36] 1990	.18	.04	.07	NM
Nair et al,[75] 1990	.05	M	M	.05
Ponciano et al,[76] 1990	.04	M	NM	NS
Scharf et al,[77] 1990	.02	.002	.002	.002
Dominguez et al,[66] 1986	.19	.002	.002	.002
Cohn,[62] 1984	.01	.01	.01	.01
Melo de Paula,[65] 1984	M	M	NS	NM
Walsh et al,[79] 1984	.002	.002	.002	.002
Aden et al,[60] 1983	.05	.05	.05	.05
Hernandez-Lara et al,[71] 1983	.01	.05	M	.03
Mendels et al,[73] 1983	M	M	M	M
Cuanang et al,[63] 1982	.01	.01	M	.59
Linnoila et al,[72] 1980	NS	NS	NS	NM
Fillingim,[69] 1979	.01	.05	.01	.01
Fabre et al,[68] 1978	.001	.001	.001	.001
No. of *P* values	18	17	10	14

*Two-tailed *P* values as reported or calculated from original studies. NM indicates not measured; M, measured, not reported; and NS, nonsignificant at .05 level but inadequate data available to calculate an effect size or a *P* value.

tion. Ideally, all 22 studies would contribute a *P* value and an effect size to be combined into summary statistics. However, by way of example, only 18 of our 22 studies presented enough information to extract a *P* value, 3 measured sleep-onset latency but did not report the result, 1 study only summarized the finding as nonsignificant, and effect sizes could be calculated for only 9. The results of the combined *P* value tests demonstrated that medication was superior to placebo for all 4 outcomes ($P<.001$). There was no significant heterogeneity of *P* values.

Nine studies reporting 1 of the 4 outcomes in a dimension of time and reporting data to allow for the calculation of an effect size were also combined to quantify the magnitude of treatment effects (Tables 4 and 5). No clear pattern distinguished the 9 studies whose data could be extracted for effect sizes from those whose effect sizes could not be, such as study date, number of patients, attrition, age, or gender. However, the 9 studies tended to report more study characteristics overall, to check patient compliance, and to have used polysomnography in addition to subjective measures. The most common reason for not being able to calculate an effect size was that only a *P* value was reported without a test statistic, treatment and control means, or SD.

A total of 680 patients (343 treatment, 337 control) with primary insomnia were represented by this subset of 9 studies. The range of ages for the 9 studies was from 18 to 65 years. The median duration of medication treatment was 7 days. The range of the duration of treatment across the 9 studies was from 4 to 35 days. Of the selected medications from the 9 studies, 4 used flurazepam hydrochloride (30 mg), 2 used temazepam (1 at 30 mg, 1 at 20 mg), 2 used zolpidem tartrate (10 mg), and 1 used estazolam (2 mg). Tables 1 and 2 include these 9 studies. Table 4 summa

rizes the data from the individual studies for the 4 outcome measures for posttreatment, between-group comparisons.

Table 5 presents the combined statistics from the individual studies for the posttreatment, between-group comparisons. Using Cohen criteria, the 4 average effect sizes obtained would be interpreted as moderate in magnitude.[57] The 95% confidence intervals for these mean effect sizes exclude zero, indicating that the average effect size for each outcome is statistically reliable. The limits of the confidence intervals for sleep-onset latency and for sleep quality remain in the moderate magnitude range; the limits of the confidence intervals for total sleep time and for the number of awakenings extend from the moderate to the large magnitude range. Because the limits of all 4 confidence intervals overlap, extrapolation as to which measure responds most strongly to medication cannot be made.

Table 5 also includes the results of the test for heterogeneity of effect sizes. The obtained values measure the variability in effect sizes across all studies examining a given outcome. When there is significant heterogeneity, examination of moderator variables (eg, type of medication) can be performed to account for the heterogeneity, as was originally planned. Our homogeneous results, however, reflected in the P values greater than .05 associated with each value of χ^2 for the effect sizes for sleep-onset latency, total sleep time, and number of awakenings, suggest that the obtained effects reflect a similar underlying phenomenon for each domain. Nonetheless, we note that temazepam and zolpidem had the largest effect sizes on sleep-onset latency (0.78 and 0.77, respectively), whereas flurazepam and estazolam had the smallest effect sizes (0.44 and 0.56, respectively). Flurazepam, temazepam, and estazolam had larger effects on total sleep time (0.84, 0.71, and 0.67, respectively), while zolpidem had the lowest (0.39).

When there is no significant heterogeneity, the combined effect size can be used to summarize the population of studies obtained. Translation of the effect size into standardized z scores provides clinically meaningful interpretations of the statistic d. From Table 4, the average medication-treated patient fell asleep faster than 71% of placebo-treated patients, slept longer than 76%, woke less often than 74%, and reported better sleep quality than 73%.

