CLINICAL REVIEW

The Efficacy and Safety of Drug Treatments for Chronic Insomnia in Adults: A Meta-analysis of RCTs

Nina Buscemi, PhD[1], Ben Vandermeer, MSc[1], Carol Friesen, MA, MLIS[1], Liza Bialy, BSc[1,3], Michelle Tubman, MSc[1], Maria Ospina, MSc[1], Terry P. Klassen, MD, MSc, FRCPC[1], and Manisha Witmans, MD, FRCPC, Dip. ABSM[2]

[1]University of Alberta/Capital Health Evidence-Based Practice Centre, Department of Pediatrics, University of Alberta, Alberta, Canada; [2]Department of Pediatrics, University of Alberta, Alberta, Canada; [3], Aberhart Centre One, Room 9428, 11402 University Avenue, Edmonton, AB T6J 2G3, Canada.

BACKGROUND: Hypnotics have a role in the management of acute insomnia; however, the efficacy and safety of pharmacological interventions in the management of chronic insomnia is unclear.

OBJECTIVE: The objective of this paper is to conduct a systematic review of the efficacy and safety of drug treatments for chronic insomnia in adults.

DATA SOURCES: Twenty-one electronic databases were searched, up to July 2006.

STUDY SELECTION: Randomized double-blind, placebo-controlled trials were eligible. Quality was assessed using the Jadad scale. Data were pooled using the random effects model.

DATA SYNTHESIS: One hundred and five studies were included in the review. Sleep onset latency, as measured by polysomnography, was significantly decreased for benzodiazepines (BDZ), (weighted mean difference: −10.0 minutes; 95% CI: −16.6, −3.4), non-benzodiazepines (non-BDZ) (−12.8 minutes; 95% CI: −16.9, −8.8) and antidepressants (ADP) (−7.0 minutes; 95% CI: −10.7, −3.3). Sleep onset latency assessed by sleep diaries was also improved (BDZ: −19.6 minutes; 95% CI: −23.9, −15.3; non-BDZ: −17.0 minutes; 95% CI: −20.0, −14.0; ADP: −12.2 minutes; 95% CI: −22.3, −2.2). Indirect comparisons between drug categories suggest BDZ and non-BDZ have a similar effect. All drug groups had a statistically significant higher risk of harm compared to placebo (BDZ: risk difference [RD]: 0.15; non-BDZ RD: 0.07; and ADP RD: 0.09), although the most commonly reported adverse events were minor. Indirect comparisons suggest that non-BDZ are safer than BDZ.

CONCLUSIONS: Benzodiazepines and non-benzodiazepines are effective treatments in the management of chronic insomnia, although they pose a risk of harm. There is also some evidence that antidepressants are effective and that they pose a risk of harm.

KEY WORDS: drug; treatment; chronic; insomnia.
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INTRODUCTION

Insomnia, defined as the inability to initiate or maintain sleep or lack of restorative sleep, is common, with an estimated prevalence of 9–12% in adults.[1,2] Chronic insomnia has a significant impact on society because it is associated with frequent use of health care services,[3,4] chronic health problems,[5,6] increased medication use,[3,4] and perceived poor health.[7] Growing evidence suggests that chronic, unremitting insomnia may predispose individuals to the development of psychiatric disorders and lead to substantial economic burden.[2,8,9]

Treatment options for chronic insomnia include pharmacological agents and non-pharmacological agents. Pharmacological agents, particularly benzodiazepines (BDZ) and non-benzodiazepines (non-BDZ), are effective in the management of acute insomnia and endorsed by the National Institute of Health[10,11], but their role in the management of chronic insomnia is uncertain because of concerns about physical dependence, withdrawal, and rebound insomnia, and long-term safety. The Food and Drug Administration recently approved Eszopiclone (Lunesta), a non-BDZ hypnotic, for management of chronic insomnia in adults. This is the only drug not limited to short-term usage. Much less data are available for antidepressants (ADP).

A number of meta-analyses have evaluated the role of pharmacological agents versus behavioral therapy for insomnia, but only one has focused on chronic insomnia.[12–16] Our goal was to conduct a meta-analysis of randomized controlled trials of the efficacy and safety of BDZ, non-BDZ, and ADP in the management of chronic insomnia in adults.

METHODS

Search Strategy

This review is derived from an Evidence Report on manifestations and management of chronic insomnia in adults[17] and covered the period up to July 2006. A research librarian conducted a comprehensive search for published literature in 21 electronic databases, including MEDLINE® (1966–2006), EMBASE (1988–2006), CINAHL (1982–2006), PsycINFO (1985–2006), Cochrane Central Register of Controlled Trials (1950–2006), International Pharmaceutical Abstracts (1970–2006), Science Citation Index Expanded (via Web of Science®, 1900–2006), and Biosis Previews (1969–2006). A combination of subject headings and keywords were adapted for each database, based on the following terms: insomnia, sleep initiation, and maintenance disorders, sleep onset delay (or latency), early awakening, sleeplessness, time zone change, jet lag, random, clinical trial, and placebo. We also searched for unpublished trials through ClinicalTrials.gov, Current Controlled Trials, and OCLC PapersFirst. We did not seek unpublished data from pharmaceutical manufacturers. Complete search strategies are available from the original Evidence Report or the corresponding author.

Study Selection

All titles and abstracts identified by the search were screened independently by two reviewers for potential relevance and were retrieved. Two reviewers independently assessed the manuscripts for inclusion using predetermined criteria. To assess the efficacy of drug treatments for chronic insomnia, we included English-language reports of randomized, double-blind, placebo-controlled trials (RCTs) that: (1) involved human adult participants suffering from chronic insomnia; (2) compared a drug treatment to placebo; and (3) reported on at least one of the following outcomes: sleep onset latency (amount of time between lying down to sleep and the onset of sleep); wakefulness after sleep onset (amount of time spent awake in bed following the first attainment of sleep); sleep efficiency (amount of time spent asleep as a percentage of the total time spent in bed); sleep quality (perceived quality of sleep); total sleep time, quality of life, or adverse events. A study population was considered to suffer from chronic insomnia if the majority of participants met at least one of the following criteria: (1) they had a sleep disturbance (either sleep initiation or maintenance problem) of 4 weeks or more; (2) they were described as having a chronic or long-standing or persistent sleep disturbance; and/or (3) they attended a sleep disorders clinic. The 4-week cut point for chronic insomnia was considered long enough to eliminate studies involving transient insomnia and short enough to include studies involving persistent insomnia. To assess the safety of drug treatments for chronic insomnia in adults, we included studies that met the criteria for the efficacy review and reported on adverse events. Disagreements regarding inclusion were resolved through discussion. The primary reason for exclusion of articles was documented.

Quality Assessment

Included studies were assessed for methodological quality using the validated Jadad scale,[18] which evaluates randomization, blinding, and reporting of dropouts and withdrawals. This scale provides an overall maximum score of five. In addition, we assessed concealment of allocation[19] as "adequate", "inadequate", and "unclear". Two reviewers assessed study quality independently with any disagreements resolved through discussion.

Data Extraction

Data were extracted using a standardized form that captured details of study design, population, intervention, and outcomes. Trained reviewers extracted relevant data, and a second reviewer verified data extracted. Disagreements were resolved through discussion.

Data Analysis

Benzodiazepines act by nonselective activation of the BDZ receptor subtypes of the gamma-aminobutyric acid (GABA) receptor complex. The newer non-BDZ agents are much more selective for the BDZ receptor subtypes ($GABA_A$) and have reportedly fewer side effects. In light of these differences, BDZ and non-BDZ were analyzed separately. Antidepressants were analyzed as a separate group. The data for four sleep outcomes (sleep onset latency, wakefulness after sleep onset, sleep efficiency, and total sleep time) were analyzed based on method of measurement (e.g., polysomnography: an overnight, monitored sleep period in a laboratory, which provides objective measures of sleep and sleep diary: a log of subjective estimates of sleep).

A priori, sleep onset latency was considered to be the primary outcome of the review, as it is an important measure of sleep-initiation insomnia and the most frequently reported outcome in the insomnia literature. Wakefulness after sleep onset was defined as the secondary outcome of the review, as it is an important measure of sleep-maintenance insomnia.

For continuous outcomes (e.g., sleep onset latency), studies were combined using a weighted mean difference (WMD) with the exception of sleep quality and quality of life, for which studies were combined using a standardized mean difference. For dichotomous outcomes (e.g., adverse events), studies were combined using a risk difference. Data were extracted in both the first and second period for all crossover trials. All meta-analyses were performed in RevMan 4.2.5 (Update Software 2004). Point estimates with corresponding 95% confidence intervals were computed for each outcome using the random effects model.

All estimates of efficacy were assessed for heterogeneity using the I-squared statistic.[20] For our primary outcome, we explored heterogeneity in subgroup and sensitivity analyses using the following variables: type of drug treatment, presence of psychiatric illness, length of treatment (short-term or long-term defined as ≤4 weeks and >4 weeks, respectively), age (adult 18–65 or elderly >65 years), gender, study quality (low, moderate, or high defined as Jadad scores of 0–1, 2–3, and 4–5, respectively). Method of measurement of sleep outcome (polysomnography or sleep diary) was analyzed post hoc. A chi-square statistic was used to test for significant heterogeneity reduction in subgroups.[21]

While active interventions were compared to placebo in the primary analyses, these interventions were compared by indirect comparisons in a secondary analysis.[22]

We tested for publication bias on our primary outcome using a funnel plot, both visually and quantitatively, with the rank correlation test,[23] bias test,[24] and trim and fill method.[25]

RESULTS

There were 20,086 records identified from database searches and 761 full-length manuscripts assessed for potential inclusion in the review. One hundred and five studies were included in the review: 52 on BDZ, 48 on non-BDZ and 8 studies on antidepressants. Figure 1 describes the flow of studies through the selection process.

Study Characteristics

Some studies examined more than one drug group and were included in multiple analyses. Detailed characteristics of each study appear in Tables 1, 2 and 3.

All studies were RCTs, and the majority (BDZ: 36/52; non-BDZ: 42/48; ADP: 5/8) had a parallel design with all others described as crossover. Of the studies reporting funding source, the majority of BDZ (20/22) and non-BDZ (27/30) received funds from private sources. Four studies on ADP were funded through private sources. Study quality across drug groups was either moderate (BDZ: 32/52; non-BDZ: 24/48; ADP: 7/8) or high (BDZ: 20/52; non-BDZ: 24/48; ADP: 1/8).

Most studies on BDZ and non-BDZ had a short treatment length (≤4 weeks) and involved non-elderly adults (42/52 and 37/48, respectively). For ADP, six studies involved short-term treatment, and all had populations of non-elderly adults of either gender. Nearly all of the BDZ and non-BDZ studies involved populations of both genders (44/52 and 45/48, respectively). Most of the populations reported in studies did not have a psychiatric disorder (BDZ: 47/52; non-BDZ: 46/48; ADP: 6/8). The mean duration of insomnia was similar for studies on both BDZ and non-BDZ, ranging from 1.1 months to 17.7 years. The mean duration of insomnia was reported in three of eight studies on ADP; ranging from 10.7–11.2 years.

Efficacy

The efficacy analysis included 47, 44, and 8 relevant studies for BDZ, non-BDZ, and ADP, respectively. The combined WMD showed that BDZ, non-BDZ, and ADP had significantly shorter sleep onset latency times compared to placebo when measured by polysomnography (WMD: −10.0 minutes; 95% CI: −16.6, −3.4; WMD: −12.8 minutes; 95% CI: −16.9, −8.8; WMD: −7.0 minutes; 95% CI: −10.7, −3.3, respectively) or sleep diary (WMD: −19.6 minutes; 95% CI: −23.9, −15.3; WMD −17.0 minutes; 95% CI: −20.0, −14.0; WMD: −12.2 minutes; 95% CI: −22.3, −2.2, respectively) (Table 4). The improvements measured by sleep diary were more prominent for all three drug groups. There was heterogene-

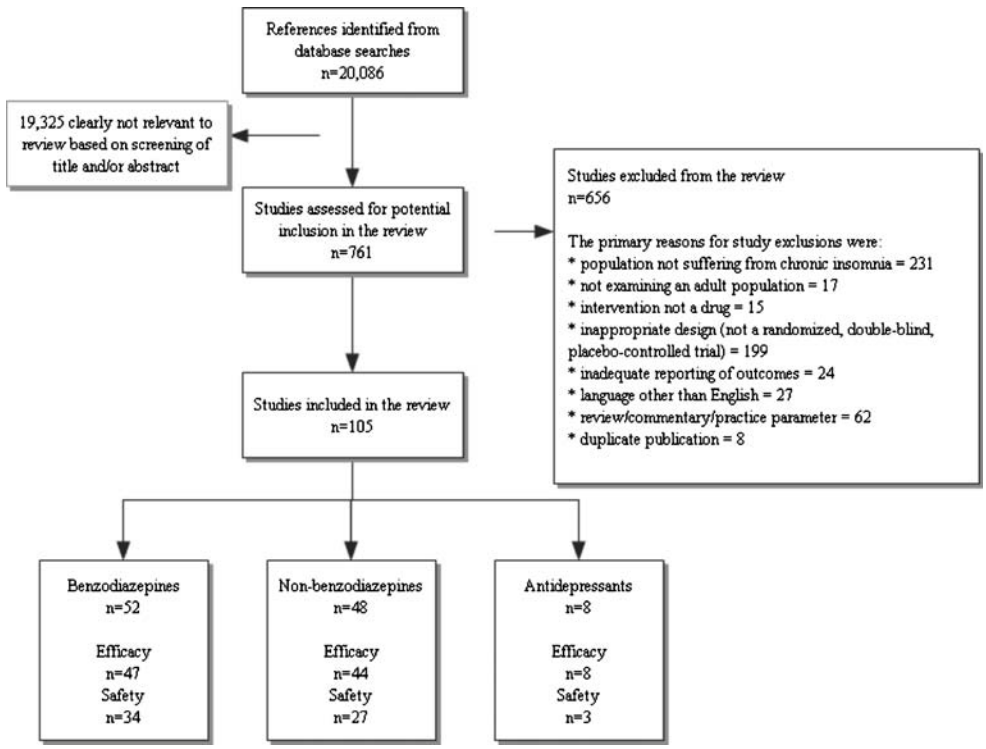

Figure 1. Study selection and retrieval

Table 1. Study Characteristics for Trials Comparing Benzodiazepines and Placebo in Adults with Chronic Insomnia