Table 4.—Raw Data and Effect Sizes for 4 Self-report Outcome Measures*

Source, y	Drug	Placebo	Pooled SD	Effect Size, d (SD)
Sleep- Onset Latency, min				
Cuanang et al,[63] 1982	35.9	64.1	35.3	0.80 (0.33)
Dominguez et al,[66] 1986	0.8†	1.0†	0.4†	0.40 (0.30)
Elie et al,[67] 1990	10.1†	10.8†	1.7†	0.43 (0.41)
Fillingim et al,[69] 1979	39.0	73.0	44.7	0.76 (0.30)
Herrmann et al,[70] 1993	40.5	72.8	32.5	1.00 (0.46)
Kripke et al,[36] 1990	34.1	44.8	34.0	0.31 (0.28)
Scharf et al,[77] 1990	2.5†	3.2†	1.4†	0.49 (0.16)
Scharf et al,[78] 1994	38.4	64.5	38.6	0.68 (0.29)
Walsh et al,[79] 1984	2.4†	3.1†	1.2†	0.56 (0.13)
Total Sleep Time, min				
Cuanang et al,[63] 1982	445.8	376.8	77.7	0.89 (0.33)
Dominguez et al,[66] 1986	2.0†	1.0†	1.0†	0.97 (0.32)
Elie et al,[67] 1990	6.9†	6.2†	1.2†	0.60 (0.42)
Fillingim et al,[69] 1979	422.0	379.0	75.2	0.57 (0.29)
Herrmann et al,[70] 1993	372.7	327.4	55.9	0.81 (0.45)
Kripke et al,[36] 1990	390	366	66	0.39 (0.29)
Scharf et al,[77] 1990	4.1†	3.0†	1.1†	1.00 (0.17)
Scharf et al,[78] 1994	361.2	345.4	71.6	0.22 (0.28)
Walsh et al,[79] 1984	1.7†	1.1†	0.9†	0.67 (0.13)
No. of Awakenings				
Cuanang et al,[63] 1982	NA	NA	NA	NA
Dominguez et al,[66] 1986	1.0	2.0	1.0	1.00 (0.32)
Elie et al,[67] 1990	3.8	5.2	1.5	0.99 (0.43)
Fillingim et al,[69] 1979	2.3	3.4	1.6	0.76 (0.30)
Herrmann et al,[70] 1993	1.8	2.3	1.3	0.38 (0.44)
Kripke et al,[36] 1990	NA	NA	NA	NA
Scharf et al,[77] 1990	1.7	2.2	0.7	0.64 (0.16)
Scharf et al,[78] 1994	NA	NA	NA	NA
Walsh et al,[79] 1984	1.8	2.1	0.5	0.57 (0.13)
Sleep Quality†				
Cuanang et al,[63] 1982	NA	NA	NA	NA
Dominguez et al,[66] 1986	1.0	2.0	1.0	1.00 (0.32)
Elie et al,[67] 1990	NA	NA	NA	NA
Fillingim et al,[69] 1979	2.2	3.5	1.6	0.76 (0.30)
Herrmann et al,[70] 1993	NA	NA	NA	NA
Kripke et al,[36] 1990	NA	NA	NA	NA
Scharf et al,[77] 1990	2.4	3.0	0.9	0.65 (0.16)
Scharf et al,[78] 1994	2.6	2.6	0.6	0.07 (0.28)
Walsh et al,[79] 1984	2.4	2.9	0.8	0.63 (0.13)

*NA indicates not available.
†Original studies' scaled scores.

Table 5.—Summary of Posttreatment Between-Group Comparisons: P Values and Effect Sizes

	Sleep-Onset Latency	Total Sleep Time	No. of Awakenings	Sleep Quality
P value analysis				
No. of studies	18	17	10	14
Unweighted summary, z	8.36	8.64	7.58	8.16
Weighted summary, z	6.95	5.64	6.66	6.49
P value of summary, z	<.001	<.001	<.001	<.001
χ^2 Heterogeneity of effect size	12.05	10.24	5.77	12.61
P value for χ^2	.20	.15	.23	.52
Effect size analysis				
No. of studies	9	9	6	9
Weighted effect size summary, d	0.56	0.71	0.65	.62
Effect size SD	0.08	0.08	0.09	0.09
95% Confidence interval	0.41-0.71	0.55-0.87	0.48-0.82	0.45-0.79
z for effect size	0.7123	0.7611	0.7422	0.7324
χ^2 Heterogeneity of effect size	3.34	8.59	2.66	5.52
P value for χ^2	.09	.38	.25	.34

COMMENT

The findings from this meta-analysis indicate that benzodiazepines and zolpidem produced reliable improvements in quantitative and qualitative subjective measures of sleep in patients with chronic insomnia. These medications had a moderate treatment effect. The average patient treated with medication reported superior outcomes compared with approximately three quarters of placebo-treated patients in the time it takes to fall asleep,

the number of awakenings at night, the total amount of sleep obtained, and the quality of sleep obtained.