First Author/Year	Sample Size, *n*, enrolled	Mean age±SD or (range), in years	Number of Females/ Males or (Percentage Female/ Male)	Psychiatric Illness	Quality Score (Jadad)	Intervention		
						Drug	Dose, mg	Duration
Aden GC/1983	57	47±NS (23–59)	29/21	NS	2	Quazepam	30	5 nights
Allain H/1998*	84	54.3±11.0	NS (67.9/32.1)	NS	4	Triazolam; zolpidem	0.125; 10	4 nights
Beary MD/1984*	6	NS (23–35)	6/0	NS	3	Temazepam	20	NS
Botter PA/1983†	40	Part 1: 1 mg loprazolam: 44.3±8; PL: 40.6±7.7 Part2: 2 mg loprazolam: 46.1±7.2; PL: 44.8±7.1	25/15	Anxiety neoroses	4	Loprazolam	1, 2	7 nights
Bowen AJ/1978	120	NS (18–60)	13/5	NS	3	Triazolam	0.5	2 nights
Campbell RD/1987	71	38±2	25/31	NS	4	Flurazepam; zopiclone	30; 7.5	3 weeks for each TR
Cohn JB/1983	53	41.5±NS (18–60)	38/15	Depression	4	Triazolam	0.25	4 nights
Cohn JB/1984	41	41.4±10.2	18/12	Various psychiatric conditions	3	Triazolam; lorazepam	0.5; 2	4 days for each TR
Cohn JB/1991	223	NS (18–65)	NS	NS	3	Estazolam; flurazepam	1, 2; 3	7 nights
Dominguez RA/1985	67	NS (20–60)	NS	NS	3	Brotizolam	0.25–0.5	21 nights
Dominguez RA/1986	74	46.6±NS (21–65)	NS (46/54)	NS	3	Estazolam; flurazepam	2; 30	7 nights
Drake CL/2000	93	Study 1: 41.6±9.5; study 2: 38.1±11.1	38/45	NS	4	Zaleplon; triazolam	Study 1: 10, 40; 0.25, study 2: 20, 60; 0.25	2 nights for each TR
Dujardin K/1998*	12	NS (40–62)	0/12	NS	3	Zolpidem; flunitrazepam	10; 1	3 weeks
Elie R/1990*	44	76±1.3	33/11	NS	3	Zopiclone; triazolam	5, 7.5; 0.125; 0.25	3 weeks
Ferguson JM/1991	120	43.4±10.9	NS (56/44)	major depression	4	Estazolam	2	7 nights
Fillingim JM/1982	75	81±NS (NS)	NS (89/11)	NS	5	Temazepam; flurazepam	30; 30	4 nights
Fleming J/1995	144	33–37±NS‡(21–60)	NS (48/52)‡	NS	3	Zolpidem; flurazepam	10, 20; 30	3 nights
Goethe, JW/1982	69	NS (19–60)	50/19	NS	2	Quazepam	15	5 nights

Table 1. (continued)

First Author/Year	Sample Size, *n*, enrolled	Mean age±SD or (range), in years	Number of Females/ Males or (Percentage Female/ Male)	Psychiatric Illness	Quality Score (Jadad)	Intervention		
						Drug	Dose, mg	Duration
Hajak G/1994†	1,507	51±11	939/566	NS	5	Zopiclone; flunitrazepam triazolam	7.5; 1.0; 0.25	28 days
Hartmann E/1983*	106	l-tryptophan: 38±NS, secobarbital: 41±NS, flurazepam: 46±NS, PL: 39±NS; (18-71)	48/48	NS	3	L-tryptophan; secobarbital; flurazepam	1,000; 100; 30	7 nights
Heidrich H/1981	62	Loremetazepam: 44.6±2; PL: 46±2	NS (67/33)	NS	4	Loremetazepam	2	2 weeks
Jacobson AF/1986	57	Brotizolam: 72±NS, PL: 69±NS; (60–82)	NS	NS	3	Brotizolam	0.125	4 nights
Lara RH/1983	36	NS (22–65)	24/12	NS	3	Quazepam	15	5 nights
Leppik IE/1997	457	69±NS (59–85)	NS (63/37)	NS	3	Zolpidem; triazolam; temazepam	5; 0.125; 15	4 weeks
Mamelak M/1987*	30	50±NS (32–60)	21/9	NS	4	Flurazepam; zopiclone	30; 7.5	12 days
Mamelak M/1989*	36	NS (60–72)	NS	NS	2	Brotizolam; flurazepam	0.25; 15	14 nights
McAlpine CJ/1984†	190	NS (18–94)	90/57	NS	4	Loprazolam; nitrazepam	1.0; 5.0	7 nights
Melo de Paula A/1984	60	1 mg lormetazepam: 29.3±NS (20–55), 2 mg lormetazepam: 30.4±NS (21–45), flurazepam: 30.6±NS (19–41), PL: 27.9±NS (20–41)	42/16	NS	3	Lormetazepam; flurazepam	1, 2; 30	2 weeks
Mendels J/1983	80	Quazepam: 47±NS (20–58); PL: 45±NS (22–60)	19/41	NS	3	Quazepam	15	5 nights
Minnekeer RJ/1988†	205	Quazepam: 53.2± 14.5, flunitrazepam: 55.4± 12.5, PL: 54.9±13.7	130/74	NS	4	Quazepam; flunitrazepam	15; 2	4 weeks
Mitler MM/1984*	21	Flurazepam: 45.5±NS (31–61), traizolam: 43.8±NS (27–59), PL: 37.7±NS (27–57)	17/4	Personality disorder	3	Flurazepam; traizolam	30; 0.5	37 nights

Table 1. (continued)

First Author/Year	Sample Size, *n*, enrolled	Mean age±SD or (range), in years	Number of Females/ Males or (Percentage Female/ Male)	Psychiatric Illness	Quality Score (Jadad)	Intervention		
						Drug	Dose, mg	Duration
Morin CM/1999*	78	65±7	50/28	NS	2	Temazepam; cognitive/ behavioral therapy (alone and combined)	7.5–30	8 weeks
Nair NPV/1990†	60	46.9±1.4	28/32	NS	3	Zopiclone; flurazepam	3.75, 7.5, 11.25, 15; 30	7 days
Reeves RL/1977	41	Triazolam: 68.6±NS, flurazepam: 69.6±NS, PL: 70.4±NS (NS)	27/14	NS	4	Triazolam; flurazepam	0.25; 15	28 nights
Rickels K/1986	63	46±12	NS (63/37)	NS	4	Brotizolam	0.5 mg	2 week
Riemann D/2002	65	Lormetazepam: 45.3±10.3, trimipramine: 47.0±10.8, PL: 48.8±11.6	23/32	NS	3	Lormetazepam; trimipramine	1; 25–200	28 days
Roehrs T/1983*	12	33.3±8.0	8/4	NS	3	Brotizolam	0.25; 0.5	1 week
Roth T/1979	16	NS (18–65)	0/16	NS	4	Quazepam	25 mg	1 night
Roth TG/1997	30	65.9±4.6	15/15	NS	2	Quazepam	7.5; 15	7 nights
Sastre-y-Hernandez M/1988	60	NS (20–76)	36/24	NS	4	Lormetazepam	1	1 week
Scharf MB/1990	75	Estazolam: 0.4±13.5, flurazepam: 42.8±13.9, PL: 41.3±13.0	NS	NS	4	Estazolam; flurazepam	2; 30	7 nights
Seidel WF/1985*	12	NS (21–60)	NS	NS	2	Buspirone–triazolam; buspirone–flurazepam; placebo–flurazepam; placebo–triazolam; buspirone–placebo	Placebo or buspirone: 5 at 0900 hours, 5 at 1400 hours, 10 at 2100 hours; 30 flurazepam; 0.5 triazolam	4 nights
Staner L/2005*	23	38.8±2.0	14/9	NS	2	Zolpidem; zopiclone; lormetazepam	10; 7.5; 1	8 nights
Steens RD/1993*	24	58.2±5.5	9/15	NS	3	Zolpidem; triazolam	5, 10; 0.25	1 night for each treatment
Stip E/1999*	60	42.6±1.6	21/29	NS	4	Zopiclone; temazepam	7.5; 30	3 weeks

Table 1. (continued)

First Author/Year	Sample Size, *n*, enrolled	Mean age±SD or (range), in years	Number of Females/ Males or (Percentage Female/ Male)	Psychiatric Illness	Quality Score (Jadad)	Intervention		
						Drug	Dose, mg	Duration
Tietz EI/1981*	15	41.2±16.8	0/15	NS	3	Quazepam	7.5, 15, 30; 45	5 nonconsecutive weeks
Tuk B/1997*	21	NS (18–78)	15/6	NS	3	Temazepam	20	2 occasions with at least 1 week between occasions
Viukari M/1983*	39	Group A: 73.2±2.9, group B: 75.1±1.5	20/17	Various psychiatric conditions	4	Flunitrazepam; nitrazepam	1; 5	2 weeks
Walsh JK/1984	379	41.1±NS (19–65)	NS (52/48)	NS	3	Estazolam	1; 2	7 nights
Walsh JK/1998	132	5 mg zaleplon: 38.9±10.3, 10 mg zaleplon: 39.6±10.0, triazolam: 39.3±11.7, PL: 43.1±9.0	77/55	NS	4	Zaleplon; triazolam	5, 10; 0.25	14 nights
Winsauer HJ/1984	60	NS (60–90)	39/21	NS	3	Quazepam	15	5 nights
Wu R/2006*	77	38±12	41/36	NS	2	Temazepam	7.5 to 30	8 weeks

ity among studies on BDZ and non-BDZ for both measures of sleep onset latency times, but the direction of the estimate was fairly consistent for BDZ. Nine out of 11 comparisons had point estimates that favored BDZ for polysomnography, while all 26 sleep diary trials had point estimates that favored BDZ (Fig. 2). For non-BDZ, all 12 studies for polysomnography and all 34 studies for sleep diary showed a point estimate that favored non-BDZ (Fig. 3). For ADP, there was moderate heterogeneity among studies in the polysomnography group and negligible heterogeneity in the sleep diary group (Fig. 4).

We conducted meta-analyses for wakefulness after sleep onset, sleep efficiency, total sleep time, and sleep quality, subcategorized by polysomnography and sleep diary for BDZ, non-BDZ, and ADP. All results were statistically significant and favored BDZ and non-BDZ with the exception of the polysomnography studies measuring wakefulness after sleep onset and total sleep time, which were marginally nonsignificant (Table 4). In contrast, for ADP, polysomnography results significantly favored ADP, but sleep diary results were fewer and nonsignificantly favored ADP for wakefulness after sleep onset and nonsignificantly favored placebo for total sleep time (Table 4).

Subgroup and Sensitivity Analyses. We conducted subgroup analyses of sleep onset latency for drug type, psychiatric illness, length of treatment, age, and gender for BDZ, non-BDZ, and ADP. Heterogeneity was significantly reduced for polysomnography for BDZ studies when subgrouping by type of drug, length of treatment, and gender; while for sleep diary, it was only significantly reduced for type of drug.

Heterogeneity was significantly reduced when we subgrouped by age for both polysomnography and sleep diary for non-BDZ studies, although the effects were opposite (elderly patients seemed to benefit more when sleep onset latency was measured by polysomnography, but less when measured by sleep diary). Drug type was the only other subgroup to show a heterogeneity reduction (sleep diary only).

There was insufficient data to conduct subgroup analyses for gender and age for ADP studies. There were no significant differences in the effect of ADP among subgroupings of any other category.

We also conducted sensitivity analyses based on study quality for each group of drugs, BDZ, non-BDZ, and ADP. This subgrouping of BDZ drugs did not significantly reduce heterogeneity in either polysomnography or sleep diary. Both meth-

Table 2. Study Characteristics for Trials Comparing Non-benzodiazepines and Placebo in Adults with Chronic Insomnia

First Author/Year	Sample Size, *n* enrolled	Mean age±SD or (range), in years	Number of Females/ Males or (Percentage Female/ Male)	Psychiatric Illness	Quality Score (Jadad)	Intervention		
						Drug	Dose, mg	Duration
Allain H/1998*	84	54.3±11.0	NS (67.9/32.1)	NS	4	Triazolam; zolpidem	0.125; 10	4 nights
Allain H/2001	245	Zolpidem: 45.6±9.6, PL: 46.7±11.5	188/57	NS	3	Zolpidem	10	4 weeks
Asnis GM/1999	273	Zolpidem: 41.6±1.2, PL: 41.6±1.0	150/40	Various psychiatric conditions	3	Zolpidem	10	4 weeks
Campbell RD/1987	71	38±2	25/31	NS	4	Flurazepam; zopiclone	30; 7.5	3 weeks for each TR
Chaudoir PJ/1983	30	50±NS (35–65)	18/7	NS	3	Zopiclone	7.5	7 nights
Deacon S/2005*	26	NS (18–65)	NS	NS	3	Gaboxadol	5; 15	6 nights
Declerk A/1999	22	54±NS (NS)	17/5	NS	3	Zolpidem	10	1 week
Drake CL/2000	93	Study 1: 41.6±9.5, study 2: 38.1±11.1	38/45	NS	4	Zaleplon; triazolam	Study 1: 10, 40; 0.25, study 2: 20, 60; 0.25	2 nights for each TR
Dujardin K/1998*	12	NS (40–62)	0/12	NS	3	Zolpidem; flunitrazepam	10; 1	3 weeks
Elie R/1990*	44	76±1.3	33/11	NS	3	Zopiclone; triazolam	5, 7.5; 0.125, 0.25	3 weeks
Elie R/1999	615	5 mg zaleplon: 42.5±12.9, 10 mg zaleplon: 42.6±12.5, 20 mg zaleplon: 42.6± 12.2, 10 mg zolpidem: 44.3±12.5, PL: 42.1± 12.0	370/204	NS	3	Zaleplon; zolpidem	5, 10, 20; 10	4 weeks
Farber R/2006*	702	46±NS	428/274	NS	2	Indiplon	10; 20	3 months
Fleming J/1995	144	33–37±NS[†](21–60)	NS (48/52)	NS	3	Zolpidem; flurazepam	10, 20; 30	3 nights
Fry J/2000	595	5 mg zaleplon: 43±12, 10 mg zaleplon: 40±10, 20 mg zaleplon: 41±13, 10 mg zolpidem: 42±11, PL: 43±12	342/244	NS	3	Zaleplon; zolpidem	5, 10, 20; 10	28 nights
Gelinas B/1985*	32	40.9±2.19	16/10	NS	4	Zopiclone	7.5	3 weeks
Goldenberg F/1994	524	Zopiclone: 42.5±8.6; PL: 43.3±9.2	291/167	NS	4	Zopiclone	7.5	14 nights—as needed for 4 weeks