As with the meta-analyses by Morin et al[42] and Murtagh et al,[43] which examined the effects of behavioral treatment on insomnia, we found inconsistent and infrequent use of polysomnography or measures of daytime well-being or functioning in controlled medication trials of chronic insomnia. A general consensus on outcome measures to include in clinical trials, as well as general guidelines on how to combine outcome measures to classify treatment responders, is clearly needed. In turn, this would facilitate the integration of accumulating evidence on which types of treatment are most effective overall as well as which treatments have more robust effects on specific aspects of insomnia. It is hoped that this meta-analysis will stimulate development of additional methods to integrate and summarize the existing body of research evidence of multiple pharmacologic agents, study designs, and outcomes used in insomnia research to better inform the design and reporting of future trials.

The duration of medication exposure during treatment trials deserves special emphasis. While the range of drug exposure was 4 to 35 days, the median duration of treatment was only 7 days. Our results indicate that patients with chronic insomnia show subjective improvement to such acute medication treatment as compared with placebo. Our analysis draws attention to the lack of well-controlled evidence regarding the efficacy of long-term exposure to benzodiazepines or zolpidem in patients with chronic insomnia. This may, in part, stem from risk-to-benefit concerns about continuous and prolonged benzodiazepine exposure to patients in research protocols. Yet, given that 10% of long-term insomnia patients who take benzodiazepines take them continuously for more than a year, such evidence is sorely needed.[1,2,24] Lastly, and in contrast to studies of the behavioral interventions in insomnia, none of the studies reviewed had any follow-up data examining the durability of treatment effects 3 or 6 months after treatment. These observations together suggest that clinical trials of medications should include longitudinal design considerations when evaluating the efficacy of hypnotics as an intervention in chronic insomnia.

One potential limitation of our results is that we excluded the so-called orphan literature, eg, dissertations, abstracts, or trials conducted by pharmaceutical companies but not published in the medical literature. A related concern is that by focusing on published study results we bias the sample toward studies that have found positive and statistically significant results. Traditional narrative reviews are subject to similar limitations. However, these issues may be approached within the meta-analysis with the formula $N_{.05} = (\Sigma z/1.645)^2$, where $N_{.05}$ represents the number of studies with $P=.05$, to determine the number of studies with null results that would have to have been systematically omitted from our review to reduce the current findings to marginal statistical significance.[41,58] The number of such omitted studies would be 135 for sleep-onset latency, 150 for total sleep time, 96 for number of wakings, and 64 for sleep quality. It is unlikely that these numbers of studies with null results were conducted and either not published or not identified in our search. This suggests that the results derived from our sample of studies would remain durable to a reasonable number of threats to the parameters of our search strategy.

A related concern focuses on our study selection criteria and, in particular, studies that used parallel-group or cross-over designs. The goal of this review was to evaluate the magnitude of treatment effects specific to medication in patients with chronic symptoms of insomnia unrelated to medical and psychiatric causes, and who were treated with a benzodiazepine in use in the United States or with zolpidem. From the potential pool of 113 English-language studies that used a placebo control and that presented efficacy data, approximately 15% were excluded because the insomnia was in the context of a major psychiatric or medical illness, 11% were excluded because patients were exclusively older than 65 years, and 21% for study design (primarily a single-cell, placebo wash-in design). Design characteristics may turn out not to influence observed treatment effects, ie, a single-group, open trial comparing premeasures to postmeasures may produce the same treatment effect as randomized, placebo-controlled, double-blind, parallel-group design. Accordingly, if study design does not influence the effects of treatment, our sample's results should have been similar whether we included other designs or limited our sample to randomized clinical trials. If, however, study design does exert important influences, we suggest that our inclusion criteria resulted in a set of studies whose results represent the most conservative effects attributable specifically to active treatment.[58]

To summarize, the available evidence resulting from randomized, placebo-controlled, double-blind treatment trials of benzodiazepines and zolpidem in the treatment of chronic insomnia demonstrates moderate, reliable treatment effects on subjective sleep-onset latency, total sleep time, number of awakenings, and sleep quality. Daytime well-being and daytime functioning need to be measured more often for the utility of these outcomes to be quantitatively reviewed. Before stronger recommendations can be made about the role of drug therapy in chronic insomnia, longitudinal and controlled clinical trials with follow-up data are needed to evaluate the effects of medication treatment beyond 4 weeks of "acute" treatment. More evidence is needed to justify the transition from benzodiazepines to sedating antidepressants in the clinical management of chronic insomnia, and alternative long-term treatment strategies such as nonsedating antidepressant and secondary prevention strategies need to be explored. Lastly, common outcomes and uniform definitions of treatment response are needed to develop evidence-based practice guidelines for the role of medication in the long-term clinical management of chronic insomnia.

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