Table 2. (continued)

First Author/Year	Sample Size, *n* enrolled	Mean age±SD or (range), in years	Number of Females/ Males or (Percentage Female/ Male)	Psychiatric Illness	Quality Score (Jadad)	Intervention		
						Drug	Dose, mg	Duration
Hajak G/1994‡	1,507	51±11	939/566	NS	5	Zopiclone; flunitrazepamtriazolam	7.5; 1.0; 0.25	28 days
Hedner J/2000	437	5 mg zaleplon: 72.5±5.9, 10 mg zaleplon: 72.5±6.3, Pl: 72.5±6.8	285/137	NS	3	Zaleplon	5, 10	2 weeks
Hermann WM/1993	25	NS (25–65)	9/12	NS	3	Zolpidem	10	2 weeks
Jacobs GD/2004*	63	TR: 45.4±9.3, PL: 46.6±10.1 (25–64)	44/19	NS	3	Zolpidem	10×28 nights; 5×14 nights	6 weeks
Krystal AD/2003	788	44±11	498/290	NS	3	Eszopiclone	3	6 months
Lahmeyer, H/1997	178	44.9±NS (19–61)	81/64	NS	4	Zolpidem	10, 15	31 nights
Lamphere JK/1989*	12	36±10	3/9	NS	2	Zopiclone	2.5, 5.0, 7.5, 10, 15	6 weeks
Lankford J/2005*	229	NS (65–85)	NS	NS	2	Indiplon	15	2 weeks
Leppik IE/1997	457	69±NS (59–85)	NS (63/37)	NS	3	Zolpidem; triazolam; temazepam	5; 0.125; 15	4 weeks
Mamelak M/1987*	30	50±NS (32–60)	21/9	NS	4	Flurazepam; zopiclone	30; 7.5	12 days
Monchesky TC/1986*	99	Zopiclone: 47.1±1.7, PL: 46.6±1.8	65/26	NS	4	Zopiclone	7.5	4 weeks
Monti JM/1996*	12	Zolpidem: 41.2±3.9, PL: 47.3±5.7	10/2	NS	3	Zolpidem	10	27 nights
Monti JM/2000*	12	Zolpidem: 53.8±1.8, Pl: 50.0±5.3	12/0	NS	3	Zolpidem	10	15 nights
Nair NPV/1990‡	60	46.9±1.4	28/32	NS	3	Zopiclone; flurazepam	3.75, 7.5, 11.25, 15, 30	7 days
Perlis ML/2004*	199	41.0±12.8 (18–64)	141/58	NS	3	Zolpidem	10	12 weeks
Scharf MB/1994	75	38±NS (22–60)	48/27	NS	3	Zolpidem	10, 15	5 weeks
Scharf M/2005	231	72.3±4.9 (65–85)	133/98	NS	2	Eszopiclone	1; 2	2 weeks
Schnitzer T/2005	153	TR: 52.3±8.1, PL: 51.8±9.5	133/20	NS	3	Eszopiclone	3	4 weeks
Shaw SH/1992‡	119	10 mg zolpidem: 74.9±1.0, 20 mg zolpidem: 72.9±1.0, PL: 75.7±0.8	81/38	Various psychiatric conditions	3	Zolpidem	10, 20	21 days

Table 2. (continued)

First Author/Year	Sample Size, *n* enrolled	Mean age±SD or (range), in years	Number of Females/ Males or (Percentage Female/ Male)	Psychiatric Illness	Quality Score (Jadad)	Intervention		
						Drug	Dose, mg	Duration
Sivertsen B/200648	48	60.8±5.4	22/24	NS	4	Zopiclone	7.5	6 weeks
Soares CN/ 2005	410	TR: 49.3±4.1, PL: 48.9±3.9 (40–60)	410/0	NS	3	Eszopiclone	3	4 weeks
Staner L/2005*	23	38.8±2.0	14/9	NS	2	Zolpidem; zopiclone; lormetazepam	10; 7.5; 1	8 nights
Steens RD/1993*	24	58.2±5.5	9/15	NS	3	Zolpidem; triazolam	5, 10; 0.25	1 night for each TR
Stip E/1999*	60	42.6±1.6	21/29	NS	4	Zopiclone; temazepam	7.5; 30	3 weeks
Walsh JK/1998	132	5 mg zaleplon: 38.9± 10.3, 10 mg zaleplon: 39.6±10.0, triazolam: 39.3±11.7	77/55	NS	4	Zaleplon; triazolam	5, 10; 0.25	14 nights
Walsh JK/1998	589	42±NS (21–65)	193/85	NS	3	Zolpidem; trazodone	10; 50	14 nights
Walsh JK/2000*	54	67.5±NS (60–79)	17/31	NS	3	Zaleplon	2, 5, 10	2 nights
Walsh JK/ 2000*	163	Zolpidem: 43.2±1.2, PL: 45.0±1.3	115/48	NS	4	Zolpidem	10	8 weeks
Walsh JK/2002*	365	Zolpidem: 43.2±1.2, PL: 45.0±1.3	115/48	NS	3	Zolpidem	10	4 weeks
Walsh JK/ 2004*	194	40.2±11.8	128/66	NS	2	Indiplon	10; 20	5 weeks
Walsh JK/ 2005	358	NS (65–80)	NS	NS	2	Indiplon	5; 10	2 weeks
Zammit GK/2004	308	TR 2 mg: 40.6±11.5, TR 3 mg: 38±11.7, PL: 40.8±11.8 (21–64)	199/109	NS	3	Eszopiclone	3; 3	44 nights

ods of measurement showed a heterogeneity reduction for non-BDZ, but the effects were opposite (high quality studies showed more benefit when measured with sleep diary, but less benefit when measured by polysomnography). Finally, the subgrouping for ADP did not significantly reduce heterogeneity, and the efficacy estimates were not significantly different between subgroupings.

Safety

To analyze the safety of BDZ, non-BDZ, and ADP, there were 34, 27, and 3 studies included, respectively. The combined risk difference showed that all drug groups had significantly more adverse events than the placebo group (Table 4). There was substantial heterogeneity among studies in the BDZ and non-BDZ groups, but it was negligible in the ADP group. The most commonly reported adverse events in studies were somnolence (n=27), headache (n=18), dizziness (n=16), nausea (n=11), and fatigue (n=11) in the BDZ group. There were no reports of falls, injury, or death. In the non-BDZ group, the most commonly reported adverse events were headache (n=16), dizziness (n=14), nausea (n=13), and somnolence (n=13). Accidental injury was reported in one study; however, there was no significant difference in the frequency of this event between non-BDZ and placebo groups. Finally, for ADP, the most commonly reported adverse events were somnolence (n=4), headache (n=3), dizziness (n=3), and nausea (n=3). There were no reports of falls, injury, or death.

Indirect Comparisons of the Three Interventions. Table 5 shows the results of indirect comparison of the three drug groups.

Table 3. Study Characteristics for Trials Comparing Antidepressants and Placebo in Adults with Chronic Insomnia

First Author/Year	Sample Size, *n*, enrolled	Mean Age±SD or (Range), in years	Number of Females/Males or (Percentage Female/Male)	Psychiatric Illness	Quality Score (Jadad)	Intervention		
						Drug	Dose, mg	Duration
Haffmans PMJ/1999*	7	44±NS (NS)	3/4	Previous severe major depression	4	Trazodone	150–250	7 nights
Hajak G/1996*	15	41.3±9.5	3/7	NS	3	Doxepin	25	5 weeks
Hajak G/2001	47	Doxepin: 47.6±11.3, PL: 47.4±16.8	36/11	NS	3	Doxepin	25–50	4 weeks
Hornyak M/2005	40	TR: 45.3±13, PL: 51.3±9.4	NS	NS	2	Doxepin	25 to 50	4 weeks
Negri L/1997*	100	42.95±13.22	70/30	Anxiety alone and mild depressive symptoms	2	Pivagabine	900	30 days
Riemann D/2002	65	Lormetazepam: 45.3±10.3, trimipramine: 47.0±10.8, PL: 48.8±11.6	23/32	NS	3	lormetazepam; trimipramine	1;25–200	28 days
Rodenbeck A/2003*	10	41.3±9.5	3/7	NS	3	Doxepin	25	1 night
Walsh JK/1998	589	42±NS (21–65)	193/85	NS	3	Zolpidem; trazodone	10, 50	14 nights

Compared to non-BDZ, BDZ showed a larger benefit on sleep diary measures of sleep onset latency, but non-BDZ was favored when measured by polysomnography—neither value was statistically significant. Non-BDZ was significantly safer than BDZ. Compared to ADP, the only significant result was that non-BDZ was significantly more efficacious in terms of sleep onset latency when measured by polysomnography—the result when measured by sleep diary still favored non-BDZ; but it was not significant.

DISCUSSION

The review suggests that BDZ and non-BDZ are effective treatments for chronic insomnia, either measured by polysomnography or sleep diary. The analysis also suggests that ADP may have a role in the management of chronic insomnia. The three drug groups pose a risk of harm. The results of the review may be more relevant to the short-term treatment of chronic insomnia because only two studies evaluated long-term efficacy of the treatments. More studies are needed on the long-term efficacy and safety of these agents for chronic insomnia. There seem to be minor differences between drug groups, particularly between BDZ and non-BDZ, but it is difficult to evaluate the clinical importance of these differences because we did not compare drugs according to potency, half-life, or dosage. However, indirect comparisons suggest that non-BDZ are safer than BDZ.

There was strong evidence of publication bias in the pooled estimates for sleep onset latency in the BDZ category of intervention by the graphical test[24] and visual inspection of the funnel plot,[26] and for the non-BDZ category of intervention by the rank correlation test,[23] graphical test,[24] and visual inspection of the funnel plot.[26] We were not able to assess publication bias in the ADP group. The majority of studies received funds from private sources (51/56), suggesting that negative results were less likely to be published. Thus, the true estimate of efficacy may be lower than the estimate calculated in the current analysis.

The majority of studies included in the review investigated hypnotics, the most commonly prescribed class of medication for insomnia. Our finding that these drugs are effective treatments for chronic insomnia is consistent with other meta-analyses.[12–15] Three meta-analyses reporting effect sizes found reliable improvements in sleep parameters using hypnotics in patients with chronic insomnia.[12,14,15] Holbrook et al. found that BDZ decreased sleep latency and increased sleep duration, although the latter effect was not statistically significant.[13] Data show modest to poor correlations between subjective reports and objective findings in insomnia research. The tendency is to overestimate sleep latency and underestimate total sleep time.[1] However, our analysis showed no statistically significant difference in results based on method of measurement (polysomnography versus sleep diary). Another meta-analysis comparing effectiveness of newer non-BDZ and BDZ reported consistent differences between drugs,[16] in contrast to our analyses. Despite the heterogeneity in the pooled estimates for BDZ and non-BDZ

Table 4. Pooled Efficacy Outcomes of Treatment Versus Placebo

Outcomes	Number of Studies	Point Estimate (95% CI)	Heterogeneity (I^2) (%)
Sleep onset latency (WMD)			
Benzodiazepine			
Polysomnography	11	−10.0 min (−16.6, −3.4)	72.6
Sleep Diary	26	−19.6 min (−23.9, −15.3)	55.5
Non-benzodiazepines			
Polysomnography	12	−12.8 min (−16.9, −8.8)	39.3
Sleep Diary	34	−17.0 min (−20.0, −14.0)	64.8
Antidepressants			
Polysomnography	4	−7.0 min (−10.7, −3.3)	34.1
Sleep Diary	2	−12.2 min (−22.3, −2.2)	0
Wakefulness after sleep onset (WMD)			
Benzodiazepine			
Polysomnography	5	−16.7 min (−25.3, −8.1)	0
Sleep Diary	4	−39.9 min (−71.0, −8.8)	68.2
Non-benzodiazepines			
Polysomnography	3	−7.0 min (−14.6, 0.7)	0
Sleep Diary	12	−15.0 min (−22.3, −7.7)	66.5
Antidepressants			
Polysomnography	2	−12.2 min (−17.5, −7.0)	0
Sleep Diary	1	−7.1 min (−19.1, 4.9)	NA
Sleep efficiency (WMD)			
Benzodiazepine			
Polysomnography	8	7.4% (5.2, 9.6)	0
Sleep Diary	5	7.9% (3.3, 12.5)	69.0
Non-benzodiazepines			
Polysomnography	7	4.7% (3.1, 6.2)	0
Sleep Diary	4	5.0% (1.5, 8.6)	0
Antidepressants			
Polysomnography	5	13.6% (9.5, 17.7)	0
Sleep Diary	0	NA	NA
Total sleep time (WMD)			
Benzodiazepine			
Polysomnography	9	32.7 min (16.0, 49.4)	66.3
Sleep Diary	12	52.6 min (38.8, 66.5)	58.9
Non-benzodiazepines			
Polysomnography	9	11.4 min (−0.5, 23.2)	33.6
Sleep Diary	25	31.5 min (25.6, 37.5)	54.3
Antidepressants			
Polysomnography	4	79.6 min (48.8, 110.3)	56.1
Sleep Diary	1	−54.3 min (−109.8, 1.2)	NA
Sleep quality (SMD)			
Benzodiazepine	24	0.79 SD (0.65, 0.92)	47.0
Non-benzodiazepines	23	0.47 SD (0.37, 0.56)	51.3
Antidepressants	4	0.59 SD (0.28, 0.90)	35.4
Quality of life (SMD)			
Non-benzodiazepines	2	0.38 SD (0.19, 0.57)	29.0
Adverse events (RD)			
Benzodiazepine	34	0.15 SD (0.10, 0.20)	69.6
Non-benzodiazepines	27	0.07 SD (0.04, 0.11)	66.8
Antidepressants	3	0.09 SD (0.01, 0.18)	0

CI Confidence interval, *NA* not applicable, *RD* risk difference, *SMD* standardized mean difference, *WMD* weighted mean difference

in the current review, virtually all of the studies favored the intervention over placebo.

Compared to BDZ and non-BDZ, there were substantially fewer studies on ADP, although the review provides some evidence that ADP, particularly doxepin and trazadone, may be effective treatments for chronic insomnia. Despite the paucity of data with respect to the safety and efficacy of ADP relative to BDZ and non-BDZ, these agents are prescribed with increasing frequency for insomnia compared to hypnotics.[27] Further studies are needed to establish long-term safety and efficacy to determine if they are equivalent to BDZ and non-BDZ.

The BDZ, non-BDZ, and ADP had a significantly greater risk of harm than placebo. The adverse events most commonly reported among studies included headache, drowsiness, dizziness, and nausea. Medications for insomnia are often used in the elderly, and BDZ have been shown to increase the risk of injury and decrease cognitive function in this group.[13,15,28] None of the studies addressed safety issues related to concurrent medication use in the elderly treated for insomnia, which may be worth exploring in future studies. In the current review, we analyzed overall adverse events, rather than specific adverse events such as tolerance and rebound insomnia. However, another meta-analysis reviewing the effects of hypnotics on rebound insomnia and tolerance suggests that pharmacological profiles of medications are important considerations with respect to side effects, and insufficient data for some agents did not allow for conclusions to be drawn regarding their long-term safety.[29]

The results of subgroup analyses with respect to the relationship between method of measurement and effect estimates were inconsistent across treatment categories: although the effect of BDZ was more pronounced in the same direction, favoring medication, over placebo, when measured by sleep diary compared to polysomnography. No significant difference was found in the effect of either the non-BDZ or ADP with respect to the method of outcome measurement. This finding may point to underpowered

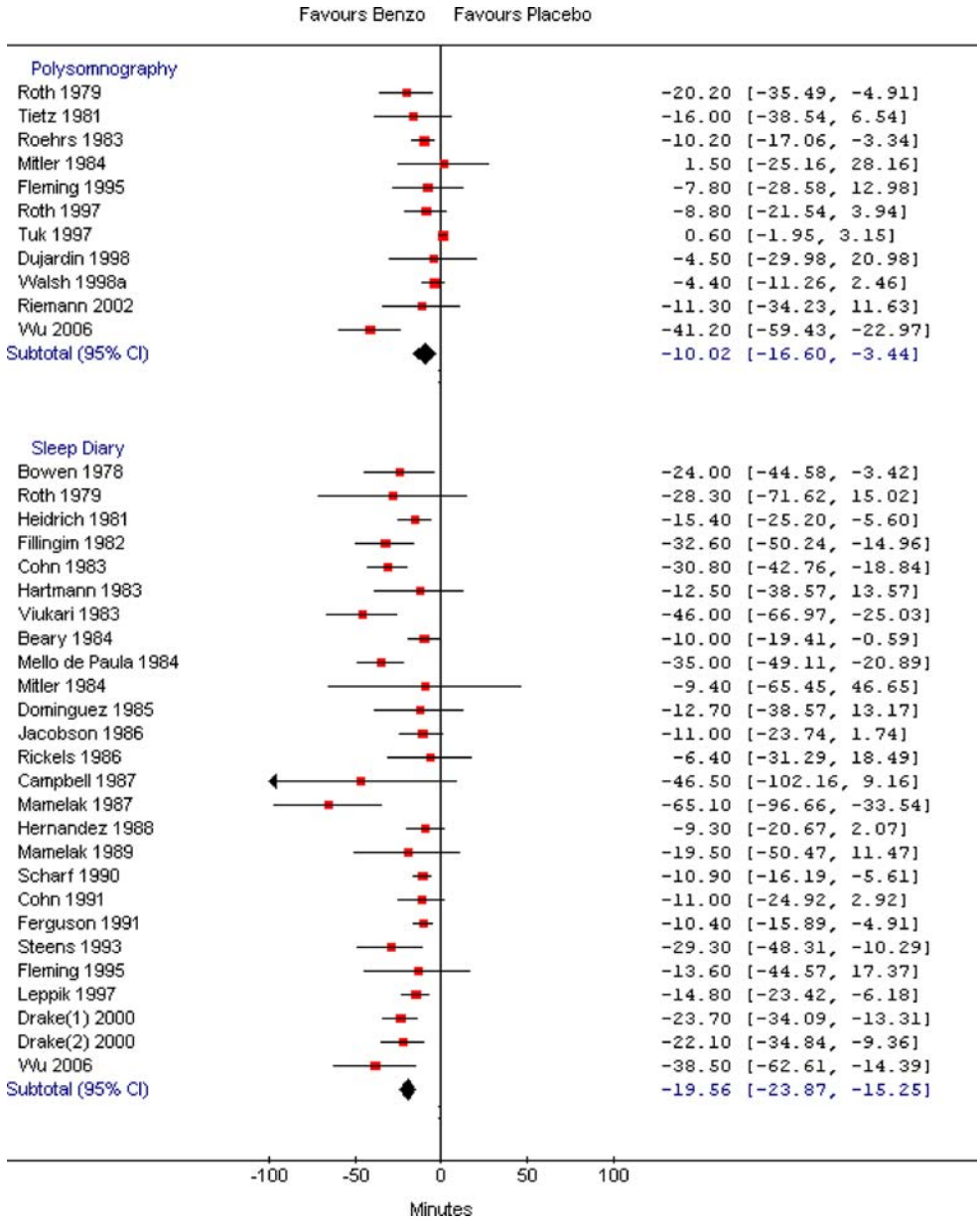

Figure 2. Meta-graph of sleep onset latency (minutes) in adults with chronic insomnia: benzodiazepines versus placebo

analyses or a lack of evidence of a true relationship between treatment effect and measurement method in these studies.

The results of this review must be interpreted with caution when applying the evidence to clinical practice for several reasons. Although it appears that these results are generalizable to insomnia patients, translating these findings to the clinical setting is not straightforward. Patients with medical or psychiatric comorbidities were excluded in most of the studies. However, in clinical practice, many insomnia patients have either medical or psychiatric comorbidity; thus, it is difficult to extrapolate these findings to these populations. In addition, this meta-analysis also was not able to answer the clinically relevant question of the long-term effects of these medications. Furthermore, the drugs were analyzed in groups irrespective of their differences in half life, potency or dosage, and direct comparisons between drugs were not made. Nevertheless, the data show that sleep parameters do improve with the use of these agents. Additional large-scale randomized trials are needed to determine the efficacy and safety of these interventions across various subsets of the chronic insomnia population. In addition, more studies are needed to explore the long-term efficacy and safety of these drugs because the current results may be relevant to short-term treatment of insomnia only.

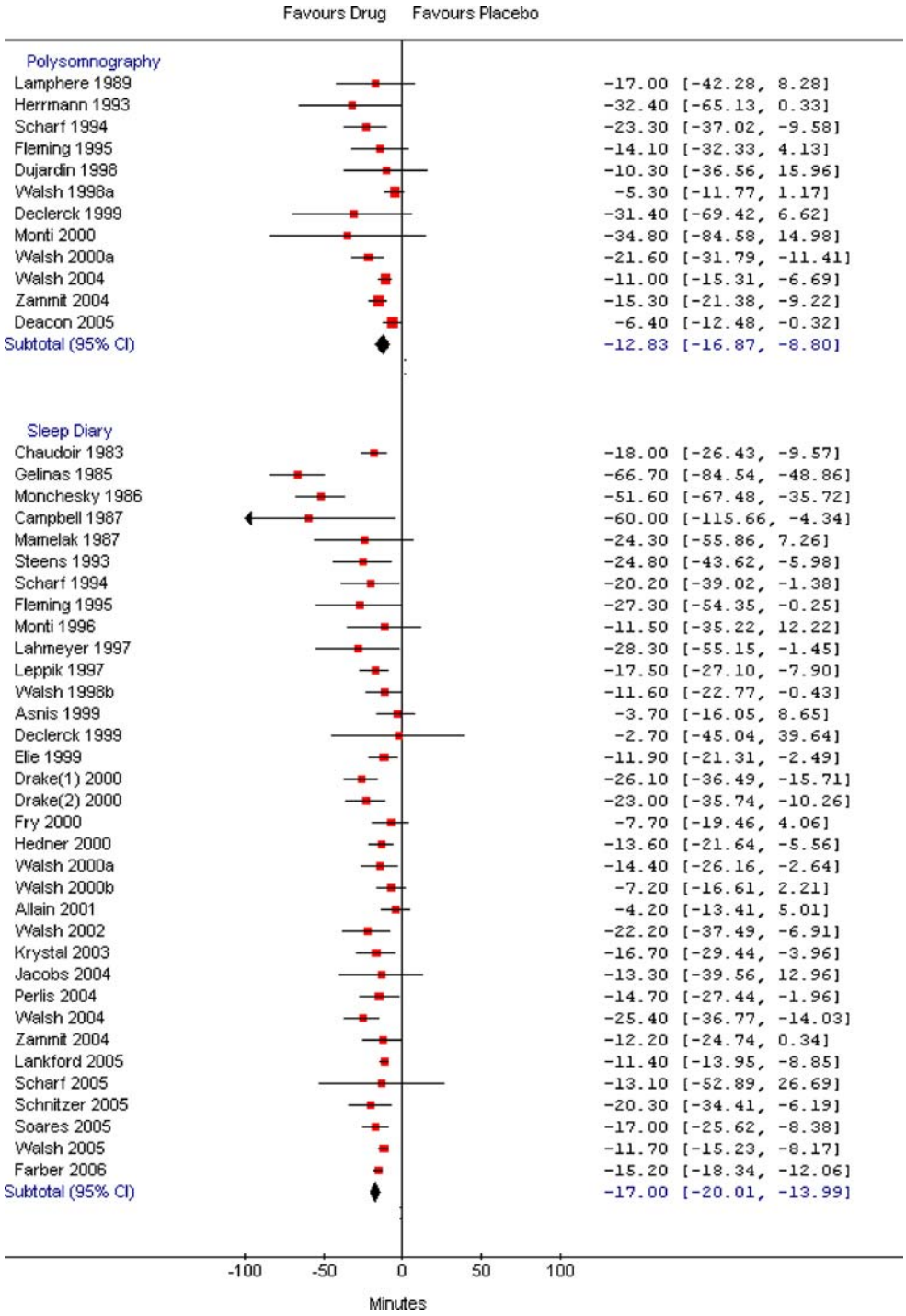

Figure 3. Meta-graph of sleep onset latency (minutes) in adults with chronic insomnia: non-benzodiazepines versus placebo

Limitations of this review include the lack of identification of unpublished data, such as data from pharmaceutical manufacturers. Furthermore, outcomes other than sleep onset latency were under-reported in the insomnia literature, despite the relevance of outcomes such as wakefulness after sleep onset, night wakings, and sleep quality to this condition.

Further research related to treatment of chronic insomnia in adults should address (1) the effect of drug treatments for chronic insomnia on quality of life and daytime functioning, (2) the safety and efficacy of pharmacotherapy for chronic insomnia in high risk or vulnerable groups such as the elderly, (3) the use of a consistent definition of chronic insomnia to determine prevalence rates and compare treatment effects

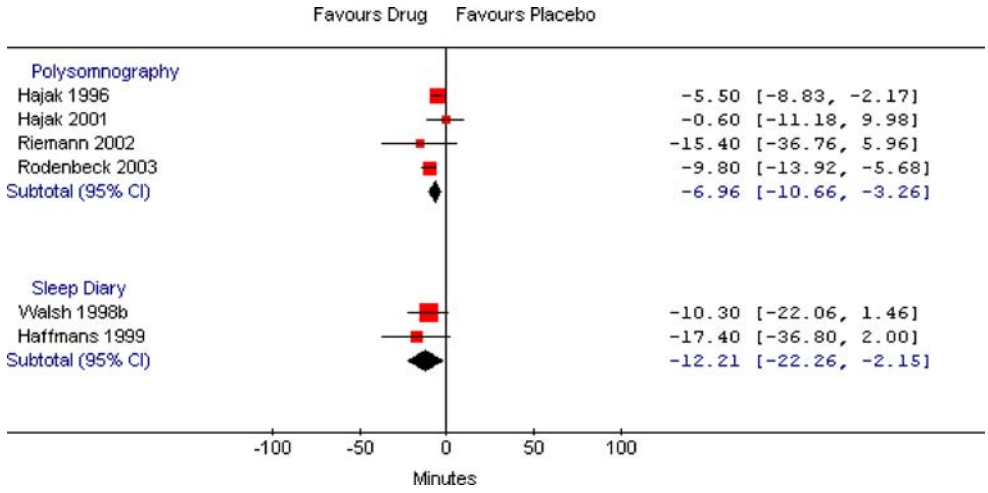

Figure 4. Meta-graph of sleep onset latency (minutes) in adults with chronic insomnia: antidepressants versus placebo

among studies, (4) the long-term efficacy and safety of drug treatments for the management of chronic insomnia, and (5) the development of a threshold for a clinically significant treatment effect in the management of chronic insomnia, such that statistically significant findings can be put into clinical context.

Table 5. Indirect Comparisons of Pharmacological Treatment Categories

Comparison	Difference in SOL (min)/ Risk Difference	95% Confidence Interval (min)	Difference Favors	Significant Difference (Yes or No)
Sleep onset latency as measured by polysomnography				
BDZ versus non-BDZ	2.8	−4.9, 10.5	non-BDZ	No
BDZ versus ADP	−3.1	−10.6, 4.5	BDZ	No
non-BDZ versus ADP	−5.9	−11.3, −0.4	non-BDZ	Yes
Sleep onset latency as measured by sleep diary				
BDZ versus non-BDZ	−2.6	−7.8, 2.7	BDZ	No
BDZ versus ADP	−7.4	−18.3, 3.6	BDZ	No
non-BDZ versus ADP	−4.8	−15.3, 5.7	non-BDZ	No
Adverse events				
BDZ versus non-BDZ	0.08	0.02, 0.14	non-BDZ	Yes
BDZ versus ADP	0.06	−0.04, 0.16	ADP	No
non-BDZ versus ADP	−0.02	−0.12, 0.08	non-BDZ	No

ADP Antidepressants, *BDZ* benzodiazepines, *min* minutes, *non-BDZ* non-benzodiazepines, *SOL* sleep onset latency

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Corresponding Author: *Liza Bialy, BSc; Alberhart Centre One, Room 9428, 11402 University Avenue, Edmonton, AB T6J 2G3, Canada (e-mail: lbialy@ualberta.ca).*

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